FIRM:UCYCLYD
TRADE NAME:BUPHENYL POWDER
GENERIC NAME:SODIUM PHENYLBUTYRATE

Summary Basis of Approval
Cover Form

Appl #: 020573
Firm: UCYCLYD
Reviewing Div: 510
Trade Name: BUPHENYL(SODIUM PHENYLBUTYRATE)POWDER
Generic Name:
SODIUM PHENYLBUTYRATE

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

NDA 20573

SBA

Approval Letter And Related Correspondence

NDA 20-573

APR 30 1996

Ucyclyd Pharma, Inc.
Attention: Norbert L. Wiech, Ph.D.
President
10819 Gilroy Road, Suite 100
HUNT VALLEY MD 21031

Dear Dr. Wiech:

Please refer to your new drug application submitted February 15, 1995, under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Buphenyl (sodium phenylbutyrate) Powder, 250 and 500 grams. Until your April 25, 1996, communication, the proposed trade name for this drug was Ammonapse.

We acknowledge receipt of your amendments dated February 13 and 22, March 4 and 7, and April 1, 8(2), 11, 12, 15 (2), 22, 24 (2), 25 (2), and 30, 1996. We also refer to our approvable letter dated February 16, 1996.

This new drug application provides for the use of this drug as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase, or argininosuccinic acid synthetase.

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 submitted on April 30, 1996 (bottle labels, package insert, and patient package insert), with the revisions listed below. Accordingly, the application is approved effective on the date of this letter. The revisions are as follows:

1. In the fifth paragraph of the INDICATIONS AND USAGE section, revise the second sentence to read "The two deaths in this group of patients occurred during episodes of hyperammonemic encephalopathy."

2. Insert a new penultimate paragraph in the INDICATIONS AND USAGE section that reads "Even on therapy, the majority of patients for whom the drug is indicated continue to experience recurrent episodes of acute hyperammonemia."

3. Revise the last paragraph of the INDICATIONS AND USAGE section to read "Buphenyl may be required life-long unless orthotopic liver transplantation is elected."

4. The CONTRAINDICATIONS section should be moved to immediately after the INDICATIONS AND USAGE section.

5. In the HOW SUPPLIED section, the NDC numbers may be deleted from the first paragraph since they are listed at the end of the section.

6. The following heading should be added to the patient package insert: "Buphenyl (sodium phenylbutyrate) Powder."

7. Add the date of last revision to the end of the patient package insert.

These revisions are terms of the NDA approval. Marketing the product before making the revisions, exactly as requested, in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit sixteen 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 20-573. Approval of this submission by FDA is not required before the labeling is used.

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

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Metabolism and Endocrine Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and
Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

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 problem that may be identified.

We remind you of your Phase 4 commitments specified in your submissions dated April 1 and 30, 1996. These commitments are listed below:

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to the NDA. For some of the Phase 4 commitments, an IND may not be necessary. In that case, data and final reports should be submitted to this NDA as correspondence. For administrative purposes, all submissions relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

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:

John R. Short, R.Ph.
Consumer Safety Officer
(301) 443-3510

Sincerely yours,

James Bilstad, M.D. 4/30/96
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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

NDA # 20-512 and 20-513 Trade (generic) names [illegible]

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 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC 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.

✓ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items:

Signature of Preparer

1/18/96
Date

cc: Orig NDA (2)
HFD-110 /Div File (2)
NDA Action Package

Medical Officers Review

APR 29 1996

NDAs: 20,572 and 20,573
Drugs: Ammonapse tablets and powder (Sodium Phenylbutyrate)
Sponsor: Ucyclyd Pharma, Inc.
Date: 4/24/96

In looking through the division file on Friday, April 5, to find the date of my telephone conversation with Dr. Wiech, President of Ucyclyd, informing him of the need to perform an analysis of the safety data for this drug, I noticed a review by Dr. D. Lee Ham, FDA Division of Oncology, dated 9/30/92. In that review, she refers to the side effects of sodium phenylacetate (phenylbutyrate is the pro drug of phenylacetate), as "...mainly CNS toxicity as irritability, nausea and vomiting, lethargy, coma and death". I called Dr. Ham on 4/5 to obtain the source of this information. She faxed to me a published article in Cancer Research 54: 1690-4, April 1, 1994 (enclosed). In this article, 17 patients with advanced solid tumors (9 prostate cancer, 7 brain tumors and 1 mesothelioma) were enrolled in a phase 1 and pharmacokinetic study of IV phenylacetate. 3 patients received a 150 mg/kg IV bolus of phenylacetate over 2 hrs. Because this large bolus yielded phenylacetate concentrations above the K_m over the 6 hr. sampling period, suggesting a non-linear nature of phenylacetate pharmacokinetics), the bolus was reduced to 60 mg/kg over 30 min. Also, the dose escalation was changed from a fixed schedule (dose levels 1 and 2: 150 and 250 mg/kg/day, respectively) to a concentration-guided escalation trial (dose levels 3 and 4, 200 and 400 ug/ml, respectively). In the latter format, each patient received a phenylacetate IV bolus dose of 60 mg/kg over 30 min., 1 week prior to beginning a 14 day continuous IV infusion of the drug. The patient-specific pharmacokinetic parameters estimated from the bolus dose was used to calculate an infusion rate that would maintain the serum phenylacetate concentration at the targeted level during the 14 day infusion. No toxicity was associated with bolus administration of the drug. The highest peak serum concentrations were measured after the 150 mg/kg bolus over 2 hrs.: 533 ± 94 ug/ml. In the following table, I list the phenylacetate (PA) and phenylacetyglutamine (PAG) concentrations (mean ± SD) per dose level during continuous IV infusion:

Dose level	PA Dose (mg/kg/day)	PA (ug/ml)	PAG (ug/ml)
1	150	49±19	90±34
2	250	104±40	150±63
3	266±40	178±85	188±55
4	374±95	397±244	306±51

Although the serum phenylacetate concentrations at dose levels 3 and 4 are near their target levels (400 ug/ml), the large standard deviations reflect the inability to maintain serum phenylacetate within the desired range, even when using adaptive control with feedback.

The authors also state that in some patients treated at dose levels 1 and 2, there was a tendency for serum phenylacetate concentration to decrease over time, such that there was a 23% mean decline in concentration from day 2 to day 11 of continuous

IV drug infusion.

With regard to clearance, PA was rapidly converted to PAG. In the 3 patients who received an IV bolus of 150 mg/kg over 2 hrs., the peak serum concentration of PAG was 224±81 ug/ml, 325±72 min. post-infusion. After the 60 mg/kg bolus, the peak serum PAG concentration was 104±33 ug/ml at 86±33 min.

The article states: **"Drug-related toxicity was clearly related to the serum phenylacetate concentration. Three episodes of CNS toxicity, limited to confusion and lethargy and often preceeded by emesis, occurred in patients treated at dose levels 3 and 4. They were associated with drug concentrations of 906, 1044 and 1285 ug/ml (1078 ± 192 ug/ml), respectively. Symptoms resolved within 18 hrs. of terminating the drug infusion in all instances."** The article states in the discussion section: "Phenylacetate serum concentrations in excess of 900 ug/ml were typically associated with CNS toxicity". It further states that "...the slightest error in the estimation of individual pharmacokinetics or in the rate of drug infusion results in large changes in drug concentration". However, the article states that intermittent drug infusion would allow some drug wash-out to occur, thereby minimizing drug accumulation.

Jean Temeck, MD

Jean Temeck, M.D.

cc. HFD-510: Dr. Sobel, Dr. Troendle, Dr. Jordan and Mr. Short
HFD-427: Dr. Ahn

Gloria Troendle 1-29-96

NDAs: 20,572 and 20,573 Drugs: Buphenyl tablets and powder
Sponsor: Ucyclyd Pharma, Inc. Date: 5/6/96

Buphenyl powder was approved on 4/30/96. In reviewing the approval letter sent to the sponsor on 4/30 and the revised labeling sent in by the sponsor on 4/30, it appears that several changes were not made. In addition, there are several minor errors in the label faxed by the sponsor to FDA on 4/30. I will summarize all remaining corrections here:

Buphenyl Powder Physician Package Insert:

1. CLINICAL PHARMACOLOGY section, Pharmacodynamics subsection:

revise the second sentence to read: "It increases waste nitrogen excretion in the form of phenylacetylglutamine."

2. INDICATIONS AND USAGE section:

revise the second sentence to read: "It is indicated in all neonatal-onset deficiency patients (complete enzymatic deficiency, presenting within the first 28 days of life) and, also, in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy." Note: in reviewing the label with Dr. Bilstad on the evening of 4/30, he stated he preferred this wording to the current one.

revise the beginning of the first sentence in the fifth paragraph to read: "In late-onset deficiency patients, including females heterozygous for ornithine transcarbamylase deficiency, who develop..."

insert a new penultimate paragraph that reads: "On therapy, acute hyperammonemic encephalopathy recurred in the majority of patients for whom the drug is indicated."

at the end of the Indications and Usage section, add: "(See CLINICAL PHARMACOLOGY, Pharmacodynamics section for the biochemical effects of Buphenyl)."

3. PRECAUTIONS section, General subsection:

first sentence: omit the letter "s" from "components"

third sentence: Dr. Bilstad requested that Dr. Jordan insert the doses of phenylacetate administered to the animals.

4. ADVERSE REACTIONS section, Clinical Adverse events subsection:

at the end of the third sentence in the introductory paragraph, delete ", or both"

sentence 7 should preceed sentence 6

regarding the last paragraph in this subsection:

revise the first sentence to read: "Neurotoxicity was reported in cancer patients receiving intravenous phenylacetate, 125-150 mg/kg/dose, administered as a one hour infusion, bid, for 14 consecutive days, with therapy repeated at four week intervals."

after the second sentence, add: "These adverse

events were mainly mild in severity."

5. DOSAGE AND ADMINISTRATION section:
The sentence which reads: "Shake lightly before use" should be placed after the sentence: "Acidic beverages are to be avoided."

Nutritional Management subsection, second paragraph, fourth sentence: "1/7" should be corrected to "1.7"

Buphenyl Patient Package Insert:

1. What is the most important information I should know about Buphenyl?
second paragraph, replace "...these medications..." with "...this medication..."

2. What other medical conditions may also be present that could increase the risk of taking Buphenyl?
in the last sentence, replace "...your doctor..." with "...the doctor..."

3. How should I or my child take Buphenyl?
Make the sentence: "If in a liquid, shake lightly before use", the last sentence of the first paragraph in this section.

4. Replace "...taking Buphenyl?" in the heading of the next section to "...on Buphenyl?"

5. What medications may affect the way the body breaks down the drug?
replace "...your doctor..." with "...the doctor..."

In addition to the above comments to be conveyed to the sponsor, a copy of my guideline for the determination of clinically significant abnormal hematologic and serum chemistry values, should be conveyed to the sponsor if Dr. Sobel and Dr. Troendle agree with the proposed guideline. The sponsor can then use this guideline to calculate the frequency of these laboratory adverse events in future submissions. Since I have made slight modifications in the guideline regarding serum total protein and albumin, I will reiterate the entire guideline here as the one to be sent to the sponsor (note: ULN= upper limit of normal):

Clinically Significant Serum Chemistry and Hematology Values

Parameter	Significant Low	Significant High
Sodium (meq/L)	< 132	≥ 150
Potassium (meq/L)	< 3.2	> 6.1
Chloride (meq/L)		> 110
CO_2 (meq/L)	≤ 18	> 30
Glucose (mg/dl)	< 45	> 120 (fasting)
Uric acid (mg/dl)		≥ 9.0

Calcium (mg/dl)		≥ 11.5
Phosphorous (mg/dl)	< 3.0 if < 18 yrs.	> 7.0 at any age
	< 2.5 if > 18 yrs.	
Total protein (g/dl)	≤ 4.3 if ≤ 3 mos.	
	≤ 5.2 if 1 yr.	
	≤ 5.6 if > 1 yr.	
Albumin (g/dl)	< 3.0 if ≤ 3 mos.	
	< 3.5 if ≥ 1 yr.	
Cholesterol (mg/dl)		≥ 300
Total bilirubin (mg/dl)		≥ 2.0
Alkaline Phosphatase		≥ 3 x ULN for age
SGOT and SGPT		≥ 3 x ULN
Hgb (g/dl)/Hct (%):		
infant	≤ 9/ ≤ 27	
1-12 yrs.	≤9.5/<30	
12-18 yrs.	≤9.5/≤32	
adult male	≤11.5/≤37	
adult female	≤9.5/≤32	
Total white blood count (cells/mm^3)	< 4,000	> 15,000
Platelets (cells/mm^3)	< 100,000	≥ 600,000

The sponsor should also revise his reference range for total protein and albumin. Normal serum total protein for ages 0-3 mos. is 4.5-7.0 g/dl, for 1 yr.: 5.4-7.5 g/dl and for > 4 yr.-18 yrs. is 5.9-8.0 g/dl. Normal serum albumin for ages 0-3 mos. is 3.2-4.8 g/dl, for 1 yr.: 3.7-5.7 g/dl and for > 4 yr.- 18 yrs. is 3.8-5.4 g/dl (source: Lange's Current Pediatric Diagnosis and Treatment, 11th edition, 1993). The normal reference range for alkaline phosphatase is age dependent and may be found in any standard pediatric textbook such as Lange's noted above or Nelson's Textbook of Pediatrics. The sponsor has requested that I check the normal reference range for amylase. Again, any standard textbook of pediatrics and medicine contains this information. Per Lange's reference, it is undetable in the newborn and, between 2-12 mos. of age, it slowly increases to adult levels which are 28-108 IU/L.

Also, Mr. Short will telephone the sponsor to inform him that it is acceptable to us if he wishes to do a phase IV safety study (see sponsor's 4/9/96 fax, attached).

Note: Both a telephone conversation I had with Dr. Brusilow on 4/26/96 and NDA 20,573, vol. 1.6, pp. 050009, were the sources for the recommended daily dietary protein intake at the suggested doses of Buphenyl in the DOSAGE AND ADMINISTRATION section, Nutritional Management subsection. Specifically, Dr. Brusilow stated that per the protocol, at the dose of sodium phenylbutyrate recommended, the suggested daily dietary protein intake from birth to 4 mos. of age is 1.6 g/kg/day and, if tolerated, may be increased to 1.9 g/kg/day. For 4-12 mos., the

recommended daily dietary protein intake is 1.4 g/kg/day but 1.7 g/kg/day is advisable. From 12 mos.-3 yrs., the recommended daily dietary protein intake is 1.2 g/kg/day, but 1.4 g/kg/day is advisable In addition, Dr. Brusilow recommends that patients with neonatal-onset CPS and OTC deficiency who are at least 6 mos. of age, receive a daily protein intake which is equally divided between natural protein and supplemental essential amino acids. He also stated that for nutritional management, the neonatal-onset ASD patients should be grouped with the partial deficiency patients.

Also, ultimately, the intent is a single label for both the Buphenyl tablets and powder.

Jean Temeck, M.D.

cc. HFD-510: Dr. Sobel, Dr. Troendle, Dr. Jordan, Dr. Moore, Dr. Markofsky and Mr. Short

Gloria Troendle
5-7-96

APR 2 9 1996

NDAs: 20,572 and 20,573
Drugs: Ammonapse tablets and powder
Sponsor: Ucyclyd Pharma

Dates submitted: 3/4, 3/8, 4/8, (2) 4/9 4/11, 4/15, 4/22 and fax 4/25/96
Dates received: 3/6, 3/11, 4/9, 4/12 4/15, 4/22 and fax 4/25/96
Date reviewed: 4/25/96

1. Revised Physician Labeling Submitted 3/4/96:

A. Ammonapse tablets:

a. DESCRIPTION section:

Remove the word "Tributyrate" from the first sentence (done by sponsor in 4/8/96 label).

b. CLINICAL PHARMACOLOGY section, Pharmacokinetics subsection:

"Excretion" - place a comma after the word "product" in the first sentence.

"Special Populations: Gender" - place a comma after "parameters" in the second sentence.

c. INDICATIONS AND USAGE section:

Make sentence 6 a separate paragraph.

d. NUTRITIONAL MANAGEMENT section:

See comments under "Ammonapse Powder". This section should be identical to that for the powder.

e. PRECAUTIONS section:

I would appreciate Dr. Troendle's opinion regarding inclusion of the following sentence

B. Ammonapse powder:

a. DESCRIPTION section:

First sentence: remove the word "Tributyrate" from the first sentence (done by sponsor in 4/8 label).

Second sentence: place the word "salty" after "strong".

b. CLINICAL PHARMACOLOGY section:

Replace "which" with "that" in the second sentence.

Pharmacokinetics subsection:

"Disposition" -

second sentence, replace: "However, it was found that the drug is metabolized..." with: "However,

the drug is known to be metabolized..."

third sentence, replace "found" with "detected"

"Excretion" and "Special Populations: Gender"- same comments as for tablets

"Special Populations: Hepatic Insufficiency"- first sentence: replace "was" with "were"; second sentence: place a comma afeter "unvalidated".

c. INDICATIONS AND USAGE section:

See comment above for the tablets. In addition, omit the word "Powder" in the first sentence. The fourth and fifth sentences were made a separate paragraph in the 4/8 label, therefore, we do not have to request this. Omit the comma after the word "transplantation" in the last sentence of this section.

d. NUTRITIONAL MANAGEMENT section:

The draft labelings submitted by the sponsor on 2/15/95, 1/6/96 and 3/4/96 contain differing statements regarding daily dietary protein intake. The latest version is non-specific. However, the NDA is very clear regarding the amount of dietary protein a patient can tolerate at the recommended dose of Ammonapse based on the specific enzyme deficiency present, its time of onset, and the patient's age. This information is contained in the February 15, 1995 submission, volume 6, page 050009. Therefore, this information should be included in this section.

e. CONTRAINDICATIONS SECTION:

Omit the word "Powder".

f. WARNINGS section:

Omit the word "Powder" from sentence 2.

g. PRECAUTIONS section:

Omit the word "Powder" after Ammonapse in all instances where this occurs (four places).

"General"- first sentence, replace "...or any of its components." with: "...or any component of this preparation." Second sentence, replace "hyperammonemic" with "hyperammonemia".

"Information for Patients"- replace "ir" with "is" (done by sponsor in 4/8 label).

Also, see comment above under "Tablets".

h. DOSAGE AND ADMINISTRATION section:

Regarding frequency of administration (sentence 3), it is not clear why the sponsor changed the frequency of dosing with the powder from "three to six times per day" to "four to six times per day". Please clarify the

instructions given by the Principal Investigator regarding frequency of dosing with the powder.

Should include a statement that the powder requires mixing (should be mixed) with milk/formula or food (this was done in the 4/8 label).

2. Patient Package Insert:

I recommend we add the following statements:

"What is the most important information I should know about Ammonapse?"

Add to the end of the first sentence: "...who have symptoms of the disease (see below) in association with an elevated blood ammonia level."

"What are urea cycle disorders?"

Bold the typical signs of the disease. After the sentence which begins: "The diagnosis...", add, in bold: **"These typical signs of the disease may recur after the diagnosis is made if your condition is not under control. If they do, notify your doctor immediately because this is a medical emergency. You should be aware that infection can cause your condition to go out of control. Therefore, if you develop a fever, see your doctor immediately."**

Add the following sentence as a new paragraph to this section and bold it: **"If you are a patient or carrier of these disorders, you should wear a Medic alert tag stating your diagnosis. In the event that you have a sudden, rapid accumulation of ammonia in your blood, and hence, in your brain, rendering you unconscious, this will alert doctors to treat you appropriately and aggressively to help prevent devastating consequences.**

"What is Ammonapse?":

"Ammonapse is a drug that helps to prevent ammonia from accumulating in the blood. Ammonapse aids the body in eliminating substances that produce ammonia. However, for various reasons, despite drug treatment, blood ammonia levels may become periodically elevated and there may be episodes of altered brain function in association with these ammonia elevations. This is why patients with urea cycle defects may be retarded; many in the newborn period are severely retarded. The full benefits of the drug in patients with disease onset after the first month of life have not yet been completely defined. Ammonapse may be used as life-long therapy or as a temporizing measure until liver transplantation is performed."

"How should I or my child take Ammonapse?"

Revise the fifth sentence of the first paragraph to read: "If powder is used, dilute it in infant formula, milk or food such as pudding." Add: "Shake lightly before use."

Revise the last sentence of the second

paragraph: replace the word "and" after ammonia with a comma; after the word "levels" add: "and plasma levels of Ammonapse and its breakdown products"; add an "s" to the word "test" and add: "and side effects" to the end of this sentence.

Revise the section entitled: "What medications should I or my child avoid while taking Ammonapse?" to read: "What medications should I or my child avoid or be cautious of taking while on Ammonapse?" Add the following sentence to this section: "Steroids may breakdown body protein and, thereby, increase blood ammonia levels. Consult your doctor before taking medications containing steroids."

"What are the most common side effects of Ammonapse?"

Revise the incidence of decreased appetite to 4% and omit the next sentence. After the sentence pertaining to decreased appetite, add: "Body odor and bad taste/taste aversion were each reported in 3% of all people treated. "

3. Safety Update:

The safety update submitted on 3/8/96, covers the period after submission of the NDA to 2/21/96. Since the NDA was filed, 46 patients have been enrolled (19 rescue, 2 prospective, 8 late-onset CPS def. and late-onset OTC males and 17 OTCF). Of these, 31 patients are evaluable (i.e. at least 1 case report form has been returned). In addition, 4 patients previously reported as unevaluable in the NDA, are now evaluable because follow-up information has been received. Therefore, there are now an additional 35 patients who are evaluable (14 rescue: 6 OTC, 1 CPS and 7 AS; 2 prospective: 1 CPS and 1 AS; 5 late-onset: 4 OTC and 1 CPS; 14 OTCF). Of these 35 evaluable patients, 19 are female and 16 are male; and the majority (30/35) are < 12 yrs. of age.

To date, 206 patients with UCD have been enrolled (160 patients in the NDA- note: this number excludes patient #'s 295 and #565 whose records could not be found during FDA's audit- and 46 patients since the NDA was filed). Of these 206 patients, 183 are evaluable (148 in the NDA and 35 in the update). The 183 evaluable patients are classified as follows: 72 rescue (25 OTC, 13 CPS and 34 AS), 14 prospective (4 OTC, 5 CPS and 5 AS); 29 late-onset (25 OTC and 4 CPS) and 68 OTCF.

Note: The sponsor states that patient # 594 was misclassified as an OTCF when, in fact, she has late-onset CPS deficiency. Also, patients #'s 575 and 576 were accidentally reversed (they are mother and daughter and are both OTCF heterozygotes).

a. Deaths:

2 additional deaths have occurred since submission of the NDA: patients 391 and 706, both OTC rescue patients. The cause of death in the former patient is not known but appears to

have been due to a severe viral infection (though not proven). This patient (# 391 presented with fever and lethargy which progessed rapidly to multiorgan shutdown with acute renal failure, DIC and ARDS. Bacterial cultures were negative and blood ammonia levels were normal. An autopsy was refused by the parents. Patient # 706 died of hyperammonemic encephalopathy.

Therefore, of a total of 206 patients enrolled, there have been 17 deaths (17/206= 8% total mortality). The breakdown by enzyme deficiency is:

Rescue: CPS- 3/14= 21%, AS- 4/40= 10%, OTC- 8/27= 30%
Overall mortality for rescue patients: 15/81=19%
Prospective: 0/15= 0%
Late-onset CPS deficiency (male and female) and late-onset OTC males: 1/35= 3%
OTCF heterozygotes: 1/75= 1%

b. Withdrawals:

There have been 12 additional withdrawals (12/206= 6%). The breakdown by enzyme deficiency is:

Rescue: CPS- the additional patient withdrew for liver transplant.

AS- the additional patients withdrew for: liver transplant- 1 patient; upset stomach and lethargy- 2 patients, one of whom also had "trembling"; formula containing phenylbutyrate rejected- 1 patient, moved out-of-state- 1 patient.

OTC- the additional patient withdrew for liver transplant.

Prospective: the additional patient withdrew for liver transplant.

Late-onset CPS deficiency and late-onset OTC males: the additional patient withdrew for liver transplant.

OTCF heterozygotes: the additional patients withdrew for: difficulty taking medication- 1 patient; non-compliance with medication- 1 patient; increased vomiting, behavioral problems and fluctuating ammonia levels- 1 patient.

The total number of withdrawals (NDA + update) for each group now is:

Rescue: CPS- 2/14= 14%, AS- 9/40= 23%, OTC- 5/27= 19%
(total withdrawal rate for rescue: 16/81= 20%)
Prospective: 5/15= 33%
Late-onset CPS def. and late-onset OTC males: 6/35= 17%
OTCF: 11/75= 15%

c. Clinical Adverse Events: (note: coma will be reported under "Frequency of Hyperammonemic Episodes"; pts. = patients, total n in NDA= 160 pts., total n in NDA + update= 206 pts., CP= cerebral palsy, SD= spastic diplegia, SQ= spastic quadriplegia, behav. chg.= behavior change, amen./menst. dysfn.= amenorrhea/menstrual dysfunction, RTA= renal tubular acidosis)

Adverse Event	#pts.(%)in NDA	#pts.in Update	#pts.(%)total

Adverse Event	#pts (%) in NDA	#pts in Update	#pts (%) total
Neurological:[a]			
Seizures	10 (6%)	0	10 (5%)
CP/SD/SQ	6 (4%)	2	8 (4%)
Hyperactive	4 (3%)	3	7 (3%)
Hostility/Behav Chg.	5 (3%)	2	7 (3%)
Speech disorder	1 (1%)	6	7 (3%)
Hypotonia	5 (3%)	0	5 (2%)
Hypertonia	5 (3%)	0	5 (2%)
Poor Motor co-ord.	0	3	3 (1%)
Syncope	2 (1%)	0	2 (1%)
Headache	1 (1%)	1	2 (1%)

a= I suspect the frequency of the above neurological signs and symptoms are vastly underrated in these patients as the majority present were most likely regarded as indicative of the patients' underlying disease and not due to drug. I agree with this assessment.

In addition to the above, 1 patient each reported the following neurological signs and symptoms as adverse events: lethargy, anxiety, confusion/disorientation and dizziness.

The majority (37/52= 71%) of the more serious neurological adverse events (n= 52 adverse events: seizures, cerebral palsy/spastic diplegia/spastic quadriplegia, hyperactivity, hostility/behavior change, speech disorder, hypotonia, hypertonia and poor motor coordination), occurred in neonatal-onset disease (rescue and prospectively treated patients). However, the less serious neurological adverse events (syncope, headache, lethargy, anxiety, confusion/disorientation and dizziness) occurred predominately (7/8= 88%) in late-onset patients (includes OTCF hets).

Adverse Event	#pts.(%)in NDA	#pts.in Update	#pts.(%)total
Psychiatric:			
Depression	2 (1%)	0	2 (1%)
Endocrine:			
Amen./menst.dysfn.[b]	9 (9/38= 24%)	1	10 (10/43=23%

b= based on number of females of menstruating age (≥ 12 yrs.)

Gastrointestinal:			
decreased appetite	7 (4%)	2	9 (4%)
vomiting	1 (1%)	3	4 (2%)
abdominal pain	1 (1%)	2	3 (1%)
gastritis	1 (1%)	2	3 (1%)
nausea	1 (1%)	1	2 (1%)
peptic ulcer dis.	1 (1%)	0	1 (< 1%)
pancreatitis	1 (1%)	0	1 (< 1%)
constipation	0	1	1 (< 1%)
rectal bleeding	0	1	1 (< 1%)
Hematologic:			
aplastic anemia	1 (1%)	0	1 (< 1%)

leukopenia	3 (3/91= 3%)	0	3 (3/115= 3%)
neutropenia	0	1	1 (< 1%)
ecchymoses	1 (1%)	0	1 (< 1%)
Cardiovascular:			
Arrhythmia	0	1	1 (< 1%)
Renal:			
Renal tubular acidosis	2 (1%)	0	2 (1%)
Skin:			
Rash	2 (1%)	0	2 (1%)
Miscellaneous:			
Body odor	0	7	7 (3%)
bad taste/taste aversion	4 (3%)	2	6 (3%)
weight gain	3 (2%)	1	4 (2%)
edema	0	1	1 (< 1%)

Pursuant to my telephone conversation with Dr. Wiech on 4/10/96, I received on 4/11 (amendment 96013) narratives for the patients listed in the sponsor's cover letter. These narratives add no additional information to the AEs reported for the patients listed.

d. Laboratory Adverse Events:

Regarding serum chemistry and hematology values, the following means were abnormal in the update:

1. SGOT: mean 57 IU/L in rescue and prospectively treated patients
2. Hemoglobin: means of 11.8 g/dl and 11.4 g/dl in rescue and prospectively treated patients < 18 yrs. of age and OTCL males < 18 yrs. of age, respectively.
3. Chloride: mean 106 mmol/L in OTCL males < 18 yrs. of age.

I developed the following guideline to determine "clinically significant chemistry and hematology abnormalities":

Serum sodium: < 132 meq/L or ≥ 150 meq/L
Serum K^+: < 3.2 meq/L or > 6.1 meq/L
Serum chloride: > 110 meq/L
Serum CO_2: ≤ 18 meq/L or > 30 meq/L
Serum glucose: < 45 mg/dl, fasting: >120mg/dl
Serum uric acid: ≥ 9 mg/dl
Serum calcium: ≥ 11.5 mg/dl
Serum phosphorous: < 3.0 mg/dl if < 18 yrs.
< 2.5 mg/dl if > 18 yrs.
> 7.0 mg/dl, any age
Serum total protein: ≤ 4.3 g/dl if < 1 yr.
≤ 5.6 g/dl if > 1 yr.
Serum albumin: ≤ 3.3 g/dl if < 1 yr.

< 3.5 g/dl if > 1 yr.
Serum cholesterol: ≥ 300 mg/dl
Serum total bilirubin: ≥ 2 mg/dl
Serum alkaline phosphatase: ≥ 3x ULN
Serum SGOT and SGPT: ≥ 3x ULN
Hgb (g/dl)/Hct(%): infant - ≤ 9/≤ 27
child (1-12 yrs.)- ≤ 9.5/< 30
12-18 yrs.- ≤ 9.5/≤ 32
adult male- ≤ 11.5/≤ 37
adult female- ≤ 9.5/≤ 32
WBC: > 15,000 or < 4,000 cells/mm^3
Platelets: < 100,000 or ≥ 600,000 cells/mm^3

Note: I changed the guideline for the following labs because I regarded the cut-off I used in my NDA review as too low: a). serum sodium: "clinically significant increase" changed from ≥ 148 meq/L to ≥ 150 meq/L b). "clinically significant acidosis" changed from ≤ 16 meq/L to ≤ 18 meq/L c). "clinically significant increased wbc" changed from > 11,000 to > 15,000 cells/mm^3.

Based on the above guideline, the frequency of "clinically significant" laboratory adverse events (note: inc.= increased, dec.= decreased) were as follows (note: patient # 295 was excluded as his record could not be found during FDA's audit):

Laboratory Parameter	# (%)pts. in NDA		# (%)pts. in Update	total # (%)pts. in NDA + Update	
Inc. Sodium	1/119=	1%	0	1/156=	1%
Dec. potassium	0		1	1/156=	1%
Inc. chloride	7/116=	6%	4	11/155=	7%
Acidosis	14/104=	13%	5	19/140=	14%
Alkalosis	5/104=	5%	5	10/140=	7%
Inc. uric acid	3/105=	3%	0	3/139=	2%
Dec. phosphorous	7/107=	7%	2	9/142=	6%
Inc. phosphorous	2/107=	2%	1	3/142=	2%
Dec. tot. protein	3/112=	3%	1	4/147=	3%
Dec. albumin	9/114=	8%	7	16/149=	11%
Inc tot. bili.	2/110=	2%	0	2/147=	1%
Inc. alk. phos.	6/113=	5%	2	8/144=	6%
Inc. SGOT	3/113=	3%	3	6/153=	4%
Inc. SGPT	4/100=	4%	1	5/136=	4%
Dec. Hgb/Hct.	8/104=	8%	5	13/148=	9%
Dec. total WBC	3/90=	3%	2	5/114=	4%
Inc. total WBC	2/90=	2%	2	4/114=	4%
Dec. platelet ct.	1/96=	1%	3	4/138=	3%
Inc. platelet ct.	2/96=	2%	0	2/138=	1%

Urinalyses:

Per the 4/9/96 update, the following abnormalities were reported for the urinalyses that were done since the NDA was submitted:

Dipstick abnormalities:

a. Protein (trace or higher) was reported in 25/78 patients= 32%. In 16 pts., protein was trace.

b. Glucose (trace or higher) was reported in 10/92 pts.= 11%.

c. Ketones (trace or higher) was reported in 14/90 pts.= 16% (ketones were trace in 8 pts.).

d. Blood was reported in 14/91 pts.= 15%.

e. Bilirubin was reported in 1/85 pts = 1%.

f. Urobilinogen was reported in 8/57 pts.= 14%.

pH abnormalities:

6/90 pts.= 7% had urine pH's > 8.5

+ Leukocyte esterase:

8/60 pts.= 13% with + leukocyte esterase

Microscopy abnormalities:

a. WBCs: 11/60 pts.= 18% had > 5 wbcs/HPF

b. RBCs: 15/56 pts.= 27% had > 2 rbcs/HPF

c. Casts: were present in 4/37 pts.= 11%.

d. Crystals (excluding amorphous crystals): were present in 7/40 pts.= 18%. These included triple phosphate and calcium oxalate crystals and urates.

Comment regarding abnormalities in UA with micro:

The clinical significance of the above abnormalities cannot be determined as pertinent medical history, physical exam findings and relevant ancillary laboratory test (e.g. urine culture) results were not provided.

e. Plasma Amino Acids:

The following means were abnormal for the essential amino acids:

Mean plasma citrulline was markedly increased in AS def. patients: mean 2828 umol/L (normal: 10-34 umol/L). It was also increased to a lesser degree in these other groups: OTCL males > 18 yrs. old with a mean of 81 umol/L; rescue/prospective (R/P) OTC and CPS def. pts. with a mean of 38 umol/L; OTCL males < 18 yr. old with a mean of 40 umol/L and OTCF > 18 yrs. old with a mean of 39 umol/L.

Mean plasma arginine was increased in rescue/prospectively treated patients with a mean of 171 umol/L (normal: 15-115 umol/L).

Mean plasma levels of the following non-essential amino acids were abnormal:

a. cysteine was the only amino acid whose mean plasma level was below normal (normal: 44-96 umol/L). This was the case for rescue/prospective pts. (mean: 38 umol/L), OTCL males < 18 yrs. (mean: 31 umol/L), OTCF < 18 yrs. (mean: 39 umol/L) and OTCF > 18 yrs. (mean: 37 umol/L).

b. mean plasma levels for the following non-essential amino acids were increased:

-taurine (normal: 10-86 umol/L): R/P with a mean of 88 and OTCL males < 18 yrs. with a mean of 120 umol/L.

-glutamic acid (normal: 1 85 umol/L): R/P with a mean of 101 and OTCL males (mean for pts.< 18 yrs.: 89 and > 18yrs.: 86 umol/L)

-glutamine (normal: 337-673 umol/L): elevated in all gps.: R/P mean of 680, OTCL males means of 676 (< 18yrs. old) and 863 (> 18 yrs. old), OTCF means 1059 (< 18 yrs. old) and 989 (> 18 yrs. old) umol/L.

-alanine (normal: 136-440 umol/L): elevated in all groups: R/P with a mean of 550, OTCL males means of 657 (< 18 yrs. old) and 665 (> 18 yrs. old), OTCF means 829 (< 18 yrs. old) and 784 umol/L (> 18 yrs. old).

-glycine (normal: 87-323 umol/L): elevated in OTCL males < 18 yrs. mean 398, OTCF < 18 yrs.: mean 424 and OTCF > 18 yrs. mean 366 umol/L.

Per Dr. Brusilow, plasma glutamine should be maintained at levels below 1,000 umol/L to promote growth and development. The # and % of patients with glutamine levels above this cut-off follows for each category:

Rescue/Prospective: 20/75= 27%
CPSL: 3/4= 75%
OTCL males: 9/21= 43%
OTCF: 49/61= 80%

Overall, 81/161 patients or 50% had plasma glutamine levels ≥ 1,000 umol/L.

f. Frequency of Hyperammonemic episodes:

The frequency of hyperammonemic episodes was updated in the 4/8/96 submission:

Of the 173 patients for which case report forms have been received, 51 patients (29%) have had no hyperammonemic episodes while receiving sodium phenylbutyrate. The breakdown by diagnostic category follows: rescue- 11 pts., prospectively treated- 4 pts., late-onset (excluding OTCF hets)- 11 pts. and OTCF hets- 25 pts.

The annualized rate of HA episodes follows for each diagnostic category along with the mean duration of phenylbutyrate treatment:

Diagnostic category	Mean # HA ep/yr.	Mean duration PB rx.
Rescue	1.25	2.93 yrs.
Prospective	1.73	2.89
Late-onset	0.37	2.79
OTCF hets	0.05	3.59

Without a baseline, no statement can be made regarding the impact of phenylbutyrate on the frequency of hyperammonemia. Also, it is important to document compliance with the therapy so an effect ascribed to the drug is valid.

g. Cognitive Update:

Updated IQ data was submitted on 4/15/96. The sponsor states that the majority of parents refused IQ testing in their

children). The additional cases were IQ was formally tested will be presented here:

Rescue:

CPSR- # 638: avg. (average, IQ 92) to SR (severely retarded, functioning at 9 mo. level at age 3 yrs. 8 mos.)

146: avg. (IQ 92) to LA (low average, IQ 80)

ASR- # 105: no change in IQ of 56= MR (mentally retarded)

510: SR

650: avg. (cognitive skills "age appropriate") to SR (IQ 40).

610: remains in LA category

OTCR- # 439 SR, # 549 MR and #352 MR

Prospective:

no new information in update

Late-onset CPS and OTC males:

CPSL # 594: low average

OTCL: # 607: LA, # 485 avg. and # 723 MR

OTCF hets:

498: remains MR

207: SR

551: MR (IQ 69) to LA (IQ 74)

636: remains avg.

<u>Summary of cognitive data: NDA + Update:</u>

Rescue:

CPSR: IQ n= 7 pts. (0 avg., 3 LA, 1 MR & 3 SR)

Therefore, by IQ testing, 3/7 CPSR pts or 43% tested in the LA range and 4/7 CPSR pts. or 57% tested in the retarded range.

IQ + narrative: n= 9 pts. (2 avg., 3 LA, 1 MR & 3 SR). "Narrative" is a description of a patient's cognitive abilities when formal IQ testing was not done. These narratives were provided by the sponsor only for patients who received no antecedent therapy. Hence, they received only sodium phenylbutyrate therapy. Therefore, the narratives were provided for only a fraction of the patients enrolled. Combining both IQ and narrative, 5/9 CPSR pts. or 56% tested in the avg. to LA range and 4/9 CPSR pts. or 44% tested in the retarded range.

ASR: IQ n= 17 pts. (0 avg., 2 LA, 3 MR and 12 SR). Therefore, by IQ testing in ASR pts., 2/17 or 12% tested in the LA range and 15/17 or 88% in the retarded range. IQ + narrative for ASR: same as IQ because no narratives provided for ASR pts.

OTCR: IQ n= 14, all of whom tested in the MR (n= 3) or SR ranges (n= 11). IQ + narrative: 2 avg, 3 MR and 11 SR: 2/16 or 12% pts. tested avg. and 14/16 or 88% tested retarded.

Prospective:

CPSP: IQ n= 1 (LA); ASP: IQ n=1 (MR); OTCP: IQ n=2 (1 avg. and 1 MR). Narratives are provided for 2 additional pts.: # 570 (LA) and # 625 (avg.).

Late-onset CPS def. and OTC males:

CPSL: IQ n= 2 (both LA). No narratives provided.

OTCL males: IQ n= 10 (2 avg., 3 LA, 2 MR and 3 SR). Therefore, by IQ testing in OTCL males, 5/10 or 50% pts. tested in the avg. to LA range and 50% in the retarded range. IQ + narrative for OTCL males: n= 17 pts. 11/17 or 65% tested in the avg. to LA range and 6/17 or 35% tested in the retarded range.

OTCF hets:

34 OTCF hets were IQ tested. Of these, 9/34 or 26% tested avg., 14/34 or 41% tested LA, 5/34 or 15% tested MR and 6/34 or 18% tested SR.

IQ + narrative was available for 41 patients. Of these, 14/41 or 34% tested avg., 15/41 or 37% tested LA, 6/41 or 15% tested MR and 6/41 or 15% tested SR.

Repeat cognitive testing on phenylbutyrate therapy was performed in 24 patients (NDA + update). Note: I excluded patient # 295 as his record could not be found during FDA's audit. I added pt. # 638. Of these 24 patients, 7 initially tested as SR. Since further cognitive deterioration could not occur in these patients, they were excluded from the analysis which calculated the number (%) of patients in which cognitive deterioration occurred (≥ 10 point decrease in IQ score between test 1 and test 2):

Rescue:

CPSR: of 3 pts. with repeat testing, IQ significantly decreased in all.

ASR: 1/3 pts., IQ significantly decreased

OTCR: no significant IQ deterioration occurred in the 1 pt. who underwent repeat testing.

Therefore, among rescue pts., a significant deterioration in IQ occurred in 4/7 pts. or 57% during phenylbutyrate therapy.

Prospective:

no repeat testing done during PB therapy.

Late-onset CPS def. and OTCL males:

CPSL: no significant IQ deterioration in the 1 pt. who underwent repeat testing.

OTCL males: no patient who was not SR underwent repeat testing.

OTCF hets:

of 9 patients, 5 or 56% demonstrated a significant deterioration in IQ on repeat testing.

h. Plasma Ammonia levels Submitted 4/19/96:

Plasma ammonia levels were submitted since the NDA was submitted through 2/21/96. Data was presented for 85 patients in whom their were 281 ammonia measurements. 45 pts. (53%) has at least 1 measurement that exceeded the upper limit of the normal (ULN) range for the laboratory in which the ammonia level was

measured.

All the ammonia levels were divided by the ULN for that laboratory and multipled by 100% yielding a percent of the upper limit of the normal range.

Enzyme deficiency		# (%) pts. with mean ammonia level within the normal range
Rescue:	CPS	4/7 (57%)
	AS	7/16 (44%)
	OTC	4/5 (80%)
Prosp.	CPS	0/2 (0%)
	AS	1/2 (50%)
	OTC	0/1 (0%)
Late-onset:	CPS	2/3 (67%)
	OTC males	8/9 (89%)
OTCF hets		23/40 (58%)

Enzyme deficiency		# (%) of pts. who had at least 1 high ammonia level
Rescue:	CPS	3/7 (43%)
	AS	11/16 (69%)
	OTC	3/5 (60%)
Prosp:	CPS	2/2 (100%)
	AS	1/2 (50%)
	OTC	1/1 (100%)
Late-onset:	CPS	1/3 (33%)
	OTC males	2/9 (22%)
OTCF hets		24/40 (60%)

Comment: late-onset CPS and OTC males was the group with the highest percentage of patients with normal mean ammonia levels and also, the group that had the lowest percentage of patients with at least one high ammonia level. Incidentally, this was also the group that had the lowest frequency of hyperammonemia episodes. However, unless baseline ammonia levels are available for comparison, and compliance with the therapy is documented, a definitive statement cannot be made regarding the effect of therapy on ammonia levels.

4. Resolution of discrepancies in causality assessment of adverse events in several patients to Ammonapse therapy:

On 4/10/96, I called Dr. Wiech and pointed out to him that there are discrepancies between the NDA and the update in causality assessment of adverse events in several patients to Ammonapse therapy. These applied to the same adverse event in the same patient for the same day and I provided him with the specific patient numbers involved. On 4/25, I received a fax resolving these discrepancies. In all cases, the initial assigment (i.e. the NDA assignment) was the correct one.

5. Revised Physician Labeling Submitted 4/8/96:

Please include my comments on the 3/4 label with the

following comments for the 4/8 label for both the tablets and powder:

I. Ammonapse tablets:

1. INDICATIONS AND USAGE section:

a. Revise the first sentence to read: "Ammonapse is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or arginosuccinic acid synthetase. It is indicated in all neonatal-onset disease patients (complete enzymatic deficiency, presenting within the first 28 days of life) and also, in patients with late-onset disease (partial enzymatic deficiency, presenting after the first month of life) who have a history of hyperammonemic encephalopathy (the database in late-onset disease consisted of patients with a history of hyperammonemic encephalopathy)."

b. Revise the third sentence to read: "However, these infants have a high incidence of mental retardation (the incidence of mental retadation by formal IQ testing is, by enzyme deficiency, ornithine transcarbamylase deficiency: 100%, arginosuccinic acid synthetase deficiency: 88% and carbamylphosphate synthetase deficiency: 57%).

c. Revise the sixth sentence to read: "As with the neonatal-onset group, deaths from acute hyperammonemic encephalopathy may occur in patients with late-onset disease, again emphasizing the importance of early diagnosis and treatment. Published reports indicate that chronic therapy with Ammonapse may decrease elevated ammonia and glutamine levels and decrease both net urea nitrogen synthesis and urinary urea nitrogen excretion. However, conclusions regarding additional

effects of Ammonapse therapy in the group of symptomatic late-onset patients were limited by inadequate baseline and/or follow-up data and failure to accurately document compliance with the therapy."

d. After sentence 7, place the sentence that was previously here and reads: "On therapy, the majority of patients continue to experience recurrent episodes of acute hyperammonemia."

2. NUTRITIONAL MANAGEMENT SECTION:

Dr. Wiech indicated In a telephone conversation with Dr. Temeck on Monday, 4/22, that he would include a statement in the label regarding the effect of phenylbutyrate therapy on growth in urea cycle disorder patients.

3. PRECAUTIONS section:

a. Add Dr. Jordan's comments as of his 4/23 review.

b. Laboratory tests subsection:

After the sentence in this subsection, add: "Serum drug levels of phenylbutyrate and its metabolites, phenylacetate and phenylacetylglutamine, should be periodically monitored."

4. ADVERSE REACTIONS section:

a. Omit the <u>Clinical Adverse Events</u> heading and sentence one. Begin this section with sentence 2 and after "Adverse events...", insert, in parentheses: (both clinical and laboratory) and insert the phrase: "...in these patients..." after the word "systematically" in the second sentence. Revise the third sentence to read: "Causality of the drug's side effects is sometimes difficult to determine in this patient population because adverse events may result from either the underlying disease, the patient's restricted diet, intercurrent illness or from Ammonapse." Omit the phrase: "...and the reports were for occurrences from recollection" from the fourth sentence.

b. Follow the fourth sentence with a subsection entitled: <u>Clinical Adverse Events</u>.

-<u>Probably Causally Related</u>:

*omit the fifth sentence which is a laboratory, not clinical, adverse event.

*in the sixth sentence, the word "amenorrhea" has been misspelled and replace 21% with 23%. **Note: The sponsor has no data in either animals or humans which studied the effects of phenylbutyrate on ovarian function. The sponsor's basis for this causality is based on the drug's inhibition of cancer and erythroid cell proliferation and their (Dr. Wiech's and Dr. Brusilow's) concern regarding the high frequency of this adverse event in the population of menstruating females with urea cycle disorders. I would appreciate input from Dr. Troendle regarding the relationship of phenylbutyrate to this particular adverse event- should it be probably causally related or possibly**

causally related?

*the ninth sentence should follow the word "Miscellaneous" and replace 5% in this sentence with 4%.

*preceed "Patients reported bad taste... with: "3% of patients" and replace "and" after "bad taste" with "or".

*end sentence eight with: "...in 3% of patients."

*clarify if sentence ten is included under the heading Probably Causally Related or is to be placed under a separate heading. In sentence ten, replace 3% with 2% and, after the word "incidence", add: (1-4 patients).
Gastrointestinal: after the word "vomiting" add: "constipation, rectal bleeding (1 patient), peptic ulcer disease (1 patient) and pancreatitis (1 patient).
Hematologic: aplastic anemia (1 patient), ecchymoses (1 patient).
After Hematologic, add: Cardiovascular: arrhythmia (1 patient), edema (1 patient).
Renal: preceed "tubular acidosis" with: "renal tubular acidosis".

-Not Related:

*clarify why the paragraph labeled "12" was included here.

*as written, sentences 13 through 15 are inappropriately included under the heading Not Related. Please place appropriately in the label. In addition, "nausea/vomiting/indigestion/cramping (36%)" in sentence 14, should follow "...headache (64%)..." in sentence 13. In sentence 15, delete "with beta-thalassemia" and add: "for an investigational use," after "...17.5 mos., ".

-After sentence 15, add: "Neurological toxicities attributed to phenylacetate therapy (150-450 mg/kg/day, intravenously, for 6-28 days) were repoted in patients receiving the drug for an investigational use. The neurotoxicities were classified as neurocortical (predominately somnolence, disorientation and confusion), neurovisual (blurred vision, diplopia, scotoma, photosensitivity and photophobia), neurocerebellar (ataxia and unsteadiness), dizziness and lethargy. The mean highest fitted plasma phenylacetate concentration (using a one-compartment nonlinear model) for each of the neurocortical and neurovisual toxicities and for dizziness, regardless of severity, were in the 320 to 420 ug/ml range and for neurocerebellar toxicity and lethargy were in the 900-1000 ug/ml range. The mean phenylacetate dose at which these toxicities occurred was approximately 250 mg/kg/day except for the patient who developed profound lethargy in whom the dose administered was ~ 710 ug/kg/day. The majority of these toxicities were mild to moderate in severity, and, were acute and reversible when the phenylacetate infusion was discontinued. In the minority of patients who developed neurotoxicities of a severe degree (e.g. severe somnolence or confusion), the mean fitted phenylacetate concentration was 486 ug/ml and the mean

dose, 215 ug/kg/day. All of these patients recovered, the majority without therapeutic intervention. Adverse events of a non-neurological nature which were more commonly reported in these studies and reported as possibly or probably attributable to phenylacetate were: nausea, fatigue, headache, vomiting, edema, neurosensory toxicity- paresthesias/numbness/ neuropathy, anemia, weight gain and taste change. It should be noted that these results are preliminary and incomplete. It should also be noted that ~ 40% of these patients had a central nervous system condition, but the acute onset and rapid reversibility of the neurotoxicities when the phenylacetate infusion was discontinued, suggests a drug effect. Neurological toxicites have not yet been observed for phenylbutyrate for this same investigational use but this is in an early stage of clinical development."

c. Laboratory Adverse Events:

*Justify your conclusion that leukopenia is probably related to Ammonapse therapy.

*Revise sentence 16 to read:

"In patients with urea cycle disorders, the frequency of laboratory adverse events were:

> 10%: acidosis (14%) and hypoalbuminemia (11%)

5-10%: anemia (9%), alkalosis (7%), hyperchloremia (7%), hypophosphatemia (6%) and increased alkaline phosphatase (6%)

< 5%: increased liver transaminases, leukopenia and leukocytosis were each 4%; decreased total protein and thrombocytopenia were each 3%; hyperurecemia and hyperphosphatemia were each 2%; hypernatremia, hyperkalemia, hyperbilirubinemia and thrombocytosis were each 1%."

* Omit sentence 17

* Revise sentence 18 to read: "The clinician is advised to routinely perform hematological, urinalysis and blood chemistry profiles and periodically monitor plasma ammonia and glutamine levels (note that glutamine may be a harbinger of hyperammonemia) and plasma levels of Ammonapse and its metabolites. The patient's nutritional status should also be periodically assessed (see NUTRITIONAL MANAGEMENT section)."

* Sentence 19 should be placed in the Clinical Adverse Events section and revised as not all deaths were due to hyperammonemic encephalopathy.

5. DOSAGE AND ADMINISTRATION section:

Justify your wording in sentence 3: "...preferably with a meal or feeding...", when, in the labeling submitted 1/6/96, the recommendation (which we found acceptable as per our 2/16/96 letter) was that the drug be taken with each meal or feeding, which was based on waste nitrogen excretion occurring after a meal.

II. Ammonapse Powder:

The comments above for the tablets also pertain to the powder.

Evaluation and Regulatory Action:

I recommend **approval** of Ammonapse tablets and powder as an adjunctive therapy to treat patients with urea cycle disorders, both in all neonatal-onset disease patients and in late-onset patients with a history of hyperammonemic encephalopathy.

The following should be conveyed to the sponsor:

1. The above labeling comments for both the tablets and powder, for both the 3/4/96 and 4/8/96 submissions should be conveyed to the sponsor (Note: input required from Dr. Troendle regarding decision to include sentence about the potential interaction between antibiotics and phenylacetylglutamine in the Precautions section and the relationship of amenorrhea/menstrual dysfunction to Ammonapse therapy).

2. The above comments pertaining to the Patient Package Insert should be conveyed to the sponsor.

3. If my guideline (page 7-8 of this review) for the determination of the frequency of hematologic and chemistry adverse events is acceptable to Dr. Sobel and Dr. Troendle, it should be conveyed to the sponsor for his use in future safety updates. Also, Ucyclyd should be informed that the normal range for serum alkaline phosphatase is age dependent and that the normal range listed in the summary chemistry data tables (amendments 95-006, 96-006 and 96-010) for serum total protein and albumin, apply to patients 0-4 months, not 0-4 yrs.

4. I recommend the following be conveyed to the sponsor as phase 4 commitments:

a. Conduct of a formal pharmacokinetic study in patients with urea cycle disorders, both children and adults, on chronic Ammonapse therapy, both tablets and powder.

b. Submission of narratives pertaining to cognitive function in patients who received antecedent therapy (with sodium benzoate and/or phenylacetate) and a narrative update in all patients.

c. In the NDA, the efficacy assessment of Ammonapse therapy in the late-onset patients was severely limited by lack of an adequate baseline and failure to adequately document compliance with the prescribed therapeutic regimen. Additional efficacy data should be collected in late-onset patients who have a history of hyperammonemic encephalopathy using each patient as his/her own control. Focus should be on collection of cognitive data, frequency of hyperammonemic events and metabolic control (plasma ammonia and glutamine levels) pre and post Ammonapse and low protein diet therapy. Compliance with Ammonapse therapy should be strictly monitored.

d. In a telephone conversation between Dr. Temeck and Dr. Wiech on Friday, 3/15/96, Dr. Wiech stated that he would be working with a nutritionist at Tuft's regarding which foods and beverages are not compatible with Ammonapse powder due to their acidicity.

Jean Temeck MD

Gloria Troendle
4-29-96

NDAs: 20,572 and 20,573 Date submitted: 4/15/96
Drugs: Ammonapse tablets and powder Date reviewed: 4/25/96
Sponsor: Ucyclyd Pharma, Inc.

Neurotoxicity of Phenylacetate

On Monday, April 8, I spoke with Dr. Robert Delap, Division of Oncolgy Drug Products (594-5784), regarding an article in Cancer Research which I obtained from Dr. D. Lee Ham, parmacologist in that Division. The article is entitled: "A Phase 1 and Pharmacokinetic Study of Intravenous Phenylacetate in Patients With Cancer" (Cancer Research 54: 1690-94, 1994). This study is being conducted at NCI. In that article, 3/17 patients with solid tumors developed CNS toxicity manifested by lethargy, confusion and emesis. All had plasma drug levels > 900 ug/ml. The phenylacetate (PA) dose levels at which these toxicities occurred were identified at dose levels 3 and 4 (mean ± SD: 266±40 and 374±95 mg/kg/day) which were being given by continuous IV infusion. Dr. Delap checked his database of adverse events with IV PA and found 1 case of "transient loss of consciousness" and 1 case of "passed out" but both had brain tumors. He also found 1 case of decreased hemoglobin. He said there was also an ongoing phase 1 trial of IV phenylbutyrate (PB) in cancer patients. He referred me to Dr. Mario Sznol in the Investigational Drug Branch at NCI (phone #: 496-8798) for further information.

I spoke with Dr. Sznol on Tuesday, April 9. I apologized for not being able to reveal why I needed to obtain information on the neurotoxicity of IV PA and PB. Dr. Sznol told me there is a greater incidence of somnolence in children receiving IV PA but interpretation of the data is confounded by the fact that they have brain tumors. Tinnitus has also been reported. He stated that there is no permanent neurotoxicity from the drug due to its short half-life. Dr. Sznol stated they are aiming to maintain a drug serum PA level in the 150-250 ug/ml range. He said there is an ongoing phase 2 trial with IV PA in patients with gliomas at UCSF (Dr. Prados) in 35 patients. He stated that neurotoxicity no longer occurred when dosing was titrated based on lean body mass. Dr. Sznol said there are 2 ongoing IV PB protocols in tumor patients (prostate, renal cell and melanoma). One protocol involves a bolus infusion of 240 mg/kg bid x 5 days. The other is a continuous IV infusion for either 5 or 7 days with the highest dose being 410 mg/kg/day. One patient at Johns Hopkins (at Hopkins, 19 patients are enrolled on the 5 day continuous IV infusion protocol) became somnolent on IV PB. Another patient, on 345 mg/kg developed a grade 3 neurotoxicity, not specified. 3 patients on 410 mg/kg/day, experienced no neurotoxicity. Dr. Sznol stated that the PK data on IV PB has not yet been analyzed, but he thinks that you probably saturate at a lower limit than for PA. He gave me names of additional people I might contact who may be able to provide me with more information: Dr. William Doug Figg, pharmacologist

at the Clinical Pharmacology Branch at NCI (phone #: 402-3622) who, Dr. Sznol said, is the most familiar with the IV PA database; Dr. Thibault at the University of Virginia

I spoke with Dr. Figg, Thursday, April 11. He stated that ~ 100 cancer patients have been studied with IV PA. From his recollection, he believes that neurotoxicity occurred at serum PA drug levels $\geq$ 550 ug/ml and that serum PA levels should be maintained below 500 ug/ml to prevent neurotoxicity. I inquired if neurotoxicity might have occurred below 500 or 550 ug/ml serum PA drug levels. He said he didn't know because he has not looked at the data for some time. I told him it was important that I find out the lowest serum PA level at which neurotoxicity occurred and apologized for not being able to divulge the reason. He said he didn't know if that type of information was available because generally, if a patient complained of neurotoxicity, the drug infusion was stopped and a blood PA level was obtained 15-20 minutes later. Therefore, the peak drug level was probably not captured. I responded that despite the limitations of the data, it is very important that I obtain this information. He asked that I send this request to him in writing (Dr. Figg's fax: 402-8606). He also referred me to a paper he co-authored on the subject in Cancer 75(12): 2932-2938, 1995, Thibault et al. I will summarize the main points of this article here:

1. 18 patients with either prostate (n= 9), CNS (n= 7), renal cell (n= 1) or sarcoma (n= 1) were enrolled. PA was delivered at two dose levels: 125 and 150 mg/kg/dose, bid, IV over 1 hr. for 14 consecutive days. Cycles of therapy were repeated every 4 weeks. Patients could escalate from one dose level to the next with sequential cycles, provided they had experienced no more than grade 1 drug-related toxicity. The maximum tolerated dose was defined at the dose at which 2 or more patients developed dose-limiting toxicity, defined as grade 3 (severe in degree) toxicity, or grade 2 (moderate in degree), if involving the CNS.

2. 12/18 patients received 14 cycles of therapy at the 125 mg/kg dose level. 4 of these patients escalated to the 150 mg/kg dose level for a second cycle. Of the latter, 2 received a third cycle at the higher dose level. Six additional patients were entered at the 150 mg/kg dose level, of whom one went on to a second cycle. In total, the 18 patients received 27 cycles of therapy.

3. Analysis of drug concentrations showed, at the 125 mg/kg dose level, peak serum concentration (mean $\pm$ SD) of 490 $\pm$ 78 ug/ml (n= 14 cycles) and, at the 150 mg/kg dose level, peak serum concentration of 623 $\pm$ 110 ug/ml (n= 13 cycles). Corresponding trough concentrations were, for the 125 mg/kg dose, 15 $\pm$ 18 ug/ml, and, for the 150 mg/kg dose, 62 $\pm$ 48 ug/ml. The time spent at serum concentrations above 250 ug/ml corresponded to 32 $\pm$ 10% of the total treatment time for the lower dose level and 48 $\pm$ 12% for the higher dose level. Drug accumulation

associated with neurologic toxicity occurred in 1 patient treated at the higher dose level. The last (and highest) phenylacetate concentration measured in this patient before interrupting therapy was 1155 ug/ml with a trough of 549 ug/ml.

4. At 125 mg/kg bid phenylacetate dose, 13 grade 1 (mild) adverse neurological events occurred (somnolence: 6, fatigue: 3, headache: 1, light-headedness: 2 and dysgeusia: 1). 1 patient experienced profound somnolence (grade 3), but was also on opiates. In addition, there were 3 events of pedal edema in 3 pts., 1 nausea, 1 vomiting and 1 rash (all of these were grade 1).

5. At 150 mg/kg bid phenylacetate dose, there were 13 grade 1 adverse neurological events (somnolence: 3, fatigue: 4, headache: 2, lightheadedness: 3 and impaired memory: 1). In addition, 4 pts. experienced grade 2 neurological toxicity (3 somnolence and 1 hypoacusis) and 2 pts., grade 3 neurological toxicity (1 disorientation and 1 exacerbation of a pre-existing neuropathy). Therefore, dose-limiting toxicity, consisting of reversible CNS depression (profound somnolence) was observed for 3 patients. The 3 patients who experienced grade 2 or 3 hypoacusis, disorientation or exacerbation of pre-existing neuropathy, achieved mean peak serum drug concentrations of 682 $\pm$ 290 ug/ml (range: 499-1016 ug/ml), with 1 of these experiencing drug accumulation. In addition, grade 1 CV toxicity occurred (3 pts. with pedal edema, 2 arrhythmias with a hx. of arrhythmia and 1 angina with a hx. of angina) as did grade 1 GI toxicity (1 nausea).

6. Note that all the drug-induced neurological toxicities were acute and reversible except for the exacerbation of pre-existing neuropathy which partially improved over the ensuing 3 mos. (in this latter patient, peak and trogh PA drug levels were 574 $\pm$ 52 ug/ml and 95 $\pm$ 59 ug/ml, respectively). The authors postulate that the neurological side effects might be due to a deficiency in acetylcholine induced by PA. The arrhythmias and angina only occurred in pts. with a hx. of CV impairment, were reversible, and attributed to fluid shifts induced by the high sodium content of the drug formulation. The 6 cases of pedal edema were controlled with short courses of diuretic therapy.

<u>In summary, the experience derived from use of phenylacetate administered intravenously to cancer patients</u> clearly demonstrates its potential neurotoxicity (see also my memo dated 4/24 for a more detailed review of the article published in Cancer Research 54: 1690-4, 1994). In cancer patients, neurotoxicity (somnolence, headache, lightheadedness and dysgeusia) occurred at phenyacetate levels of 490 ug/ml in the blood. This was achieved with phenylacetate 125 mg/kg/dose, IV over 1 hr., bid. This dose is quantitatively equal to 250 mg/kg/day continuous infusion of phenylacetate. At a higher drug phenylacetate blood level, > 600 ug/ml, impaired memory, profound somnolence, disorientation, hypoacusis and exacerbation of an underlying neuropathy, have been reported.

On Wednesday, 4/24, I received Dr. Figg's

response to our April 12, 1996 letter. 68 patients were enrolled (29 with brain tumors, 24 prostate cancer and 15 other types of tumors). Therefore, 43% of the patients had brain tumors. The range of serum phenylacetate levels in the cancer trials at which neurotoxicity was reported definitely overlap with the levels reported in both normal subjects and urea cycle disorder patients in the Ammonapse NDA. I summarized my review of this data in my 4/25/96 review of the drug labeling submitted on 4/8/96, ADVERSE REACTIONS section. I called Dr. Figg on Thursday, 4/25, and inquired how far along the phenylbutyrate trials are for cancer. He informed me that they are early. He also stated that the highest fitted drug concentration was based on a one-compartment nonlinear model and faxed to me the criteria for grading of toxicity used by NCI (grades 1-4).

Additional reports of neurotoxicity of phenylacetate in the human and in animals:

Dr. Brusilow has reported obtundation (in the absence of hyperammonemia), progressive encephalopathy, CV collapse and death when patients with urea cycle disorders receive an overdose of intravenous sodium benzoate and phenylacetate to treat acute hyperammonemia. The specific cases reported received a 5-10 fold overdose of this combination which is recommended to be given at 250 mg/kg/day of each drug over 24 hrs. as a maintenance infusion after the same dose is used as an initial IV bolus.

The neurotoxicity of phenylacetate was reported as far back as 1914 in the J of Biol Chem, vol. XVIII, pp 113-9. In this paper, the maximum human production of glutamine was determined by measuring the output of phenyacetylglutamine. An adult male was asked to ingest 2.5 g of phenylacetic acid on day 5 of the experiment, followed by 5 g on day 7, 7.5 g on day 10, 10 g on day 13 and 15 g on day 21. The subject reported thirst, dizziness and nausea the 5 g dose and, at 15 gms, it was noted that the subject displayed "...signs of poisoning, not unlike those following ingestion of large quantities of alcohol."

In IND # 1/3 adult subjects given a 540 mg/kg/day dose of oral sodium phenylbutyrate (which is the pro drug of PA) for 1 day, experienced abdominal pain, nausea, dizziness and loss of consciousness for a few seconds. It was unclear to the investigator if the LOC was due to the drug or was a vasovagal reaction.

The neurotoxicity of phenylacetate has been studied in rat pups being used as a model for PKU in the human. PA caused decreased proliferation and increased loss of neurons and a CNS myelin deficit. Phenylacetate retards maturation of cerebral synapses and reduces the number of functioning nerve terminals in the cerebrum as determined by a reduction in the velocity of high affinity synaptosomal uptake of choline and GABA. DNA content is decreased in the affected brain cells and its synthesis is impaired. The net effect is impaired brain growth in the animal model. Prenatal exposure of rat pups to

phenylacetate produces lesions in layer 5 cortical pyramidal cells; dendritic spines are larger and thinner than normal and reduced in number. Loo postulated (J Neurochem 45: 1596-1600, 1985), that in experimental PKU, phenylacetate and/or its metabolic products may exert its neurotoxic action by selectively reducing the availability of acetyl-CoA (due to formation of phenylacetyl-CoA) which plays a vital role in a number of metabolic reactions (metabolism of carbohydrates and fatty acids, in the biosynthesis of cholesterol and acetylcholine, etc.) that are critical to the development of the brain. In the articles I read, I could not find blood phenylacetate levels in the rats, but I have asked Dr. Jordan, supervisory pharmacologist, to completely review the animal data. In Stanbury's The Metabolic Basis of Inherited Disease, sixth edition, 1989, chapter 15, pp. 516, it is stated that the metabolites of phenylalanine (which includes phenylacetate) are not found in sufficiently high concentrations in the PKU patient to disturb metabolic and chemical relationships in the brain as described in the animal model. On Friday, 4/19, I spoke with Dr Seymour Kaufman, Chief, Laboratory of Neurochemistry at the National Institute of Mental Health (phone #: 496-3579), an author of this chapter on PKU in Stanbury, regarding plasma phenylacetate levels in untreated PKU. He will get bach with me on this next week. I also left a message asking for similar information with Dr. Charles Scriver, Dept. of Biology and Pediatrics at Mc Gill University in Montreal (phone #: 514-934-4418), who is also an author of this chapter on PKU. Dr. Kaufman called back, Monday, 4/22. Serum phenylacetate levels in untreated PKU range from 6.65-19.45 umol= 0.006-0.019 mM which is = 0.948-3.002 ug/ml (Biochemical Medicine 34: 203-6, 1985).

Correlation of blood phenylacetate levels in the cancer studies with those reported in the Ammonapse NDA:

I have asked Dr. Hae Young Ahn, biopharmacologist, to check the NDA for the highest phenylacetate level reported. She informed me it was 524.7 ug/ml after 3 days of sodium phenylbutyrate, 20 gms/day administered to a patient with portal hypertension secondary to cirrhosis. Note: 20 gms/day of sodium phenylbutyrate is the highest dose recommended in the NDA and is the recommended adult dose. Per Dr. Ahn's calculations based on trough levels (see her 4/15/96 review), the drug accumulation factor was estimated to be about 5. She said that this patient reached steady state on day 3, the last day of drug administration in this patient.

I am aware of 3 articles published by Dr. Brusilow in which plasma drug levels are reported in urea cycle disorder patients (Pediatric Research 29: 147-150, 1991; NEJM 310: 1630-1634, 1984 and Metabolism 42: 1336-1339, 1993). First article: on oral phenylbutyrate (PB) therapy, 306-650 mg/kg/day in 10 children, fasting am PB and phenylacetate (PA) drug levels were below the limits of detection (i.e. < 9.3 ug/ml for PB and < 4.7 ug/ml for PA) in all but 2 patients. One patient on PB 440 mg/kg/day had a plasma PB level of 225 ug/ml and a non detectable

PA level. Another patient on PB 600 mg/kg/day, had a PA level of 118.5 ug/ml and a non-detectable PB level. In the course of the day, plasma PB and PA levels in 3 of these children on PB (490-600 mg/kg/day) and 1 child on PA (500 mg/kg/day) ranged from 0 - 162.2 ug/ml for PB and 4.1 - 295.5 ug/ml PA. Dr. Brusilow concluded: "With few exceptions, neither phenylacetate nor phenylbutyrate accumulated in the plasma". Second article: a 38 yr. old male with OTC deficiency received PB 16.5 gms po for 3 days. Fasting am PB and PA were below the limits of detection (< 9.3 ug/ml and < 4.7 ug/ml, respectively). Intraday levels were < 204.6 ug/ml for PB and < 173.8 ug/ml for PA. Third article: Single dose PK data are graphically presented after IV priming infusions of PA and benzoate (each 250 mg/kg over 1-2 hrs.) to treat acute hyperammonemia in 2 patients. They appear to be in the 630-790 ug/ml range for PA.

Ucyclyd Pharma responded to this issue on 4/15 stating that the peak plasma levels of phenylacetate in normal subjects who received a single 5 gm. dose (Dr. Ahn called Dr. Wiech to confirm that the 10 gm. dose stated in his reply should have read 5 gms.) of sodium phenylbutyrate ranged from 50-65 ug/ml which is far below the drug levels at which neurotoxicity occurred in the cancer patients. This response is inadequate and I have reviewed this issue in detail above.

Evaluation and Regulatory Action:

In summary, phenylacetate is a neurotoxin in man and animals. In the NCI trials, the acute onset and rapid reversibility of the neurotoxicities when the phenylacetate infusion was discontinued, suggests a drug effect. However, it should be noted that ~ 40% of the patients enrolled in these trials had brain tumors. Also, these results are preliminary and incomplete. Today, 4/25, I requested Dr. Figg to send me plasma phenylacetate levels in the patients who did not develop neurotoxicity and to clarify the discrepancy between the total number of patients enrolled in the cancer trial which are less than the number of patients in which neurotoxicity was reported (this precluded my calculation of incidence of adverse events in these studies). Nevertheless, the blood phenylacetate levels at which neurotoxicity occurred in the NCI cancer trials definitely overlap with the levels reported in both normal subjects and urea cycle disorder patients in the Ammonapse NDA. A consult has been requested of Dr. Ahn, biopharmacologist, regarding the NCI studies, the PK data in the Ammonapse NDA and Dr. Wiech's 4/15 response to this issue. Cancer trials at NCI are also investigating phenylbutyrate (the pro drug of phenylacetate). Per Dr. Figg, neurotoxicity has not been observed to date with phenylbutyrate in cancer patients, but these studies are only in early development at NCI. Dr. Jordan informed me that he could not find reports of blood drug levels in the animals in whom CNS toxicity has been reported.

The neurotoxicities reported to date in humans with phenylacetate are not as serious as the potentially devastating

consequences of not treating urea cycle disorder patients who are prone to hyperammonemic encephalopathy.

The neurotoxicities reported in the cancer trials will be stated in the Adverse Reactions section of the label as well as the need to monitor plasma drug levels of both phenylbutyrate and phenylacetate in patients with urea cycle disorders on chronic phenylbutyrate therapy. Dr. Jordan has recommended that a statement be placed in the Precautions section of the Ammonapse label regarding the neurotoxicity of phenylacetate in rat pups (see his 4/23/96 review).

Dr. Wiech will be asked to conduct a phase 4

Jean Temeck, M.D.

cc. HFD-510: Dr. Sobel, Dr. Troendle, Dr. Jordan and Mr. Short
HFD-427: Dr. Ahn

Gloria Troendle 4-29-96

JAN 16 1996

NDAs: 20,572 and 20,573 Date submitted: 12/21/95
Drugs: Na Phenylbutyrate, tabs & powder Date received: 12/22/95
Sponsor: Ucyclyd Pharma Inc. Dates reviewed: 12/22/95 and 1/5/96

Please refer to my previous comments dated 12/22/95 which are to be conveyed to the sponsor and given on that day to Ms. Lana Pauls.

The sponsor has responded to points 1-5 of FDA's clinical deficiency letter dated 11/21/95.

Point 1: it is clear that the sponsor has included all patients (both evaluable and not evaluable) in the deaths, withdrawals, clinical and laboratory adverse event databases.

Point 2: the sponsor has adequately responded to this question.

The drug interaction in patient 159 was a mixed matabolic acidosis and respiratory alkalosis and hypokalemia secondary to the patient's underlying disease and to treatment with IV sodium benzoate and phenylacetate.

A possible drug-induced aplastic anemia could not be ruled out in patient 618. This adverse reaction occurred both during treatment with oral phenylbutyrate as well as with the IV combination of benzoate and phenylacetate.

Facial "spiders" and "angioma" were reported in patient 576 as "ecchymoses". Although platelet count, PT and LFTs were ordered, these results were not provided.

Patient 618 had a pancreatic pseudocyst before starting phenylbutyrate therapy. However, pancreatitis recurred while on phenylbutyrate.

Renal tubular acidosis (RTA) was congenital in patient 629. However, in patient 642 it initially occurred during arginine therapy. However, the patient had 2 subsequent episodes of RTA on phenylbutyrate therapy.

The rash in patient 485 was mentioned in one physical examination of this patient by his physician. No specific diagnosis was made. The rash in patient 613 was skin biopsy proven to be secondary to arginine deficiency.

Point 3: the sponsor provided the raw database for total leukocyte counts and urinalyses/microscopy. High and low leukocyte counts were noted. No analysis of this data was done by the sponsor. The following is my analysis of this data:

A. Total leukocyte counts:

I will regard "high" values as those > 11,000 cells/ul of the mean for age and "low" values as < 4,000 cells/ul. The results, by enzyme deficiency, and time of onset were:

"High" white blood cell counts:

AS deficiency:

rescue- 2/18 (11%)- pt. #'s 105 and 610 with respective wbc's of 21,000 and 20,500.

CPS deficiency: none

OTC deficiency:

late-onset males- 1/12 (8%)- pt. # 620 with wbc 13,800.

Therefore, of a total of 91 patients in which wbc were measured, 3 (3%) had "high" wbc's (all were > 11,000) during phenylbutyrate therapy.

"Low" white blood cell counts:
AS deficiency:
rescue- 1/18 (6%)- pt. # 410 with wbc of 3,200-3,800.
CPS deficiency: none
OTC deficiency:
late-onset males- 1/12 (8%)- pt. # 566 with wbc 3,700.
female heterozygotes- 1/36 (3%)- pt. # 633 with wbc 3,800.

Therefore, of a total of 91 patients in which wbc were measured, 3 (3%) had "low" wbc's i.e. < 4,000 during phenylbutyrate therapy.

B. Urinalyses/microscopy:

Dipstick abnormalities:

a. Protein n= 17/62 patients = 27%. 11 of these 17 patients had trace protein. (AS deficiency: n= 7/11= 64%, CPS def.: n= 1/7= 14%, OTC def.: n= 9/44= 20%).

b. Glucose n= 6/62 patients = 10%. 3 of these 6 patients had trace glucose (AS def.: n= 1/11= 9%, CPS def.: n= 0/7= 0%, OTC def.: n= 5/44= 11%).

c. Ketones n= 8/60 patients = 13%. 3 patients with trace, 1 small, 2 patients with 2+, 1 patient with 4+ and 1 patient with 0.5 mm. (AS def.: n= 2/11= 18%, CPS def.: n= 0/6= 0%, OTC def.: n= 6/43= 14%).

d. Blood n= 10/62 patients = 16%. 3 patients with trace, 1 small, 4 patients with 1+, 2 patients with moderate blood. (AS def.: n= 1/11= 9%, CPS def.: n= 1/7= 14%, OTC def.: n= 8/44= 18%).

e. Bilirubin n= 1/55 patients = 2% (OTC late onset male # 505).

Ph abnormalities:

8/61 patients = 13% had urine ph's > 8.5. (AS and CPS def.: 0%, OTC def. 8/44= 18%).

+ Leukocyte esterase:

6/32 patients = 19% with positive leukocyte esterase.

Microscopy abnormalities:

a. White blood cells > 5/HPF: 10/39 patients = 26% (AS and CPS def.: 0%, OTC def.: 10/30= 33%. Note: in only half of these patients, was bacteria noted and ranged from trace to many).

b. Red blood cells > 2/HPF: 6/39 patients = 15%. (AS def.: 1/8= 13%, CPS def.: 0/1= 0%, OTC def.:

5/30= 17%).

c. Casts (hyaline and/or granular) were present in 2/25 patients = 8%. (AS def.: 1/7= 14%, CPS def.: 1/1= 100%, OTC def.: 0%).

d. Crystals were detected in 4/27 patients = 15% (calcium oxalate crystals in 3 patients and triple phosphate crystals in 1 patient). (AS def.: 1/7= 14%, CPS def.: 1/1= 100%, OTC def.: 2/19= 11%).

Comment regarding abnormal urinalyses/microscopy results: the clinical relevance of the above abnormalities is difficult to determine because there was no corresponding control group for comparison, pertinent medical history/physical exam findings are not provided and pertinent ancillary laboratory tests (e.g. urine culture results in patients with high urine wbc's or menstrual history in female patients with "hematuria") are not provided.

Point 4: there still appears to be some confusion regarding the deterioration in cognitive function of the 9 yr. old female with untreated late-onset OTC deficiency whose case was submitted to FDA on August 10, 1995. The final paragraph of this narrative states that the patient was bright and interactive until age 9 (her present age), at which time she became withdrawn and inattentive with a present IQ of 70. However, since all her hyperammonemic (HA) episodes occurred before age 5, it appears that her intellectual deterioration occurred several years after these HA episodes. **The sponsor should clarify this.** The case (# 674) submitted by the sponsor to clarify this issue appears to involve a different patient: age and medical history differ from the aforementioned case and, no formal cognitive evaluation was done in patient # 674.

Point 5: The sponsor has adequately responded to this question.

Evaluation and Regulatory Action:

The following points should be conveyed to the sponsor:

1. Provide pertinent medical history/physical examination and/or results of ancillary laboratory tests to explain abnormal total leukocyte counts and urinalyses/microscopy results obtained during sodium phenylbutyrate therapy (e.g. infection to explain leukocytosis). If these abnormal results cannot be explained by concomitant or pre-existing conditions, they should be noted (indicating incidence) in the drug label, Adverse Reactions section.

2. The case submitted 12/21/95 (patient # 674) to clarify the one submitted on August 10, 1995, appears to involve a different patient (different age and medical history). Clarify if intellectual deterioration in the untreated 9 yr. old with late-onset OTC deficiency, occurred several years subsequent to her hyperammonemic episodes which the last paragraph of the 8/10/95 narrative suggests.

3. Ms. Paula- please refer to my 12/22/95 written

comments given to you at that time (copy attached) and include points 2 and 3.

Jean Temeck, M.D.

cc. Dr. Troendle and Ms. Pauls

NDAs: 20,572 and 20,573
Drug: Sodium Phenylbutyrate
Sponsor: Ucyclyd Pharma Inc.
Date: 12/22/95

Lana,

With regard to amendment 95-013 submitted 12/22/95, please include the following in our approvable letter to the Sponsor to be issued next week:

1. Provide explanations, if available, for the abnormalities noted in total leukocyte counts and urinalyses. For example, note if an infection was present to account for an elevated leukocyte count.

2. In a telephone conversation with Dr. Jean Temeck on 12/21/95, you stated that the labeling revisions in our 11/21/95 letter were acceptable. Please submit revised labeling.

3. As requested in our 11/21 letter, a package insert for patient/parent/guardian use needs to be submitted.

4. Further comments may be forthcoming regarding amendment 95-013 submitted on 12/22/95.

Jean Temeck 1/11/96
Jean Temeck, M.D.

cc. Dr. G. Troendle, Ms. L. Pauls and Ms. J. Weber

Gloria Troendle
1-16-96

NOV - 7 1995

NDAs: 20,572 and 20,573 Date submitted: 2/17/95
Drug: Sodium Phenylbutyrate Date received: 2/21/95
Tablets and Powder
Sponsor: Ucyclyd Pharma, Inc. Date reviewed: 10/23/95

Includes amendments: 95-003 (Sub 5/22), 95-004 (Sub 6/27), 95-006 (Sub 7/31), corrected Summary 95-30 (Sub 8/7), Submission dated 8/10 8/21, amend. 95-009 (Sub 8/24), amend's 95-010, 95-011, 95-012

Drug: Sodium Phenylbutyrate (abbreviated in this document as NaPB or PB).

Indication: Adjunctive therapy for the chronic management of patients with urea cycle enzymopathies

Proposed route of administration: oral

Note: both NDAs contain the same clinical database, therefore, only a single review will be done.

Non Clinical Pharmacology and Toxicology:

Phenylbutyrate is the pro-drug of phenylacetate. Phenylbutyrate is rapidly oxidized to phenylacetate by mammalian liver and kidney. In higher primates phenylacetate is rapidly conjugated with glutamine to form phenylacetylglutamine (PAG). PAG may serve as an alternate vehicle for waste nitrogen excretion. No toxicological studies have been performed with phenylbutyrate.

Phenylbutyrate and phenylacetate have been found to affect the cell growth pattern of certain cancer cell lines. Sodium phenylacetate inhibits cell proliferation of androgen independent prostate cell lines. In addition, it induces reversion of the prostatic cells to a nonmalignant phenotype, as evidenced by their reduced invasiveness and loss of tumorigenicity in athymic mice. Similar treatment with sodium phenylacetate did not significantly inhibit normal replication of human endothelial cells and skin fibroblasts. Phenylacetate treatment of promyelocytic leukemia HL-60 cells results in the rapid decline of myc ongogene expression, followed by cessation of growth and granulocyte differentiation. Similarly, the drug inhibits cell proliferation in human leukemic K562 cell line cultures. Phenylacetate also inhibits cell proliferation and neurite outgrowth and reduces N-myc protein levels in human neuroblastoma cells. The combination of phenylacetate with retinoic acid results in complete cessation of cell growth and loss of malignant properties of human neuroblastoma cells. It also inhibits the growth of human rhabdomyosarcoma cells.

Both phenylacetate and phenylbutyrate diminish DNA synthesis and arrest growth of cultured human glioblastoma cells as well as decrease cholesterol production in these cells. Both drugs also prevent carcinogenesis induced by 5-aza-2'-deoxycytidine in premalignant ras-transformed fibroblasts.

Either phenylacetate or phenylbutyrate will increase fetal hemoglobin production in erythroid precursor cells from normal donors and patients with sickle cell anemia or B-thalassemia and in human leukemic K562 cells.

Phenylacetate has also been shown to inhibit mevalonate incorporation into sterols in rat brain and rat liver homogenates.

Rats with gliosarcomas receiving phenylacetate (in

doses that can be achieved clinically in humans) survived longer than untreated animals and electron microscopy of treated tumors indicated cell differentiation in contrast to undifferentiated cells in untreated tumors.

Clinical Background and Rationale:

Urea cycle disorders (UCD) are characterized by the failure to synthesize and excrete waste nitrogen resulting in the accumulation of ammonia and glutamine in the plasma. Because UCD is rare: incidence of 1:10,000 live births, sodium phenylbutyrate (NaPB) has been given orphan drug designation. These NDAs pertain to deficiencies of the urea cycle enzymes arginosuccinate synthetase (AS), carbamylphosphate synthetase (CPS) and ornithine transcarbamylase (OTC). Patients with onset in the neonatal period have complete or near complete enzyme deficiency. They present with hyperammonemic encephalopathy at 24-36 hrs. of life. Upon resolution of the acute episode, treatment with a low protein diet and essential amino acids will extend life for several months. Patients with onset beyond the neonatal period are classified as "late-onset" patients. Clinically, they comprise a heterogenous group- from asymptomatic and detectable only with sophisticated nitrogen balance studies to symptomatic with recurrent episodes of hyperammonemic encephalopathy.

Chronology of therapy:

In 1980, a therapeutic approach was developed based upon the generation of compounds- hippuric acid and phenylacetylglutamine (PAG)- which would serve as alternates to urea for the elimination of waste nitrogen. Initial treatments based on this theory pertained to the use of sodium benzoate (NaB) and sodium phenylacetate (NaPA). In 1983, sodium phenylbutyrate (NaPB or PB) replaced phenylacetate due to its sensory (taste and smell) advantages. In 1987, sodium phenylbutyrate monotherapy replaced the combination therapy.

Rationale for dose of sodium phenylbutyrate:

Following oral administration, sodium phenylbutyrate is rapidly absorbed and metabolized to phenylacetate. Phenylacetate conjugates with glutamine forming phenylacetylglutamine (PAG) which is excreted by the kidney and serves as an alternate to urea for the elimination of waste nitrogen. One mole of phenylacetylglutamine contains two moles of nitrogen and is, therefore, comparable to urea. The recommended daily dose of NAPB was developed from an empiric calculation which estimated nitrogen intake (using a low protein intake), waste nitrogen production and urea formation and the molar replacement of PAG derived from a dose of NaPB. (It was empirically calculated that 1 mole of NaPB will be metabolized to 1 mole of PAG). The stoichiometry was confirmed by in vivo measurements of PAG excretion. Children aged 6-24 mos. on a low protein diet (1.25 gms/kg/day), generate approximately 0.1 gms/kg/day of urea nitrogen which represents ~47% of dietary nitrogen. One gram of NaPB activates the biosynthesis and excretion of 0.12-0.15 gms of PAG nitogen. The recommended dose

for neonates, infants and children weighing <20 kg is 0.45-0.60 g/kg/day and for patients weighing >20 kg, the dose is 9.9-13.0 g/M^2/day.

Review of the NDA database:

On Wednesday, March 15, an internal meeting was held to discuss filability of the above NDAs. At that meeting (see Dr. Spires' 3/15/95 memorandum of meeting minutes), it was agreed that the applications were filable for the neonatal rescue and prospectively treated groups. However, they were not filable for the late-onset or OTC female heterozygote groups due to failure to submit baseline (pre-drug) data regarding cognitive function, growth, frequency of hyperammonemic episodes, etc. When I spoke to Dr. Weich about this deficiency prior to this meeting, he said he did not know how much baseline data could be retrieved and in how many patients because it was not required on the CRFs. On 3/15, I telephoned Dr. Norbert Wiech of Ucyclyd Pharma, Inc. and informed him of this decision. He requested a meeting with FDA as soon as possible to discuss the deficiencies. This meeting was held on Monday, March 20 (see Dr. Spires' memorandum of meeting minutes). However, on 5/22/95, Dr. Wiech sent in an amendment which included data on late onset and OTC female heterozygotes. I telephoned Dr. Wiech on 6/26/95 (see 6/26/95 memo of that telephone conversation) and told him that because the Agency had not filed the late onset and OTC female het groups, a new NDA needed to be submitted. Although he acknowleged our phone conversation on 3/15 notifying him of this refusal to file, he stated he did not receive this in writing and did not know that this meant submission of a new NDA for these 2 patient groups. He said he would notify his attorney. I subsequently conferred with Drs. Sobel, Troendle and Spires and Ms. Galliers and it was agreed that due to the misunderstanding, the Agency would file for these 2 patient groups (see Memorandum of Teleconference dated 6/26/95).

The NDA database was drawn from 35 US sites and 63 co-investigators. Since 1985, 162 patients have been enrolled in the study. Of 162 patients enrolled, 148 were evaluable (14 patients lacked or had incomplete follow-up data). Evaluable patients were defined as patients with follow-up submitted either a) within the last 12 mos. of the study (6/1/93-6/1/94) or b) within the 6 mos. preceeding death or withdrawal. Of the 148 evaluable patients, 61 or 41% received only NaPB and 87 or 59% received other oral therapies prior to NaPB. Of the 148 evaluable patients, 118 are currently being treated.

The NDA database is divided into 4 diagnostic categories: neonatal rescue (UCD diagnosed within the first 28 days of life), prospective (UCD diagnosed during gestation and treated immediately upon birth), late-onset males (diagnosed after 28 days of life) and OTC females (a subgroup of late-onset which includes women with partial OTC deficiency, generally diagnosed later in life). The numbers in each category by enzyme

deficiency were:

Category (time of onset)	OTC	CPS	AS	Total
Neonatal rescue (R)	19	12	27	58
Prospectively treated (P)	4	2	4	10
Late onset males (L)	21	2	0	23
OTC female hets	55	0	0	55

*** : on 9/21/95, Gus Turner called me from the Division of Compliance to state that during an audit of Dr. Moscovich, the records could not be found for CPS patients, prospectively treated, # 565 (patient transplanted) and # 295 (patient died), and, therefore, they have been removed by me, as per his instructions, from the database. Hence, there are only 10 patients in this group, not 12.**

The sponsor states (amendment 95-03, pages 8 and 50) that in neonatal rescue patients, hyperammonemia and respiratory alkalosis occurred. In prospectively treated patients, a diagnosis of OTC or CPS was confirmed on the basis of plasma and urine substrate analysis and AS by elevated plasma citrulline levels. In late-onset patients, a hyperammonemic episode always occurred. In some patients, the urea cycle defect was confirmed by liver biopsy.

Demographics (initial February submission and amendment 95-03) for these 4 diagnostic categories are as follows (note: A= antecedent therapy, NA= no antecedent therapy):

Rescue	AS		CPS		OTC	
	A	NA	A	NA	A	NA
n	23	4	7	5	12	7
Gender	12F,11M	2F,2M	3F,4M	1F,4M	all M	all M
Mean age last visit (yrs.)	9.08	1.61	8.55	0.85	5.27	1.08
# pts. <2 yrs.	0	3(75%)	1	4(80%)	3	6(86%
# pts. >10-<18	9(39%)	0	4(57%)	0	2(17%)	0
# pts. ≥18yrs.	0	0	0	0	0	0
Age oldest	17.58	2.83	11.58	2.08	13.75	3.00
Mean duration of PB rx.(yrs.)	2.87	1.59	1.6	0.75	2.91	1.02
# rx'd <1 yr.	5(22%)	1(25%)	3(43%)	4(80%)	3(25%)	4(57%
# rx'd ≥1-<2yrs.	2(9%)	2(50%)	0	0	2(17%)	2(29%
# rx'd ≥2-<3yrs.	5(22%)	1(25%)	3(43%)	1(20%)	2(17%)	1(14%
# rx'd ≥3-<5yrs.	8(35%)	0	1(14%)	0	3(25%)	0
# rx'd ≥5 yrs.	3(13%)	0	0	0	2(17%)	0

Prospective	AS		CPS		OTC	
	A	NA	A	NA	A	NA
n	3	1	2	0	0	4
Gender	1F,2M	1M	1F,1M			all M
Mean age last	8.42	0.11	10.0	0		1.86

	AS A	AS NA	CPS A	CPS NA	OTC A	OTC NA
visit (yrs.)						
# pts. <2yrs.	0	1(100%)	0	0		3(75%
# pts. >10-<18	1(33%)	0.11	1(50%)	0		0
# pts. ≥18yrs.	0	0	0	0		0
Age oldest	10.08		12.75	0		3.83
Mean duration	3.38	0.11	5.23	0		1.81
of PB rx.(yrs.)						
# rx'd <1 yr.	1	1(100%)	0	0		1
# rx'd ≥1-<2yrs.	0	0	0	0		2
# rx'd ≥2-<3yrs.	0	0	0	0	0	
# rx'd ≥3-<5yrs.	0	0	0	0		1(25%)
# rx'd ≥5 yrs.	2(67%)	0	2(100%)	0		0

Late onset males	AS A	AS NA	CPS A	CPS NA	OTC A	OTC NA
n	0	0	1	1	9	12
Gender			1F	1M	all M	all M
Mean age last visit (yrs.)			32.08	20.42	9.56	12.83
# pts. <2yrs.			0	0	0	0
# pts. >10-<18 yrs.			0	0	1(11%)	2(17%
# pts. ≥18yrs.			1	1	1(11%)	3(25%
Age oldest			32.08	20.42	20.67	38.83
Mean duration of PB rx.(yrs.)			1.98	4.12	2.19	1.93
# rx'd <1 yr.			0	0	1	3
# rx'd ≥1-<2yrs.			1	0	2	3
# rx'd ≥2-<3yrs.			0	0	5	4
# rx'd ≥3-<5yrs.			0	1	1	2
# rx'd ≥5 yrs.			0	0	0	0

OTC Female heterozygotes	OTC A	OTC NA
n	29	26
Gender	all F	all F
Mean age last visit (yrs.)	14.37	16.26
# pts. < 2 yrs.	0	0
# pts. > 10-18 yrs.	11(38%)	5(19%
# pts. ≥18 yrs.	8(28%)	9(35%)
Age oldest	31.83	54.42
Mean duration of PB rx.(yrs.)	3.29	2.82
# rx'd. < 1 yr.	1	5
# rx'd ≥1-<2 yrs.	5	4
# rx'd ≥2-<3 yrs.	9	8
# rx'd ≥3-<5 yrs.	10	7
# rx'd ≥ 5 yrs.	4	2

The following points summarize the above demographics tables:

1.Unlike AS and CPS deficiencies, OTC deficiency is an X-linked disorder. Hence, all homozygous patients are male. The females are heterozygotes.

2.While OTC deficiency may present at any age, AS deficiency was limited to neonatal onset and CPS deficiency was predominately neonatal onset.

3.The majority of neonatal resue patients (R), received antecedent therapy. Those who did, were older at the time of their last visit than those who did not (combining all enzyme groups: mean age 7.9 yrs. for pts. receiving antecedent therapy vs. mean age 1.1 yr. for those who did not). Consequently, neonatal onset patients who received antecedent therapy, received PB monotherapy longer (2.7 yrs. vs. 1.1 yrs. for those receiving antecedent therapy and those who did not, respectively).

4.In the prospectively treated group (P), there are only 10 patients. Half the patients received antecedent therapy and half did not. Their mean age at last visit was comparable to the rescue group, but, because the prospective patients were treated at birth, their mean duration of PB monotherapy is longer (antecedent rx. P vs. R: 4.12 vs. 2.7 yrs., no antecedent rx.- P vs. R: 1.5 vs. 1.1 yrs.).

5.The majority of late onset male patients have OTC deficiency and none have AS deficiency. Although their mean age at last visit is higher than for neonatal onset disease patients at last visit, the mean age remains in the pediatric age group. Only 4/21 patients in the late onset male group with OTC deficiency, are adults (i.e. > 18 yrs.). Their mean duration of PB monotherapy is ~ 2 yrs.

6.The OTC female heterozygotes are the oldest age group. Their mean ages at last visit are in the adolescent age range. 31% of these patients (17/55) are adults. They have received PB monotherapy for ~ 3 yrs.

Results: Efficacy:

(Note: per submission dated 8/21/95, compliance cannot be documented because distribution of the drug to each patient was not reported on the CRF. In some cases, the co-investigator noted if the patient was compliant or not, but there was no quantification. Since an average adult requires 30-40 tablets/day, compliance over a chronic dosing period was not expected).

Survival is the prime measure of efficacy. (Note: I updated the following tables per amendment 95-006, submitted on 7/31/95):

The following data applies to the 148 evaluable patients (note: # wd 2° to tx.= number of patients who withdrew secondary to liver transplant, # withdrew- number of patients who

withdrew for reasons other than liver transplant):

	AS		CPS		OTC	
	A	NA	A	NA	A	NA
Rescue:						
n	23	4	7	5	12	7
# pts. active	17(74%)	3(75%)	5(71%)	3(60%)	7(58%)	4(57%
# withdrew	3(13%)	0	0	0	0	0
# wd 2° to tx.	0	0	0	1(20%)[a]	1(8%)	1(14%
# expired	3(13%)	1(25%)	2(29%)	1(20%)	4(33%)	2(29%
Prospective:						
n	3	1	2	0	0	4
# pts. active	3(100%)	1(100%)	2(100%)	0		1(25%
# withdrew	0	0	0	0		0
# wd 2° to tx.	0	0	0	0		3(75%
# expired	0	0	0	0		0
Late onset males:						
n	0	0	1	1	9	12
# pts. active			1	1	7(78%)	9(75%
# withdrew			0	0	0	3(25%
# wd 2° to tx.			0	0	1(11%)	0
# expired			0	0	1(11%)	0
OTC Female heterozygotes:						
n	0	0	0	0	29	26
# pts. active					26(90%)	23(88%
# withdrew					2(7%)	3(12%
# transplanted					0	0
# expired					1(3%)	0

a= patient # 651 was classified as "active" per volume 6, appendix B, but per CRF for this patient in volume 9, the patient received a liver transplant.

The above statistics demonstrate that survival is 100% for prospectively treated patients, 98% for OTC female heterozygotes and 96% for late-onset males. Survival was lowest in the neonatal rescue group (45/58= 78%). In the R group, patients with AS deficiency had the lowest mortality rate (15%) compared to CPS and OTC deficiencies (25% and 32%, respectively). The deaths in the late onset males and OTCF het groups were due to OTC deficiency.

The group with the highest transplant rate is the P group. **It is interesting to note, that the majority (3/5 or 60%) of prospectively treated patients who have been most recently enrolled into the study (i.e. patients receiving PB monotherpy only) have received liver transplants while older prospectively treated patients (i.e. those who received antecedent therapy), have been treated with medical therapy only. I asked Dr. Brusilow**

in our 3/20/95 meeting with him, if PB monotherapy is now regarded as a temporizing measure in these situations, and he replied that he does not recommend one regimen over the other. Transplants were also done in 3 patients with neonatal onset OTC or CPS deficiencies receiving rescue therapy and 1 male patient with late onset OTC deficiency.

Another primary measure of efficacy were the **anthropometric measurements**. In the initial submission, only the height and weight from the most recent case record were provided. Since growth refers to change in height and weight over time, FDA requested all values be submitted. These were provided in amendment 95-03.

For patients in each of the 4 diagnostic categories, all available heights and weights on treatment and their corresponding percentiles were provided. For patients < 18 yrs. of age, a Z score was calculated for both height and weight (adjusted for both age and gender per my 7/11/95 telephone conversation with Dr. Wiech). The difference between the initial mean Z score (closest to the initiation of PB monotherapy) and the mean Z score at the last recorded visit was reported for all enzyme groups and all diagnostic categories in amendment 95-03, table 53. In this table, a significant increase in either weight or height (which I will define as a change in Z score $\geq$ 1 from initial to last recorded visit), occurred in weight for prospectively treated patients with AS deficiency who received antecedent therapy (n= 2) and in height, for OTCF hets. who received no antecedent therapy. However, in the latter group, this significant increase in height was due to 2 patients, #'s 594 and 15, where the height at the last visit increased from the 2% to the 91% in the former patient and from the 14% to the 99.8% in the latter patient, both increases occurring over ~ 1 yr. This seems implausible and, therefore, I redid this analysis omitting these 2 measurements, and the difference in mean Z scores between the initial and final visits for height in this group, was not significant (+0.02).

I noted that in table 53, the number of patients in some of the groups, did not match the number of patients in the raw database (e.g. per table 53, regarding weight, there were 8 CPS rescue patients who received antecedent therapy and for which at least 2 weight values are available, but in the raw database, there were only 5 such patients. Therefore, I redid this table, but looked at the data in two different ways: change in Z scores for height and weight from baseline to the last recorded visit and change in Z scores during treatment. In each case, I included only patients on PB treatment for $\geq$ 1 yr.

Change in Z scores of weight and height for age from baseline (initial) to $\geq$ 1 yr. on PB rx. (last) in patients < 18 yrs. old (note: AT= antecedent therapy, No AT= no antecedent therapy):

	Weight		Height	

	Weight				Height			
	Initial	Last	Diff.		Initial	Last	Diff.	
Rescue:								
AS AT n=8								
No AT n=0	-1.08	-1.63	-0.55;	n=6	-1.98	-2.62	-0.64	
CPS AT n=0								
No AT n=0								
OTC AT n=5								
No AT n=1	-2.60	-1.53	+1.07[a];	n=3	-3.60	-2.60	+1.00[b]	
AT + No AT n=6	-2.41	-1.39	+1.02;	n=4	-3.00	-2.47	+0.53	
	-1.43	-0.68	+0.75;	n=1	-1.19	-2.09	-0.90	
a and b= significance (i.e. change in Z score ≥ 1) due to one patient: # 288.								
Prospective:								
AS AT n=0								
No AT n=0								
CPS AT n= 1								
No AT n=0	-0.86	+0.41	+1.27;	n=1	-1.67	-0.53	+1.14	
OTC AT n=0								
No AT n=0								
Late-onset males:								
OTC AT n=1	-0.06	-0.06	0.00;	n=1	-0.04	-0.11	-0.07	
No AT n=1	-0.14	-0.20	-0.06;	n=1	-0.61	-0.42	+0.19	
AT + No AT n=2	-0.10	-0.13	-0.03;	n=2	-0.33	-0.27	+0.06	
OTCF hets.:								
OTC AT n=4								
No AT n=1	-0.43	-0.10	+0.33;	n=3	-1.63	-1.14	+0.49	
AT + No AT n=5	-1.08	-0.03	+1.05;	n=1	-0.81	-0.38	+0.43	
	-0.56	-0.09	+0.47;	n=4	-1.42	-0.95	+0.47	

The following conclusions can be drawn from the above table:

Growth is most severely affected in the rescue patients and least affected in the late onset males. The significant improvement (change in Z score ≥ 1) in both height and weight after ≥ 1 yr. on PB monotherapy compared to baseline, was due to 2 patients- OTC rescue patient # 288 and prospectively treated CPS patient # 341. (Note: although the Z score for height significantly improved for patient # 288, the absolute height remained well below the 3% for age).

Regarding change in Z scores of weight and height for age during treatment with PB therapy for ≥ 1 yr.in patients < 18 yrs. old:

	Weight			Height		
	Initial	Last	Diff.	Initial	Last	Diff.

	Weight [10]			Height		
	Initial	Last	Diff.	Initial	Last	Diff.
Rescue:						
AS AT n=17	-1.55	-1.81	-0.26;	n=15 -2.04	-2.23	-0.19
No AT n=3	-1.35	-1.32	+0.03;	n= 3 -1.75	-1.48	+0.27
AT + No AT n=20	-1.52	-1.73	-0.21;	n=18 -1.99	-2.11	-0.12
CPS AT n= 3	+0.57	+0.15	-0.42;	n= 3 -0.43	-0.83	-0.40
No AT n=2	-1.27	-2.05	-0.78;	n= 2 -2.53	-2.19	+0.34
AT + No AT n=5	-0.17	-0.73	-0.56;	n= 5 -1.27	-1.37	-0.10
OTC AT n= 8	-2.18	-0.92	+1.26[a];	n= 7 -3.15	-2.81	+0.34
No AT n=1	-2.93	-1.27	+1.66;	n= 1 -2.16	-0.52	+1.64
AT + No AT n=9	-2.26	-0.96	+1.30;	n= 8 -3.03	-2.52	+0.51
a= significance due to two patients, # 288 and 613.						
Prospective:						
AS AT n= 2	+1.08	+2.33	+1.25;	n= 2 -0.67	-0.32	+0.35
No AT n=0						
CPS AT n=1	-0.56	+0.41	+0.97;	n= 1 -1.34	-0.53	+0.81
No AT n=0						
OTC AT n=0						
No AT n=2	+0.50	+2.80	+2.30[b];	n= 2 -1.14	-0.58	+0.56
b= significance due to one patient, # 563.						
Late-onset males:						
OTC AT n=6	-0.37	-0.69	-0.32;	n= 6 -0.59	-0.78	-0.19
No AT n=4	-1.07	-0.45	+0.62;	n= 3 -0.03	-0.46	-0.43
AT + No AT n=10	-0.65	-0.59	+0.06;	n= 9 -0.40	-0.67	-0.27
OTCF hets.:						
OTC AT n=18	-0.23	-0.24	-0.01;	n=18 -0.80	-0.92	-0.12
No AT n= 11	-0.45	+0.15	+0.60;	n=10 -0.75	-0.83	-0.08[a]
AT + No AT n=29	-0.31	-0.20	+0.11;	n=28 -0.78	-0.89	-0.11

The following conclusions can be drawn from the above table:

Again, rescue patients show the greatest negative deviations from the norm for both height and weight. After at least one year of PB monotherapy, significant increases in weight were noted only in the prospectively treated and OTC rescue groups. Within these groups, the significant weight increases were due to 6 patients- #'s 28, 30 and 563 in the prospective group and #'s 288, 613 and 604 in the OTC rescue group. However, a significant increase in height occurred in only 1 patient (OTC rescue pt. # 604).

To summarize the findings in the above tables:

1. Patients with urea cycle disorders tend to be shorter and lighter than average.
2. Height is more severely affected than weight.

3. Growth is most severely affected in the rescue patients.

4. PB monotherapy significantly improves growth in only a few patients.

Cognitive development:

Formal IQ test scores are available in some patients. Since IQ testing was done in only some patients, the sponsor, at FDA's request (amendment 95-03, submitted 5/22/95), provided narratives of cognitive function in others to provide us with some knowlege regarding their level of cognitive functioning. This was done only in those patients who received no antecedent therapy. (Note: initially, I thought these narratives were also useful in that they contain ratings of the patient's compliance with PB therapy. However, per my phone conversation with the sponsor on 8/10, these compliance ratings are not necessarily accurate as compliance was determined not by pill counts but just by patient's report of how compliant they believed they were with the medication. The sposor submitted this in writing, at my request, on 8/21/95). The IQ data was classified according to the following scheme:

IQ score range		Classification
90-109	Average (Avg.)	4
70-89	Low average/borderline (LA)	3
50-69	Mentally retarded (MR)	2
<50	Severely retarded (SR)	1

Please note that a variety of psychological tests were used to evaluate IQ both within a single patient, at different timepoints, and among patients. Also note, that in some severely retarded patients, it was not possible to calculate an IQ score but a description of their cognitive level of functioning placed them clearly in the SR classification, and, therefore, they are included in the IQ group. The following table summarizes the IQ data in each of the patient groups and uses the following abbreviations: R= rescue, P= prospectively treated, L= late onset male, AT= antecedent therapy, No AT= no antecedent therapy, Av= average intelligence, LA/B= low average/borderline, MR= mentally retarded, SR= severely retarded. (Note: after each enzyme deficiency in eacg group, is a fraction- the numerator is the # of patients in whom IQ testing was done, and the denominator, the total number of patients in that group with that enzyme deficiency. Also, note that this summary table will be followed by a detailed narrative of all available cognitive data for each group).

Diagnostic category		Aver n(%)	LA/B n(%)	MeRe n(%)	SeRe n(%)
R: AT:	CPSD 4/7	1(25%)	2(50%)	0	1[a] (25%)

Category		Aver n(%)	LA/B n(%)	MeRe n(%)	SeRe n(%)
R:	AT : CPSD 4/7	1(25%)	2(50%)	0	1[a](25%)
	No AT: CPSD 3/5	1(33%)	0	1[b](33%)	1(33%)
	AT + No AT: CPSD	**2(29%)**	**2(29%)**	**1(14%)**	**2(29%)**
	AT: OTCD 7/12	0	0	1(14%)	6[c](86%)
	No AT: OTCD 4/7	0	0	0	4(100%)
	AT + No AT: OTCD	**0**	**0**	**1(10%)**	**9(90%)**
	AT: ASD 13/23	0	1(8%)	3(23%)	9[d](69%)
	No AT: ASD 4/4	1[e](25%)	1[f](25%)	0	2(50%)
	AT + No AT: ASD	**1(6%)**	**2(12%)**	**3(18%)**	**11(65%)**
All R gps combined		**3(9%)**	**4(12%)**	**5(15%)**	**22(65%)**

(Note: a, c and d refer to the addition of several patients- #'s 52, 287, 333, 397 and 520- all of whom were SR per the patient mortality and discontinuation of therapy case report forms. b refers to patient # 651. Per the initial February NDA submission, pt. # 651 had an IQ of 64 on PB rx., but per the May amendment, no IQ is given and the patient is classified in the LA range. I used the IQ of 64 in the above table. e and f refer to the addition of patient #'s 650 and 610, respectively per amendment 95-03.

		Aver	LA/B	MeRe	SeRe
P:	AT: CPSD 1/2	0	1(100%)	0	0
	No AT: CPSD 0/0	0	0	0	0
	AT + No AT: CPSD	**0**	**1(100%)**	**0**	**0**
	AT: OTCD 1[a]/1	1(100%)	0	0	0
	No AT: OTCD 1/4	0	0	1(100%)	0
	AT + No AT: OTCD	**1(50%)**	**0**	**1(50%)**	**0**
	AT: ASD 1/3	0	0	1(100%)	0
	No AT: ASD 0/1	0	0	0	0
	AT + No AT: ASD	**0**	**0**	**1(100%)**	**0**
All P gps combined		**1(25%)**	**1(25%)**	**2(50%)**	**0**

a= addition of pt. # 167 in whom IQ data was provided in the narrative pertaining to discontinuation of therapy. Therapy was discontinued in this patient due to receipt of a liver transplant at 3 11/12 yrs.

Note: CPS patients, #'s 295 and 565, have been omitted from this analysis as their records could not be found during FDA's audit of this NDA.

		Aver	LA/B	MeRe	SeRe
L:	AT: CPSD 0/1	0	0	0	0
	No AT: CPSD 1/1	0	1(100%)	0	0
	AT + No AT: CPSD	**0**	**1(100%)**	**0**	**0**
	AT: OTCD 4/9	0	1(25%)	1(25%)	2(50%)
	No AT: OTCD 3/12	1(33%)	1[a](33%)	0	1(33%)
	AT + No AT: OTCD	**1(14%)**	**2(29%)**	**1(14%)**	**3(43%)**

	Aver (n (%))	LA/13 (n (%))	MR (n (%))	SR (n (%))
All L gps combined	1(13%)	3(38%)	1(13%)	3(38%)

a= patient # 702 was reported to have an IQ of 83 (LA) in the initial NDA submission, but, in the May amendment (95-03), was classified as "average" per Bayley assessment.

OTCF hets: AT: 17/29	5(29%)	7(41%)	3(18%)	2(12%)
No AT: 12[a]/26	1(8%)	4(33%)	3(25%)	4(33%)
Both OTCF het gps	6(21%)	11(38%)	6(21%)	6(21%)

a= I omitted patient # 637 from the analysis because a specific IQ score was not reported.

Summary of the above table pertaining to IQ in patients with UCD:

The majority of rescue patients (27/34 or 79%) are MR or SR with the majority being SR. In those testing in the average or LA IQ range, 3/7 (#'s 610, 638 and 650), were tested at < 1 yr. of age. In addition, > 1 yr. has elapsed from the time of IQ testing to the date of the last report in 3 of these 7 patients.

Only 4/11 (36%) prospectively treated patients were IQ tested- with 2 testing in the average to LA range (note: the oldest patient in this category was 5 yrs. at the time of testing) and 2 in the MR range. (Note: patient #'s 295 and 565 were excluded from this database as their records could not be found by FDA during the audit of this NDA).

Only 8/23 (35%) late-onset males were formally IQ tested. 50% tested in the average to LA range and 50 % in the MR or SR range.

29/55 (53% OTCF hets were formally IQ tested. Of these, 17 (59%) tested in the average to LA range and 12 (42%) in the MR or SR range.

Additional cognitive information provided for each patient group:

<u>Rescue patients:</u>

Compliance was rated in 10/11 rescue patients who received no antecedent therapy. The rating was "good" or "excellent" in all of them.

Narratives of cognitive function on PB rx., has been provided for 4 patients who received no antecedent therapy (2 CPS- #'s 672 and 725 and 2 OTC- #'s 720 and 709). The CPS deficiency patients were both described as demonstrating normal development but assessments were done at 3 and 8 mos., respectively. The OTC def. patients, were described as average, but assessments were done at ≤ 18 mos. of age. Assessments are all up-to-date in these patients.

Pre and post PB IQ testing was available in the following patients (excluding patients who were SR pre PB rx.):

AT: n=3 The IQ's in these 3 patients were in the average to LA range and they remained stable (test score differences -2 to -7) over a mean period of 2.9 yrs.

No AT: n= 0.

Repeat IQ testing on PB rx. (excluding those SR on initial testing) revealed the following:

AT: n=2 (# 180 with OTC def. and # 407 with ASD def.). Both patients were initially classified as MR and there was no significant change between test scores (i.e. differences < 10 points) in the ≤ 1.5 years that these patients were retested.

No AT: n=1 (# 651 with CPS def.). This patient was initially classified as LA (IQ= 87) and dropped IQ by 23 points to 64, MR range in 1.15 yrs. This occurred with compliance rated as "good to excellent". Note, however, the initial test was performed at 5 mos. of life.

In summary, the majority of rescue patients- 79%- are MR or SR. Of the 11 rescue patients with IQ's in the average or LA range, or with narratives suggesting an average-LA level of cognition, assessment was done at a very early age (< 18 mos.) in 7 patients. There is a paucity of data regarding pre and post PB rx. IQ and repeat IQ tesing on PB therapy.

Prospectively treated patients:

Narratives of cognitive function on PB rx., has been provided for 2 additional patients- #'s 625 and 570. The narratives suggest that these patients were functioning in the average and LA ranges, but both received liver transplants at < 1.5 yrs. of age and, therefore, no further information is available.

Compliance was rated in the patients who received no antecedent therapy. It was rated as "good" in patients 570 and 625 and "good to excellent" in patient 563 (MR).

Pre and post PB rx. IQ data:

In 1 patient- # 341- IQ was measured on antecedent therapy and was 85. After 5 yrs. on PB rx. IQ remained essentially unchanged (-2 point difference).

Repeat IQ testing on PB rx.:

N= 0 because patient # 295 has been removed from the database (record could not be found by FDA during their audit).

In summary, only 4 patients in the prospectively treated group have been IQ tested. 2 patients tested in the average to LA range and 2, in the MR range. Cognitive narratives were provided in 2 additional patients, indicating average and LA performance, but drug therapy was discontinued at < 1.5 yrs. of age in both due to receipt of liver transplants.

Late Onset Male Patients:

For late-onset male patients, the following applies:

AT: OTC:	mean age at entry into PB protocol:	4.50 yrs.
	mean age at IQ testing:	6.01 yrs.
	age range at IQ testing:	3.05-9.13 yrs.
	mean duration of PB rx.:	1.34 yrs.

Excluding withdrawals and SR patients, IQ testing was up-to-date in 2/2 patients.

No AT: CPS: age at IQ testing was 19.92 yrs. after 4.58 yrs. on PB and testing is up-to-date

OTC: mean age at entry into PB protocol: 4.06 yrs.
mean age at IQ testing: 4.92 yrs.
age range at IQ testing: 2.25-8.25 yrs.
mean duration of PB rx.; 0.85 yrs.
Excluding withdrawals and SR patients, IQ testing is up-to-date in 2/2 patients.

Compliance with PB monotherapy was only provided for the no antecedent therapy patients. In those in whom IQ was tested, compliance was rated as "good" to "excellent" in 4/4 pts. (corresponding IQ's were 2 pts. in the average category and 1 pt. in each of the LA and SR categories).

Narratives of cognitive function on PB rx., where formal IQ testing was not done, was provided in 8 patients who received no antecedent therapy. Sufficient information to classify the patient was provided in 7 of these. 6 were functioning in the avg. or LA range (6/7= 86%) and 1 in either the MR or SR range. Insufficient data was provided for patient #642 who was noted to have language delay and poor coordination. Compliance with PB rx. for 5/6 pts. whose narratives suggested cognitive functioning in the average or LA range indicated it to be "good" in 2 of these pts. and variable (ranging from "poor" to "exce;;ent") in each of the remaining 3 pts.

In addition, the mortality CRF for patient # 429 who received antecedent therapy, stated he had attended college and worked in a wood working shop but was not compliant with his medication.

Pre and post PB IQ testing (again, note, this analysis excludes patients who were SR pre PB rx.):

AT: n=2 In 1 patient (#448) there was a significant deterioration in IQ (-11 points) over a 2.57 yr. period, but the patient's classification remained MR. The IQ in the remaining patient remained essentially unchanged (+3 point difference) in 1.35 yrs.

No AT: n=1 (#538) and IQ was essentially unchanged (-1 point difference) 4 yrs. later. Compliance with PB rx. was "excellent".

In an additional 5 patients (# 702, 550, 566, 556 and 490), all of whom received no antecedent therapy, a comparison of cognitive performance pre and post PB rx. was possible using narratives (SR patients pre PB were excluded). In all these 5 patients, cognitive classification remained unchanged. Compliance was "good" to "excellent" in 3 and variable in 2.

In no late-onset male patient was IQ repeated during PB rx.. However, the narratives of 4 patients indicate no change over time in 1 and improvement in 3. Specifically, the narrative of patient #550 indicates no change. On PB, the patient was "normal" in the first grade, did poorly in second grade when he was taking half the prescribed dose of PB, and grades again became "good" in third and fourth grades when the dose was

doubled. The narratives of the following 3 patients suggest improvement on PB therapy:

#490- according to the patient, PB helped earn a college degree in computers by allowing him to work "longer and harder". Note: patient is taking half the recommended dose.

#550- on half the prescribed PB dose, the patient was noted to have poor grades and behavioral problems. When the dose was doubled, the patient's grades improved to "good".

#566- on PB, the patient's parents reported "fewer episodes of confusion" and behavior was easier to control.

OTCF heterozygotes:

For OTCF hets, the following applies:

AT: (antecedent rx.)	mean age at entry into PB protocol:	11.27 yrs.
	mean age at IQ testing:	14.04 yrs.
	age range of patients IQ tested:	6.02-24.74 yrs.
	mean duration of PB rx.:	2.77 yrs.
	# adults (i.e. ≥ 18 yrs.) IQ tested:	3
	mean age at IQ testing if exclude adults:	12.12 yrs.

Excluding patient withdrawals and SR patients, IQ testing was up-to-date (i.e. done within 2 yrs. of NDA file date) in 10/13 patients (77%). IQ testing was not up-to-date in patient #"s 303, 313 and 324 who tested avg, MR and LA, respectively.

No AT: (no antecedent rx)	mean age at entry into PB protocol:	8.18 yrs.
	mean age at IQ resting:	10.79 yrs.
	age range of patients IQ tested:	2.93--23 yrs.
	mean duration of PB rx.:	2.61 yrs.
	# adults IQ tested:	2
	mean age at IQ testing if exclude adults:	8.85 yrs.

IQ testing was up-to-date (excluding withdrawals and SR patients) in 7/8 patients (88%). IQ testing was not up-to-date in patient # 575 who tested in the LA range.

Compliance ratings in patients who were IQ tested and received no antecedent therapy were as follows:

Of 10 pts., compliance was "good" to "excellent" in 6, with IQ's in the avg. to LA range in 3 of these and in the MR or SR range in the remaining 3. Compliance was "fair" in 1 SR pt; "poor" in 1 LA pt. and variable (ranging from "poor" to either "good" or "excellent" in 1 LA and 1 SR pt. Therefore, compliance does not appear to be related to cognitive outcome.

Narratives of cognitive function on PB treatment, where formal IQ testing was not done, was provided in 10 patients (10/26= 38%) who received no antecedent therapy. In my opinion, there was sufficient information to categorize the patient's level of cognitive functioning in 6 of these. Intellectual functioning was average in 5 (#'s 680, 654, 684, 609 and 681) and MR in 1 (#637). Information was insufficient to categorize the patient's level of cognitive function in 4 patients (#'s 506 and 618 were reported to be in special education classes, # 602 is a housekeeper and # 212, a Nurse's Aide).

Pre and post PB IQ testing was available in the following patients (note: patients had to be on PB for > 6 mos.and in this analysis, I omitted patients who tested SR pre PB rx.):

AT: n=10 A significant change from baseline (difference between IQ scores > 10 points) occurred in only 1 patient (# 207) in whom the IQ deteriorated by 20 points, moving the patient from the MR category to the SR category.

No AT: n=4 A significant change occurred in only 1 patient (#71) in whom the IQ dropped by 18 points, moving the patient from the average to the LA range. **Therefore, in the majority of OTCF hets, where pre and post PB IQ testing was done, the IQs remained stable on PB rx.** Compliance with PB rx. in the patient whose IQ deteriorated (#71) was reported as "poor". (In the patients with stable IQ compliance was rated as "excellent" in 1, ranged from "good to poor" in another and was unknown in the third).

Sufficient information was available from narrative in 6 additional patients (#'s 581, 636, 684, 637, 609 and 681), **to assess intellectual functioning pre and post PB rx.** Patients classified as SR pre PB rx. were excluded. **Again, cognitive function remained stable from baseline in the majority of patients**: (5/6= 83%). In patient # 581, cognitive performance appeared to deteriorate from LA to MR with compliance being rated as "good" or "excellent". Compliance in those who remained cognitively unchanged was: "good" or "excellent" in 4 and was variable in 1 (ranging from "poor to excellent").

Repeat IQ testing on PB rx. (tests administered > 6mos. apart and excluding those SR on initial testing), revealed the following:

AT: n=3, mean duration between tests= 3.86 yrs. A significant difference (≥ 10 points) between test scores occurred in 1 of 3 patients (# 446) in whom IQ decreased by 16 points, moving the patient from the average to the low average range. Note, this patient had the longest interval between tests- 6.64 yrs., of all 3 pts. in this group.

No AT: n=4, mean duration between tests= 3.03 yrs. (patient #'s 581, 393, 636 and 71). A significant deterioration in IQ occurred in 1 patient (# 393), in whom a deterioration by 22 points between tests, dropped the patient from the MR to the SR range. This patient also had the longest interval between tests- 7.21 yrs. and compliance with PB treatment ranged from "poor to excellent". (Note: although patient # 594 also exhibited a significant difference between tests administered on PB rx.- minus 19 points- comparison of the pre PB test score- IQ 88, was essentially unchanged from the last IQ test on PB- IQ 86. Therefore, I rated this patient as no change). Drug compliance ratings in the 3 patients demonstrating no significant change in IQ ranged from "good" to "excellent".

Therefore, IQ remained stable in the majority of patients where IQ testing was repeated on PB rx.

Per the cognitive narrative for patient #

654, the patient's functioning remained normal in the intervening 7 mos.

The narratives of 2 patients (#'s 637 and 664) state that they improved on PB rx. # 637 demonstrated improvement in "some subtest areas" on the Griffith's test and # 664 demonstrated improvement in "thinking and alertness" per the patient and her daughter.

Safety:

Hyperammonemic Episodes:

Hyperammonemic episodes were included in the safety database. I asked the sponsor (Dr. Wiech) why this was placed in safety rather than efficacy and he replied that it is because phenylbutyrate does not prevent hyperammonemia.

The initial NDA did not analyze the frequency of hyperammonemic episodes by enzyme deficiency. Furthermore, baseline (pre-drug) frequency of hyperammonemic episodes was not submitted for late-onset groups (males and OTCF hets). In addition, for some of the groups, the number of patients reporting no HA episodes since initiation of PB therapy, as reported in table 77 did not correlate with the HA raw database provided in appendix E. There were also problems with table 78 in that the mean # HA episodes/yr. for each group, did not correlate with the result that was obtained by dividing the mean total # of episodes by the mean duration of PB therapy for that group. These problems and requests were conveyed to the sponsor. Subsequently, the sponsor reanalyzed this data and did so by enzyme deficiency (amendment 95-03). Further statistical analyses were done by the sponsor regarding the frequency of HA episodes and submitted 6/27/95 as amendment 95-04. (Note: FDA statistician, Mr. Dan Marticello, had questions regarding the statistical analysis of amendment 95-04- see e-mail he addressed to me dated 8/3- and subsequently, a corrected analysis was sent to FDA on 8/7). On 8/10, I telephoned Dr. Weich and requested him to provide the raw database for amendment 95-03, tables 164-7 which were inadvertently omitted and the "Primary Data Listing" for amendment 95-04 which was also inadvertently omitted. I further requested he explain the difference between the "Primary" and "Second Data Listings" in amendment 95-04. He faxed me this data on that same day. On 8/10, 8/11 and 8/15, I telephoned Dr. Weich (on 8/10, I also spoke one of Dr. Weich's statisticians, Mr. Dave Clissold), to point out discrepancies in these various raw databases- specifically, for some patients, the total number of HA episodes differed among the databases. He stated he would review all these databases and make the appropriate corrections. Subsequently, amendment 95-07 was submitted on 8/24/95 and per the sponsor, contains the corrected HA database and analysis. Dr. Weich explained that the discrepancies were due to recording of some HA events twice or recording HA events past the data cut-off of June, 1994.

Given all the above problems, I did my own analysis

regarding the frequency of HA in the various groups, using the raw database contained in amendment 95-007. Since, the database lacked a baseline frequency for the late-onset patients (males and OTCF hets), I telephoned Dr. Weich and Mr. Dave Clissold, on 8/16, to request this data. Dr. Weich informed me that this information was not requested on the CRF. Mr. Clissold stated that there would be a major problem in attempting to retrieve this type of data. Many patients who had symptoms which could be attributable to hyperammonemia, such as lethargy and confusion, did not have an accompanying plasma ammonia measured, and, therefore, the symptoms could not be definitively attributable to hyperammonemia. Furthermore, once an elevated ammonia was obtained, the patient was then generally referred to Dr. Brusilow for treatment. I asked that this response be formally sent in to the Agency. (note: this information was submitted on 8/21). Therefore, the following calculations are limited to the frequency of hyperammonemia on PB monotherapy:

Summary of HA episodes in all groups:

In those treated with PB ≥ 1 yr., the frequency of hyperammonemia on treatment was:

Disease onset	Enzyme def.	N	Mean # HA episodes/yr.	Mean duration of PB rx.
Rescue:	AS	21	1.18	3.26
	CPS	5	0.75	2.50
	OTC	12	1.54	3.18
Prospective	AS	2	1.30	5.03
	CPS	2[a]	1.92	5.23
	OTC	3	3.41	2.14
Late-onset males	CPS	2	0.00	3.05
	OTC	17	0.67	2.35
OTCF hets.	OTC	49	0.85	3.36

a= CPS prospectively treated patients, #'s 295 and 565, have been omitted because their records could not be found during FDA's audit.

The above table indicates that late-onset patients (males and OTCF hets.) have a lower frequency of HA episodes, averaging < 1 episode/yr. compared to neonatal onset patients. Patients with late-onset OTC deficiency have a lower HA frequency than neonatal onset OTC deficiency, confirming that the degree of severity of the disease is related to time of onset which is related to the amount of residual enzyme activity. Patients with neonatal onset disease are presumed to have little or no enzyme activity while late-onset patients are presumed to have more enzyme activity but which may not be enough to prevent episodic HA. Although prospectively treated patients appear to have a higher frequency of HA than rescue patients, the small number of patients in the former group warrants cautious interpretation.

Without baseline data, no statement can be made regarding the effect of PB on the frequency of HA.

The following is a detailed analysis of the HA frequency in each group.

Frequency of Hyperammonemic Episodes on PB monorx.

Disease Onset	Enzyme def.	n	mean # HA/yr.	mean duration of PB rx.(yrs.)
Rescue:				
AT	AS all rx'd	23	2.10	2.87
	rx'd ≥ 1 yr.	18	1.34	3.51
No AT	AS all rx'd	4	0.43	1.59
	rx'd ≥ 1 yr.	3	0.22	1.79
AT	CPS all rx'd	7	2.54	1.6
	rx'd ≥ 1 yr.	4	0.69	2.62
No AT	CPS all rx'd	5	0.65	0.75
	rx'd ≥ 1 yr.	1	1.00	2.00
AT	OTC all rx'd	12	1.12	2.91
	rx'd ≥ 1 yr.	9	0.93	3.63
No AT	OTC all rx'd	7	3.39	1.02
	rx'd ≥ 1 yr.	3	3.36	1.82

Comment: Note the wide variability in hyperammonemic frequency, and, except for the AS, AT group, sample sizes are small. Thus, a few patients with frequent HA episodes can markedly inflate the mean rate for the group. This was the case in 3 patients with AS deficiency, AT; 3 patients with OTC deficiency, no AT; and 2 patients with CPS deficiency, AT. Therefore, one must be cautious in drawing conclusions from this data. Furthermore, the lack of a baseline frequency, limits the usefulness of this data.

Prospective: Frequency of Hyperammonemia on PB monorx.

	Enzyme def.	n	mean # HA/yr.	mean duration of PB rx.(yrs.)
AT	AS all rx'd	3	13.36[a]	3.38
	rx'd ≥ 1 yr.	2	1.30	5.03
No AT	AS all rx'd	1	0	0.11

Frequency of HA on PB monorx.

		n	mean # HA / yr.	mean duration PB monorx
OTCF hets; AT	OTC all rx'd	29	0.96	3.29
	rx'd ≥ 1 yr.	28	0.74	3.38
No AT	OTC all rx'd	26	0.80	2.82
	rx'd ≥ 1 yr.	21	0.99	3.33

Comment: similar to late onset OTC deficiency male pts., OTCF hets, have < 1 HA episode/yr. There is essentially no difference in frequency of HA episodes between the antecedent and no antecedent therapy groups.

Incidence of No Hyperammonemic Episodes on PB monorx.

Disease Onset	Enzyme def.	AT/no AT	total n	# (%) pts. with no HA
Rescue	AS	AT- all pts.	23	1/23 (4%)
		- rx'd ≥1yr.	18	0/18 (0%)
		No AT- all pts.	4	2/4 (50%)
		- rx'd ≥1yr.	3	2/3 (67%)
	CPS	AT- all pts.	7	3/7 (43%)
		- rx'd ≥1yr.	4	2/4 (50%)
		No AT- all pts.	5	3/5 (60%)
		- rx'd ≥1yr.	1	0/1 (0%)
	OTC	AT- all pts.	12	2/12 (17%)
		- rx'd ≥1yr.	9	1/9 (11%)
		No AT- all pts.	7	1/7 (14%)
		- rx'd ≥1yr.	3	0/3 (0%)
Prospective	AS	AT- all pts.	3	0/3 (0%)
		- rx'd ≥1yr.	2	0/2 (0%)
		No AT- all pts.	1	1/1 (100%)
		- rx'd ≥1yr.	0	
	CPS	AT- all pts.	2	0/2 (0%)
		- rx'd ≥1yr.	2	0/2 (0%)
		No AT- all pts.	0	
		- rx'd ≥1yr.	0	
	OTC	AT- all pts.	0	

			Total	# (%) of pts. free of HA
Prospective	OTC	No AT- all pts.	4	1/4 (25%)
		-rx'd ≥1yr.	3	0/3 (0%)
Late onset	CPS	AT- all pts.	1	1/1 (100%)
		- rx'd ≥1yr.	1	1/1 (100%)
		No AT- all pts.	1	1/1 (100%)
		- rx'd ≥1yr.	1	1/1 (100%)
(males)	OTC	AT- all pts.	9	5/9 (56%)
		- rx'd ≥1yr.	8	4/8 (50%)
		No AT- all pts.	12	9/12 (75%)
		- rx'd ≥1yr.	9	8/9 (89%)
OTCF hets	OTC	AT- all pts.	29	9/29 (31%)
		- rx'd ≥1yr.	28	9/28 (32%)
		No AT- all pts.	26	10/26 (38%)
		- rx'd ≥1yr.	21	5/21 (24%)

Summary incidence of no HA episodes in pts. rx'd ≥ 1 yr.:
Rescue: AS 2/21 (10%), CPS 2/5 (40%), OTC 1/12 (8%)
Prosp.: AS 0/2 (0%), CPS 0/2 (0%), OTC 0/3 (0%)
Late-onset OTC males: 12/17= 71%, CPS 2/2 (100%)
OTCF hets.: 14/49= 29%

Summary incidence of no HA episodes in pts. rx'd ≥ 3 yrs.:
Rescue: AS 0/11 (0%), CPS 0/1 (0%), OTC 0/5 (0%)
Prosp.: AS 0/2 (0%), CPS 0/2 (0%), OTC 0/1 (0%)
Late-onset OTC males: 3/3 (100%), CPS 1/1 (100%)
OTCF hets.: 9/23 (39%)

Comment: Late onset OTC males had the highest number of patients who were free of HA on PB monotherapy. Significantly more patients with late onset disease- OTC males and OTCF hets- were free of HA episodes on PB monotherapy compared to neonatal onset (rescue and prospectively treated) OTC deficiency. This data again suggests that severity of OTC deficiency is related to time of onset of disease- the earlier the onset, the more severe it is. Neonatal onset AS deficiency is similar to neonatal onset OTC deficiency in that few patients treated for more than 1 yr., had no HA episodes. In the neonatal onset rescue group, CPS deficiency had the highest number of patients treated > 1 yr. who were HA-free. Again, as with the HA frequency analysis above, lack of baseline data for comparison to post drug data, limits the value of these data in the late onset group (CPS and OTC male and OTCF hets).

In amendment 95-004, corrected summary statement submitted 8/7/95, the sponsor states that the incidence of HA

episodes was significantly increased by: longer treatment duration and AS deficiency. **Since AS deficiency occurs only in the neonacal onset group, one cannot exclude the effect of disease onset on the HA frequency. (For example, with OTC deficiency, HA frequency is significantly less with late onset disease than neonatal onset disease)**. Patients with late onset disease (excluding OTCF hets) were significantly less likely to have HA episodes than either rescue or prospective patients. The sponsor also states that there is a significantly higher risk of HA episode among patients who had antecedent therapy but that this effect is partially confounded by the fact that pts. in the no antecedent therapy group had both proportionately fewer long-term patients and proportionately more short-term patients (i.e treated < 1 yr.). My analysis indicates no consistent trend for HA frequency difference between those who received antecedent therapy and those who did not. I also discussed these data with FDA statistician, Dan Marticello, and we concluded that inequality in baseline HA episode frequency between groups could account for the statistical differences found on drug. Hence, baseline data is essential for comparison, but, per the sponsor is not retrievable.

Plasma Ammonia and Glutamine levels:

The initial NDA did not contain any plasma ammonia levels. Both baseline and on treatment plasma ammonia levels were requested by FDA. Subsequently, the sponsor submitted a statement on 8/21, that plasma ammonia levels were often not measured prior to the hyperammonemic episode leading to enrollment. In addition, it was stated that since the methodology has not been validated, physicians were not required to report these values. However, it further states that plasma glutamine is also a measure of nitrogen homeostasis, and it was often measured. A potential problem with plasma glutamine is pointed out- due to its lability, delays in sample analysis may result in artifactually low values.

The following analysis was based on data submitted in amendment 95-010, on 9/11/95. Plasma ammonia and glutamine levels were obtained at random on PB rx. and reported on the CRFs of the 148 evaluable patients during routine office visits:

Plasma **ammonia** during treatment with NaPB (Note: patient # 295 has been excluded):

651 ammonia levels were reported in the 148 evaluable patients. Of these, 430 ammonia levels (from 89 patients) came from a laboratory reporting a normal range. The normal ranges were very diverse. The values were normalized by dividing by the upper limit of the normal range and multiplying by 100, yielding a percent of the upper limit of the normal range. Results:

308/430 normalized ammonia levels (71.6%) were $\leq$ the ULN.

122/430 " " " (28.3%) were > the ULN and, of these, 53/122 were attributable to 1 patient (rescue patient with AS def.). If exclude this 1 patient, then :

303/372 normalized ammonia levels (81%) were ≤ the ULN
69/372 " " " (19%) were > the ULN

51/89 patients (57%) had only normal ammonia levels
32/89 " (36%) " a mixture of high and low levels
6/89 " (7%) " only elevated values

However, cautious interpretation is required because patients in whom only normal values were reported, approximately half (24/51 or 47%), had only a single ammonia measurement. The greater the number of ammonia levels measured, the greater the likelihood of abnormal values:

Of the 89 patients with ammonia levels measured in labs who reported their normal range, 61 (69%) patients had ≤ 3 ammonia measurements. Of these 61 patients, only normal levels were reported in 74% (45/61) patients. In contrast, of 28 patients with ≥ 4 ammonia measurements, only normal values were reported in 25% (6/28) patients.

Per time of onset and enzyme deficiency, the # of patients with only normal ammonia levels (denoted as: # O Nl), with a mixture of high and normal values (# mix) and with only elevated values (# O E) were:

Time of onset	Total n	# (%) O Nl	# (%) mix	# (%) O E
AS rescue	19	8 (42%)	10 (53%)	1 (5%)
CPS rescue	6	5 (83%)	1 (17%)	0 (0%)
CPS prosp.	2	1 (50%)	1 (50%)	0 (0%)
CPS late	2	1 (50%)	1 (50%)	0 (0%)
OTC rescue	9	5 (56%)	3 (33%)	1 (11%)
OTC prosp.	4	2 (50%)	1 (25%)	1 (25%)
OTC late males	7	5 (71%)	2 (29%)	0 (0%)
OTCF hets	40	24 (60%)	13 (33%)	3 (7%)

The above data indicates that almost all patients had some normal ammonia levels. However, to be clinically meaningful, the ammonia levels need to be correlated with dietary and drug compliance.

Per time of onset and enzyme deficiency, the # of ammonia measurements which were normal and abnormal were:

Time of onset	Total # meas.	# (%) normal meas.	# abnormal meas
AS rescue	122	45 (37%)	77 (63%)
CPS rescue	10	9 (90%)	1 (10%)
CPS prosp.	7	6 (86%)	1 (14%)
CPS late	5	4 (80%)	1 (20%)
OTC rescue	74	66 (89%)	8 (11%)
OTC prosp.	64	60 (94%)	4 (6%)
OTC late males	20	18 (90%)	2 (10%)
OTCF hets.	128	100 (78%)	28 (22%)

The above data indicates that AS rescue patients had the lowest number of normal ammonia levels.

Plasma **glutamine** during treatment with NaPB (submitted 8/21):

(normal range: 337-673 mMol/L)

See zeroxed table 1 **(note: this table includes prospectively treated patients #'s 295 and 565 who should be removed from the database).**

The table indicates that plasma glutamine levels obtained at random from rescue and prospectively treated patients are approximately in the normal range, but are elevated in the remaining groups. This data is not very meaningful unless correlated with dietary and drug compliance. This data will be dealt with in greater detail later on under the heading "Plasma Amino Acid Levels".

The sponsor should be requested to report all deaths, withdrawals, clinical and laboratory adverse events in all patients- both evaluable and not.

Patient deaths:

In the initial NDA submission, there were 13 deaths. 3 additional deaths were reported in amendment 95-06, submitted 7/31 (Note: since the record for patient # 295 could not be found during audit by FDA, this patient should be omitted from the database. Therefore, there were 15 deaths).

Of the 160 patients (ommission of patient #'s 295 and 565), there were 15 deaths (9%). The overwhelming cause of death was hyperammonemic encephalopathy (11/15= 73%). Per time of onset and enzyme deficiency, the breakdown was:

Rescue: 13/62= 21%

The breakdown by enzyme deficiency was:

CPS: 3/12= 25%- 2 from HA encephalopathy and 1 had pre-morbid development of fever and respiratory distress, but an ammonia level was not obtained

AS: 4/29= 14%- 2 from hyperammonemic encephalopathy, 1 from cerebral ischemia secondary to status epilepticus and 1 from gastroenteritis- ammonia level not done at parenteral request

OTC: 6/21= 29%- 5 from hyperammonemic encephalopathy and 1 from accidental overdose (5.4 fold) IV benzoate and phenylacetate being administered for hyperammonemia. The patient who received the overdose developed respiratory distress, hyperventilation and acidosis.

Prospective: 0/13= 0%

Late-onset males: 1/26= 4%

The patient had OTC deficiency and died from HA encephalopathy with multi-organ system failure.

OTCF hets: 1/59= 2%

The patient died from HA encephalopathy and cerebral edema.

Patient withdrawals:

In the initial NDA submission, table 82, page 050116, 17 patients were listed as withdrawals, but narratives were provided for 24 patients (these additional 7 patients were "not evaluable" for efficacy). On 7/31, amendment 95-06 was

submitted, containing narratives on 3 additional patient withdrawals since the NDA was filed. Therefore, a total of 27 patients withdrew. However, one of these was prospectively treated patient # 565 who should be removed from the database as his record could not be found during FDA's audit of this NDA). Thus, I have included only 26 patient withdrawals in my analysis.

In summary, of the 160 patients, there were 26 withdrawals (16%). The reasons were: liver transplant, 9 patients; poor compliance, 8 patients; parenteral request, 7 patients and unknown in 2. Per time of onset and enzyme deficiency, the breakdown was:

Rescue: 9/62= 15%

CPS: 1/12= 8% patient received a liver transplant due to an increased frequency of HA episodes

AS: 4/29= 14% (2 for poor compliance- with 1 of these patients reporting headaches on NaPB, 1 at parentefal request- mother requested Ucephan due to 4 episodes of HA in the past 7 mos on NaPB and 1 due to 2 episodes of renal tubular acidosis for which a possible drug effect was raised)

OTC: 4/21= 19% (3 for liver transplant and 1 poor compliance)

Prospective: 4/13= 33% (all for liver transplants- and all with OTC deficiency)

Late-onset males: 5/26= 19% (1 liver transplant, 4 poor compliance- all requested either Ucephan or sodium benzoate due to "bad taste" of NaPB, or due to "vomiting and upset stomach" on NaPB or unknown why compliance was poor in 1).

OTCF hets: 8/59= 14% (6 poor compliance with 1 of these patients reporting "bad taste and odor" on NaPB, 1 parenteral request and 1 unknown).

Clinical Adverse Events:

The clinical adverse events were reported in the initial NDA submission. At FDA's request, the sponsor submitted amendment 95-06, on 7/31, assessing the relationship of the adverse event to the drug treatment.

Clinical AEs were reported in 69/160 patients (43%). (Note: I excluded patient # 295 because his record could not be found during FDA's audit of this NDA. Proximal RTA was reported in this patient. No clinical AE's were reported for the other patient, # 565, whose record could also not be found). The most frequently reported AEs were those related to the nervous system and, in the vast majority of cases, were due to the patient's underlying medical condition. Other frequently reported AEs were classified as urogenital, the majority of which were amenorrhea or menstrual dysfunction; body, the majority of which were infections; digestive, the majority of which were decreased appetite; and respiratory, the majority of which were asthma or pneumonia. With regard to assessment of the relationship of the AE to the study drug, the principal investigator classified all AEs except 1, as either "probably not related" or "unknown". The 1 AE classified as "possibly related" was an unspecified drug

interaction in patient #159. **We should request more information on this case.**

Given the infrequent occurrence of the following AEs, **additional information**, if available, **should be requested** from the sponsor, and they should be noted in the label, although their relationship to the study drug is unknown:

aplastic anemia 1/160 patients (1%)
ecchymoses 1/160 (1%)
pancreatitis 1/160 (1%)
renal tubular acidosis 2/160 (1%)- **ask sponsor if these are congenital cases**

Additional AEs which I recommend be included in the label are:

abdominal pain, gastritis and vomiting 3/160 (2%)
bad taste/taste perversion 4/160 (3%)
bad odor 1/160 (1%)
headache 1/160 (1%)
depression 2/160 (1%)
weight gain 3/160 (2%)
rash 2/160 (1%)

In fasting normal adult subjects receiving a single dose (5 gms.) of NaPB as tablet or powder, the most common AEs were: nausea/vomiting/indigestion/abdominal cramping 8/22 patients (36%)
headache 14/22 patients (64%)
light-headedness 6/22 patients (27%)

In adult patients with beta thalassemia or sickle cell, receiving NaPB 20 gms/day with meals for 1.5-17.5 mos., the following AEs were reported:

epigastric discomfort 7/12 patients (58%)
peripheral edema 3/12 pts. (25%)- in 1 pt., it was associated with a 3.5% increase in body weight; in 1 pt., thiazide diuretic treatment was begun; and in 1 pt., an increased diuretic dose was needed.
infection in 4/12 pts. (33%)- septicemia in 2 splenectomized pts. not on penicillin prophylaxis; staph epidermidis septicemia in 1 pt. from an indwelling central venous catheter; and pneumonia and shigella in another patient.
1 spinal cord compression (8%)
1 deep venous thrombosis (8%)
1 hemorrhage from a gastric ulcer in a pt. also on aspirin therapy (8%)
bad body odor in 3 pts. (25%) attributed to in vivo beta oxidation of phenylbutyrate to phenylacetate.

Laboratory Adverse Events:

Note: the sponsor states that for abnormal values, there was no accompanying narrative or indication of follow-up testing or implementation of corrective measures.

The initial NDA contained neither raw data nor an

analysis of the serum chemistry and hematology levels in the patients. At FDA's request, this raw data was submitted on 5/22 as amendment 95-03 with the analysis of this data, submitted 7/31 as amendment 95-06.

Regarding serum chemistry and hematology values, the following **means** were abnormal:

1. SGOT: mean 57 IU/L (slightly incresed) in rescue and prospectively treated pts.

2. Hemoglobin: mean 11.88 g/dl (slightly decreased) in rescue and prospectively treated pts.

Regarding **individual patient abnormalities:** (Note: I removed patient # 295 from this analysis. No laboratory safety assessment was performed in patient # 565).

1.Serum sodium elevated in 2/120 patients (2%).

2.Total bilirubin elevated in 4/111 patients (4%)- #'s 286, 439, 478 and 506. Note: I excluded patient # 490 because baseline bilirubin was elevated. Total bilirubin was significantly elevated ($\geq$ 2 mg/dl) in 2/111 patients (2%).

3.SGOT/SGPT was significantly elevated ($\geq$ 3 x ULN) in 5/101 patients (5%) (#'s 115, 439, 635, 708 and 712).

4.Alkaline phosphatase was significantly elevated ($\geq$ 3 x ULN) in 6/114 patients (5%) (#'s 477, 478, 637, 640, 659 and 681).

5.Significant hypophosphatemia (P < 3.0 mg/dl in patients < 18 yrs. of age and < 2.5 mg/dl for an adult), occurred in 7/108 patients (6%) (#'s 218, 393, 505, 551, 566, 571 and 664).

6.Significant disturbances in acid-base metabolism: alkalosis (CO_2 > 30 mmol/L) or acidosis ($CO_2 \leq$ 16 mmol/L) each occurred in 5/105 patients (5%). (Alkalosis: #'s 174, 390, 407, 550 and 664; acidosis: 324, 563, 650, 654 and 672).

7.Significant hyperchloremia (Cl > 110 mmol/L) occurred in 7/117 patients (6%) (#'s 71, 441, 478, 571, 659 666 and 712).

8.Significant hyperuricemia (uric acid $\geq$ 9 mg/dl in patients < 14 yrs. old) occurred in 3/106 patients (3%).

9.Significant anemia (hemoglobin $\leq$ 9.5 gm/dl and/or hematocrit $\leq$ 31%), occurred in 8/105 patients (8%) (#'s 207, 363, 477, 615, 650, 654, 661 and 709).

Note: total leukocyte counts were not analyzed as this parameter was not included on the case report form.

Plasma Amino Acid Levels:

Per my telephone conversation with Mr. David Clissold, statistician at Ucyclyd Pharma, on Wednesday, 9/27, most of the plasma amino acids were done at the

I requested that Ucyclyd obtain the age-adjusted reference range for the plasma amino acids from the Mr. Clissold stated that only 1 reference range was provided in the NDA because

who heads the stated that "there is essentially no difference" in plasma amino acids among various age groups. I spoke with myself the next day and he confirmed this. He stated that only one reference range is used for plasma amino acids, but the urine levels are age-adjusted. **The sponsor should clarify the units of reporting for the plasma amino acid levels and, for patients with "0" values, if this means the level of the respective amino acid was zero or the assay was not done.**

The mean amino acid levels reported in the initial February submission, vol.6, pages 050161-6, were calculated from the **last visit only**. At FDA's request, the sponsor recalculated the means for each group, including values obtained from **all visits** (raw data in amendement 95-03, analysis in amendment 95-06).

1.Regarding **mean** plasma amino acid levels (Note: patient # 295 is included in this analysis. Plasma amino acids were not measured in patient # 565):

A.Essential amino acids:

The means were normal for all groups.

B.Non-essential amino acids:

a.The following **mean was decreased** with % decrease below the LLN given in parentheses for each group:

cysteine (R/P: 20%, late onset OTC males < 18 yrs. old: 20%, OTCF < 18 yrs. old: 14% and OTCF > 18 yrs. old: 12%).

Sponsor's comment: cysteine is metabolized to pyruvate which is converted to alanine, and this may account for the lower than normal level. Also, the sponsor suggests that this may be attributable to the sulfur content of the nutritinal supplement which is prescribed for the majority of patients.

b.The following **means were increased** with % above the ULN given in parentheses for each group:

citrulline (AS R/P: > 10 fold ULN, CPS or OTC R/P: 21%, late onset OTC males > 18 yrs. old: 107%, OTCF < 18 yrs. old: 118%).

glutamic acid (R/P: 30%, late onset OTC males > 18 yrs. old: 19%)

glutamine (R/P: < 1%, late onset CPS males: 121%, late onset OTC males < 18 yrs. old: 6%, late onset OTC males > 18 yrs. old: 56%, OTCF < 18 yrs. old: 59%, OTCF > 18 yrs. old: 48%)

alanine (R/P: 20%, late onset CPS males: 62%, late onset OTC males < 18 yrs.: 22%, late onset OTC males > 18 yrs. old: 64%, OTCF < 18 yrs. old: 81% and OTCF > 18 yrs. old: 41%).

glycine (late onset OTC males < 18 yrs. old: 14%, OTCF < 18 yrs. old: 37% and OTCF > 18 yrs. old: 1%).

taurine (late onset OTC males < 18 yrs. old: 5%).

Comment:

In patients with urea cycle disorders, glutamine, glutamic acid and alanine, all of which are amino acids which accept waste nitrogen, are the ones which are most commonly elevated. Glycine, which also accepts waste nitrogen, may also be elevated. With adequate treatment (adherence to a low protein diet and sodium phenylbutyrate), the levels of these amino acids should normalize. Non-adherence to either the diet or drug therapy regimen, may result in elevations in these amino acids. The sponsor states that elevations in taurine may be due to nutritional supplementation, **but the rationale for this explanation is not clear to me.** The marked elevation in citrulline in patients with AS deficiency is secondary to the urea cycle enzymatic block in converting citrulline to arginosuccinic acid. The less marked elevations in citrulline in patients with CPS and OTC deficiencies is due to nutritional supplementation.

2.The following is an additional analysis which I did (Note: I removed patient # 295 from this analysis as no record was found for this patient during FDA's audit. Plasma amino acids were not measured in the other patient, # 565, whose record could also not be found) :

Regarding **% and number** of patients with significantly decreased plasma amino acid levels (levels $\leq$ 1/3 LLN) or significantly increased levels (levels $\geq$ 2 x ULN):

A.Essential amino acids:

a.Significant decreases:

Valine 8% pts. (10/123). Note: 8/10 pts. with low values were R/P pts. with AS deficiency.

Isoleucine 28% pts. (34/123).

Leucine 33% pts. (40/123).

Significant decreases were noted in < 5% pts. for the following essential amino acids: histidine 4%, lysine 3% and phenylalanine 2%.

b.Significant increases were noted in < 5% of pts. for the following essental amino acids: threonine and methionine, each 2%.; lysine and histidine, each 1%.

Comment:

Although the mean values for the branched chain amino acids (valine, isoleucine and leucine) were normal for each of the groups, a number of patients had significantly low values. The branched chain amino acids (BCAA) are necessary for normal growth and development and are generally supplemented in the diet of patients with urea cycle disorders. Inadequate supplementation may produce low levels of the BCAA leading to the poor growth observed in many of these patients.

B.Non-essential amino acids:

a.Significant decreases:

cysteine 53% pts. (64/120).

arginine 41% (50/122).

citrulline 22% pts. (22/98). Note:

CPS and OTC deficiency patients only.

Significant decreases were noted in < 5% pts. for the following: asparagine 5%; ornithine 2%; serine, proline, taurine and tyrosine, each 1%.

Comment:

Based on the biochemistry of the urea cycle, patients with CPS and OTC deficiencies, have low arginine and citrulline levels and patients with AS deficiency, have low arginine and high citrulline levels. Arginine is an essential amino acid in patients with urea cycle defects. Therefore, pts. with AS deficiency receive arginine supplementation. For pts. with CPS and OTC deficiencies, citrulline (which is converted to arginine) is supplemented instead, because citrulline adds only 1 nitrogen atom to the free amino acid pool per mole administered, as compared to arginine which adds 2 nitrogen atoms per mole administered. A significant number of patients have low arginine levels +/_ low citrulline levels suggesting non-compliance with dietary supplementation or inadequate supplementation. The low arginine levels may have contributed to the poor growth observed in these patients.

The explanation for the low cysteine levels is not clear to me but the sponsor provided a possible explanation stated above under the mean plasma amino acid values.

b.Significant increases (note: defined as ≥ 2 x ULN except for glutamine which is defined as ≥ 1,000 u mol/L):

glutamine: 44% (55/124).
citrulline: 100% for AS deficiency pts. and 33% for CPS and OTC deficiency pts.
alanine 31% (39/124).
glutamic acid 30% (36/122).
taurine 15% (18/120)
aspartic acid 13% (14/106)
arginine 9% (11/123)
ornithine 7% (9/124)
glycine 6% (7/124)

Significant increases were noted in < 5% patients for the following: serine and proline, each 2%; and asparagine, 1%.

Comment:

for an explanation of the elevations in glutamine, alanine, glutamic acid, aspartic acid and glycine, refer to 1.B.b. above. The elevation in arginine reflects dietary supplementation. For CPS and OTC patients, the elevation in citrulline reflects dietary supplementation, but for patients with AS deficiency, it is secondary to the enzymatic block. For an explanation in the elevation in taurine, refer to 1.B.b. above. The elevation in ornithine occurred primarily in OTC deficiency patients in whom it is due to the enzymatic block.

Literature:

The majority of published articles submitted were authored by Dr. Brusilow. Efficacy and safety from these papers will not be re-presented here (except for # 5) as the NDA patient database is comprehensive in this regard. The following is a review of articles written by others:

1."Ornithine Transcarbamylase Deficiency- A Cause of Bizarre Behavior in a Man" by DiMagno et al:

A 29 yr. old male had a 6 yr. hx. of recurrent episodes of nausea and vomiting associated with jaundice and bizarre behavior (he would become confused, passive, withdrawn, agitated and tearful during these episodes). Hyperammonemia was documented during these episodes. Urinary orotic acid was elevated. OTC activity was assayed in a liver specimen obtained by needle biopsy and was found to be 26% of normal. Hence, a diagnosis of OTC deficiency was definitively established. Cognitive function testing yielded an IQ of 87 (low average intelligence). The patient was placed on protein restriction only and no further episodes occurred.

The authors state that late-onset male patients are generally subject to recurrent episodes of hyperammonemia and therefore require treatment with dietary protein restriction, dietary supplementation with essential amino acids and citrulline and activation of alternate pathways of waste nitrogen synthesis and excretion with sodium benzoate and phenylacetate. Their residual OTC activity generally ranges from 5-30% of normal. The above patient was unusual for his mild clinical presentation and the behavioral abnormalities associated with the HA. The authors also state that his mild clinical presentation is unlike that which occurs in affected female heterozygotes in whom protein restriction alone is often sufficient. Therefore, this patient was treated only with protein restriction.

2."Late onset Ornithine Carbamoyl Transferase Deficiency in Males" by Drogari and Leonard

This article points out the wide phenotypic expression of late-onset OTC deficiency in males and hence, differences in treatment recommendations. Some may be treated with protein restriction only and others may require treatment with agents that activate alternate pathways of waste nitrogen excretion, such as sodium benzoate.

3."Hyperammonemia A Variant Type of Deficiency of Liver Ornithine Transcarbamylase" by Levin et al

A case is described of a child who presented with vomiting and failure to thrive from the age of 6 mos. Acute hyperammonemic coma occurred at 8.5 mos. A diagnosis of OTC deficiency was made by assay of OTC activity in a liver specimen obtained by biopsy. The patient was placed on protein restriction and appears to be growing and developing normally.

4."Partial Ornithine Transcarbamylase Deficiency Associated

with Recurrent Hyperammonemia, Lethargy and Depressed Sensorium" by Oizumi et al

This paper is a detailed presentation of a 6 yr. old boy with late-onset OTC deficiency. Infection would precipitate acute hyperammonemia in this patient. He was diagnosed with OTC deficiency by the finding of a decreased OTC enzyme activity in the liver (16% of normal). He was placed on a low protein diet and arginine supplementation and has since been HA free. Cognitive evaluation on treatment revealed an IQ of 85.

5."Natural History of Symptomatic Partial Ornithine Transcarbamylase Deficiency" by Rowe et al (Brusilow is last author):

13 female patients with **symptomatic partial** OTC deficiency were studied. They presented as early as the first week of life or as late as the sixth year. All presented with episodic irritability, vomiting and lethargy. 46% had a history of coma.Delayed physical growth was present in 38% and developmental delay in 38%. Neurologically 23% had seizures. Five patients had IQ scores < 70 (i.e. were mentally retarded) at the time of diagnosis. All had elevated plasma ammonia levels at diagnosis. Plasma glutamine was elevated in all patients. Urinary orotic acid levels were elevated in 11 patients. The diagnosis of OTC deficiency was confirmed in 8 pts. by finding decreased OTC enzyme activity (2-55% of normal) in liver biopsy specimens. The dx. was confirmed in the other 5 pts. by orotic aciduria associated with HA or episodic HA and a mother with orotic aciduria demonstrated on oral protein challenge. It is recommended that children with partial OTC deficiency be treated with a low protein diet and that alternate pathways of waste nitrogen synthesis and excretion be activated due to the success of this regimen in treating patients hemizygous for OTC deficiency.

Additional information submitted:

On 8/10/95, Dr. Weich submitted a case report of an untreated OTCF heterozygote. The patient presented at age 3.5 yrs. with listlessness and unintelligble speech. At age 4 she presented with another episode marked by restlessness, ataxia and incoherent speech. Plasma ammonia and glutamine levels were elevated. On follow-up 1 week later, the patient appeared to have recovered. Over the ensuing 4 mos., she had 2 more episodes of combativeness or lethargy, inability to stand and incoherent speech. During the last episode of hyperammonemic encephalopathy, an elevated urinary orotate level was found and a diagnosis of OTC deficiency was made. She was treated for acute hyperammonemia at Johns Hopkins Hospital with IV benzoate, phenylacetate and arginine. Although plasma ammonia returned to normal within 24 hrs., she awoke from coma, cortically blind (confirmed by visually evoked responses). Over the next several weeks, on sodium phenylbutyrate, her vision improved and she became ambulatory and communicative. Her most recent school evaluation

reveals an IQ of 70. The case history synopsis states: "...she changed from a bright interactive 9 yr. old to a withdrawn, inattentive confused child". A malpractice suit is pending.

Labeling Review:

Dr. Weich has indicated to me during several phone conversations that he would be sending in revised labeling. However, to date we have not yet received it. Therefore, I will work with the label submitted in February. (Note: Dr. Weich has agreed to a package insert for parents and adult patients).

For the tablets:

Description section:

This section should be revised as per chemistry's recommendations. The sponsor's first two sentences do not belong in the "Description section" and, therefore, should be omitted.

Clinical Pharmacology section:

Rewrite the first paragraph to read: "Sodium phenylbutyrate is a pro-drug and is rapidly metabolized to phenylacetate. Phenylacetate is a metabolically active compound which conjugates with glutamine via acetylation to form phenylacetylglutamine. Phenylacetylglutamine is then excreted by the kidney. On a molar basis, it is comparable to urea (each containing two moles of nitrogen). Therefore, phenylacetyl-glutamine provides an alternate pathway for waste nitrogen excretion.

Omit the second and third paragraphs.

Retain the fourth and fifth paragraphs which begin, respectively: "Pharmacokinetic studies have not bee conducted..." and "Significant gender differences..."

Indications and Usage section:

Revise this section to read: "Ammonapse is indicated as adjunctive therapy in the chronic management of patients with urea cycle disorders involving partial or complete deficiencies of carbamylphosphate synthetase, ornithine transcarbamylase or arginosuccinate synthetase. When combined with dietary protein restriction and essential amino acid supplementation (see Nutritional Supplementation section), the survival rate in newborns diagnosed soon after birth with this disease, previously almost universally fatal within the first year of life, is now approximately 80%. However, approximately 80% of these infants are mentally retarded with the majority being severely retarded. In prospectively-treated patients (diagnosed during gestation and treated immediately at birth) survival is 100%, suggesting that early diagnosis and therapy are important for improving survival. However, there is insufficient data regarding cognitive outcome in prospectively treated patients. The effects of therapy in the late-onset group are difficult to assess due to inadequate baseline and/or follow-up data and failure to accurately document compliance with the therapy. Reversal of pre-existing neurological impairment is not likely to occur with treatment and

neurologic deterioration may continue in some patients."

"On therapy, the majority of patients continue to experience recurrent episodes of acute hyperammonemia."

"Ammonapse may be used for life-long therapy or as a temporizing treatment until liver transplantation is performed."

Nutritional Management:

Rewrite the first seven sentences to read: "To promote growth and development, plasma levels of ammonia, arginine, branched chain amino acids and serum protein should be maintained within normal limits and plasma glutamine maintained at levels less than 1000 umol/L. The allocation of dietary nitrogen into natural protein and essential amino acid is a function of age, residual urea cycle enzyme activity and the dose of sodium phenylbutyrate. At the recommended dose of sodium phenylbutyrate (see Dosage and Administration section), infants with neonatally expressed disorders may tolerate as much as "x" **(clarify if 1.6 but OTC deficiency is up to 2.0)** grams per kg per day of natural protein for the first three months of life. Protein tolerance will decrease as the growth rate decreases requiring a reduction of nitrogen intake. After six months of age, the daily nitrogen intake for these neonatally expressed disorders is "y" **(clarify if 1.25 or 1.40)** grams per kg per day, equally divided between natural protein and amino acid supplementation." Retain sentences 8-12 of this paragraph.

Contraindications section:

Rewrite this section to read: "Ammonapse should not be used to manage acute hyperammonemia which is a medical emergency."

Warnings section:

Rewrite the second paragraph: "Since Ammonapse is primarily excreted by the kidney, use caution when administering the drug to patients with renal insufficiency."

Precautions section:

Omit the first, second, fourth and fifth paragraphs. Retain only the third paragraph which begins: "Ammonapse should not be administered to patients with known hypersensitivities..."

Drug Interactions section:

Replace this section with: "None have been reported."

Pediatric Use:

See Dosage and Administration.

Omit the next paragraph.

Adverse Reactions section:

Replace this section with the following:

Clinical Adverse Events:

In patients with urea cycle disorders, the most

common clinical adverse reaction reported was amenorrhea/menstrual dysfunction which occurred in 6% patients. Other adverse reactions reported in ≤ 3% of patients and for which relationship to drug is not established are: Gastrointestinal- abdominal pain, gastritis, nausea, vomiting, peptic ulcer disease, pancreatitis; Hematologic- aplastic anemia, ecchymoses; Renal- renal tubular acidosis; Psychiatric- depression; Integumentary- rash; Miscellaneous- bad taste/taste perversion, bad odor, headache, syncope and weight gain.

Fasting normal adult subjects receiving a single 5 gram oral dose of Ammonapse, most frequently reported: nausea/vomiting/indigestion/cramping (36% of patients); headache (64% of patients) and light-headedness (27%). These adverse events may be attributable to the drug and/or fasting.

In 12 adult patients with beta thalassemia receiving Amonapse 20 grams/day, in three divided doses, with meals, for 1.5-17.5 mos., epigastric discomfort was reported by 58%, peripheral edema (assocoated with weight gain in one patient, requiring either initiation of thiazide diuretic therapy or an increased dose in two other patients) and bad body odor were each reported by 25% of the patients.

Laboratory Adverse Events:

In patients with urea cycle disorders, the following laboratory adverse events were reported in > 5% of patients: anemia (8%), hyperchloremia (6%) and hypophosphatemia (6%). The following occurred in ≤ 5% of patients: increase in liver transaminases (5%), increases in alkaline phosphatase (5%), acidosis or alkalosis (each 5%), hyperbilirubinemia (4%), hyperurecemia (3%) and hypernatremia (2%). (Note: total leukocyte counts were not reported in these patients).

Overdosage section:

This section is acceptable.

Dosage and Administration section:

Second paragraph:

second sentence: omit the phrase "...as an adjunctive therapy..."

fourth sentence: add "...(i.e. three times per day)." to the end of this sentence.

Omit the third paragraph which begins: "Ammonapse is not intended..."

Labeling for the Powder:

Description section:

This section is identical to the one for tablets and, therefore, **should be revised as per chemistry's recommendations** to reflect the powder.

Dosage and Administration section:

Second paragraph:

omit the second sentence which reads: "It may also be used by adults."

the third and fourth sentences of this paragraph contain several typographical errors: children, 0.60, 13.0. **Please justify your dosing frequency for the powder: 3 to 6 divided doses (per the NDA, volume 6, page 050020, 3 to 4 equally divided doses is recommended.**

Note: Dr. Markofsky should be asked to comment on the accuracy of the seventh sentence in this section.

All my comments pertaining to labeling revisions for the tablets also pertain to the label for the powder.

Post-marketing studies suggested by the sponsor:

Dr. Weich informed me that the following were his suggestions regarding post-marketing studies:

Evaluation and Regulatory Action:

Sodium phenylbutyrate provides an alternate pathway for waste nitrogen excretion in patients with urea cycle enzymatic defects. On this basis, the drug, in conjunction with a low protein diet and amino acid supplementation, permits the majority of patients with the neonatal onset form, to survive a disease that previously was almost universally fatal. In addition, in patients with partial deficiencies, sodium phenylbutyrate may also suppress the patient's residual urea synthesis capacity, which then may be recruited to maintain nitrogen homeostasis under conditions which threaten maintenance of nitogen balance (Brusilow and Finkelstien, Metabolism: 42: 1336-1339, 1993). For these reasons, **sodium phenylbutyrate is approved as adjunctive therapy in the management of patients with urea cycle enzymatic defects.**

Survival in the neonatal onset rescue group is accompanied by retardation in 80% of these patients, with the majority being severely retarded. As a group, despite treatment, these patients grow poorly (probably due to a combination of chronic disease with recurrent hyperammonemia and to the low

levels of branched chain amino acids which were seen in a number of patients) and are subject to recurrent episodes of hyperammonemia.

It is difficult to draw definitive conclusions from the prospectively treated group due to the small sample size, early age of cognitive testing and inadequate follow-up data (due to receipt of a liver transplant in a number of cases). It should be noted that despite treatment at birth, three patients in this group experienced acute hyperammonemia requiring dialysis in the first few days of life. In addition, these patients are also subject to recurrent episodes of hyperammonemia.

It is also difficult to draw definitive conclusions in the late-onset group. Although the biochemical rationale for efficacy has been well established, the degree of clinical benefit is hard to define in this group. Due to the wide phenotypic variability in late-onset patients, a clearly defined baseline is essential to determining efficacy of the therapy as well as reliable assessment of the degree of compliance with the therapeutic regimen. Baseline data was lacking in the majority of patients and compliance was not accurately determined.

Sodium phenylbutyrate has an acceptable safety profile as detailed in my review.

The following are additional requests to be conveyed to the sponsor:

1. Deaths, withdrawals, clinical and laboratory adverse events, should include both evaluable and not evaluable patients.
2. Provide details regarding the following clinical adverse events:
   - drug interaction- patient #159
   - aplastic anemia- #618
   - ecchymoses- #576
   - pancreatitis- #618
   - renal tubular acidosis- #'s 629 and 642
   - rash- #'s 485 and 613
3. On Ammonapse, were abnormalities noted in either total leukocyte counts or urinalyses/microscopy?
4. Clarify the cognitive outcome of the 9 yr. old untreated OTC female heterozygote patient whose case was submitted on 8/10.
5. Revise the label for Ammonapse tablets and powder (CSO: see my comments above under "Labeling Review").
6. Submit a package insert for patient/parent/guardian use.
7. Regarding plasma amino acid levels, please report units of measurement and, for patients with "0" values, clarify if the level was zero or the assay was not done.

Jean Temeck
Jean Temeck, M.D.

enclosures: 1. Dr. Brusilow's hand-out for 3/20/95 meeting with FDA
2. Memorandum of FDA internal meeting, 6/14/95
3. Memoranda of teleconferences 6/26 and 7/7/95 with sponsor.

Gilbert Trawick
11-7-95

4.Mr. Marticello's e-mail to me dated 8/3/95 regarding the sponsor's statistical analysis of the hyperammonemic episodes.

cc. HFD-510: Dr. Sobel, Dr. Troendle, Dr. Moore, Dr. Markofsky, Ms. Galliers and Ms. Pauls
HFD-427: Dr. Ahn

Statistical Review

NDA 20-572 (Ammonapse tablets, 500 mg)
NDA 20-573 (Ammonapse powder)
Ucyclyd Pharma, Inc.

Statistical Review

No Statistical Review was required, because there were no controlled studies

4/23/96

BIO Review

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA 20-572/573
Ammonapse
Sodium phenylbutyrate, 500 mg tablets/powder

SUBMISSION DATE: April 15, 1996

Ucyclyd Pharma, Inc.
Baltimore, MD

REVIEWER: Hae-Young Ahn, Ph.D.

SUBMISSION TYPE: Amendment

APR 24 1996

SUBMISSION:

A couple of literature references which report neurotoxicity resulting from infusions of phenylacetate to cancer patients were sent to the Division of Pharmaceutical Evaluation II. In one article (Cancer, 75, 2932-2938, 1995), neurotoxicity was observed at peak plasma level of 490 μg/mL and greater, and in the other article (Cancer Res. 54, 1690-1694, 1994) it was observed at 900 μg/mL. This reviewer was asked by the reviewing medical officer to investigate whether any plasma levels of phenylacetate higher than 490 μg/mL were reported in the original NDA submitted on February 15, 1995. There was one male cirrhotic patient with portal hypertension who had a peak plasma level of phenylacetate of 3.300 mM (mol. wt of phenylacetate: 159.14, 524.70 μg/mL) after he received 20g/day of sodium phenylbutyrate orally as tablets for 3 days. The patient had a peak concentration of 1.74 mM (276.90 μg/mL) on Day 1. The accumulation factor was estimated to be about 5 based on trough levels (Attachment).

4/24/96

Hae-Young Ahn, Ph.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD initialed by J. Hunt, Deputy Director 4/23/96

FT initialed by J. Hunt, Deputy Director 4/24/96

cc: NDA 20-572/573, HFD-510(Temeck and Short), HFD-880(Fleischer), HFD-860(Malinowski), HFD-870 (Ahn and M. Chen), HFD-340(Vish), HFD-850 (Lesko), HFD-870 (Chron, Drug, Review), FOI(HFD-205)

SEP 1 5 1995

NDA 20-572/20-573
Ammonapse
Sodium phenylbutyrate, 500 mg tablets
Sodium phenylbutyrate, powder

SUBMISSION DATE: February 15, 1995
May 16, 1995
July 14, 1995

Ucyclyd Pharma, Inc.
Baltimore, MD

REVIEWER: Hae-Young Ahn, Ph.D.

SUBMISSION TYPE: Original (NME) CODE: 1P

SYNOPSIS: The sponsor has submitted two NDAs for sodium phenylbutyrate that is in the oral dosage forms of tablets and powder. Sodium phenylbutyrate was designated as an orphan drug indicated for the treatment of urea cycle disorders (UCD) in patients with inborn errors of ureagenesis. The use of tablets is indicated for children weighing more than 20 kg and adults. The usual total daily dose of Ammonapse tablets as an adjunctive therapy for UCD patients is 9.9 - 13.0 g/m^2/day. The tablets are to be taken in equally divided amounts with each meal. The use of Ammonapse powder is primarily indicated for neonates, infants and children weighing less than 20 kg. It may also be used by adults. The usual total daily dose of Ammonapse powder for neonates, infants and children diagnosed for UCD is 0.45 - 0.60 g/kg/day given as three to six equally divided doses. For those patients weighing more than 20 kg, the total daily dose is 9.9 - 13.0 g/m^2/day. The powder is recommended to be diluted in four to eight ounces of infant formula or milk and administered with meals. Ammonapse is not intended as sole therapy for UCD patients. It should be combined as adjunctive therapy with dietary management consisting of a defined protein diet, amino acid supplementation in some patients and caloric supplementation for optimal results. The proposed daily dose for patients are as follows:(Note:For all patients, the daily dosage is to be taken in 3-4 equally divided doses.)

Patient	Body Weight (Kg)	Grams/day
Neonate	3.3	2.0 (0.6 g/kg/d)
One Year	10.0	6.0 (0.6 g/kg/d)
Three Year	14.0	8.0 (0.57 g/kg/d)
Five Year	17.0	10.0 (0.59 g/kg/d)
Ten Year	34.0	15.0 (0.44 g/kg/d)
Fifteen	57.0	18.0 (0.32 g/kg/d)
Adult		20.0

Limited pharmacokinetic information (plasma levels of phenylbutyrate, phenylacetate, and phenylacetylglutamine) was submitted from uncontrolled studies in normal male subjects, adult patients with cirrhosis, children patients with UCD and adult patients with homozygous beta thalassemia.

The sponsor has conducted a three-way cross-over bioequivalence study comparing the clinical trial tablet formulation, the to-be-marketed tablet formulation and the clinical trial powder

formulation under fasting conditions. The clinical trial tablet formulation and the to-be-marketed tablet formulation were found to be bioequivalent. It was also found that the clinical trial tablet formulation and the clinical trial powder formulation were bioequivalent. (Note: The formulations of clinical trial powder and the to-be-marketed powder are identical but the manufacturing processes are different.) Statistically significant gender differences were found in the pharmacokinetics of phenylbutyrate and phenylacetate, but not for phenylacetylglutamine.

The proposed package insert indicates that the drug be taken with each meal. A food effect study was not conducted but this reviewer was told by the sponsor that clinical trials were uncontrolled studies and the drug was taken with or without food. It was also indicated that people who had participated in the bioequivalence study made complaints about stomach pain because the drug was taken under fasting conditions.

RECOMMENDATION:

The Division of Biopharmaceutics (HFD-420) has reviewed 1) NDA 20-572 and NDA 20-573 which were submitted on February 15, 1995 and 2) the two NDA amendments that were submitted on May 16, 1995 and July 14, 1995. HFD-420 finds NDA 20-573 approvable but for NDA 20-572, additional dissolution data on the to-be-marketed tablet formulation are needed as covered under Comment #1 prior to its approval. HFD-420 also finds that limited pharmacokinetic information which was submitted from uncontrolled studies in normal male subjects, adult patients with cirrhosis, children patients with urea cycle disorders and adult patients with homozygous beta thalassemia are less than desirable and can not be validated.

Please convey the Recommendation, as appropriate, Comment #1 - #3 and the Labeling Comments #1 and #2 to the sponsor.

(Note: The Division of Biopharmaceutics is retaining the review's Appendix II and Attachment I within its drug file and it may be obtained upon request.)

TABLE OF CONTENTS

	Page
Synopsis	1
Recommendation	2
Background	3
Summary	
Bioavailability/Bioequivalence	3
Uncontrolled Studies	4
Pharmacokinetics of Phenylacetate	4
Assay	5
Formulations	5
Dissolution	6
Comments	7
Labeling Comments	7
Appendix I	9
Appendix II	15
Attachment I (package insert)	16

BACKGROUND:

Sodium phenylbutyrate is the pro-drug of phenylacetate which conjugates with glutamine to form phenylacetylglutamine. Sodium phenylbutyrate when administered to patients with UCD provides a vehicle for the elimination of waste nitrogen. Urea cycle disorders is a rare disease characterized by the partial or complete absence of one of the following enzymes of the urea cycle: a) carbamylphosphate synthetase; b) argininosuccinic acid synthetase or c) ornithine transcarbamylase. As a result of the deficiency of any one of these enzymes, the synthesis of urea is nearly completely inhibited or, if present to such a small degree, nitrogen homeostasis is difficult to maintain. Currently there are only 118 patients under treatment with sodium phenylbutyrate. For patients that are untreated, the disease is fatal within the first year of life.

SUMMARY:

Bioavailability/Bioequivalence:

From Study No. 139-01-10753, following a single oral dose of 5g phenylbutyrate, phenylbutyrate was measurable in the plasma within 15 minutes. Measurable levels of phenylacetate were found 30 minutes after dosing and phenylacetylglutamine was found shortly thereafter. Neither phenylbutyrate, phenylacetate nor phenylacetylglutamine were measurable in the plasma 12 hours after dosing. The two tablet formulations (the clinical trial formulation and the to-be-marketed formulation) were found to be bioequivalent with the Agency's Two One-Sided Tests Procedure (90% confidence intervals), using log transformed AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} data for phenylbutyrate, phenylacetate and phenylacetylglutamine. It was also found that the clinical trial tablet formulation and the clinical trial powder formulation (the to-be-marketed powder) were bioequivalent for the three analysts, except for phenylbutyrate C_{max}. It was found that females had larger AUC and higher C_{max} for phenylbutyrate and phenylacetate than males.

No gender differences were observed for the pharmacokinetic parameters of phenylacetylglutamine. (Note: No significant differences in body weights are found between genders.)

Uncontrolled Studies:

The following information was provided from uncontrolled studies: (Note: A few studies employed only one subject. The maximum number of subjects who were evaluated in a study was six.)

Normal Subjects in two case studies received a single oral dose of 2.5 g (n=2) or 5 g (n=1) of sodium phenylbutyrate. Sodium phenylbutyrate was found to be rapidly absorbed and converted to phenylacetate. PAA was then excreted in the urine as phenylacetylglutamine. A majority of the administered sodium phenylbutyrate (70 to 100%) was excreted by the kidney within twenty-four hours as phenylacetylglutamine.

Seven children with urea cycle disorder received 0.45 - 0.6 g/kg/d of sodium phenylbutyrate. One blood sample from each child was drawn in next moring and there were no detectable levels of sodium phenylbutyrate or phenylacetate approximately 10 hours after the last dose. Mean plasma level (±SD) of phenylacetylglutamine was 0.13 (±0.08) mM.

Patients with cirrhosis in three case studies received a single oral dose of 2.5 g of sodium phenylbutyrate or multiple doses of sodium phenylbutyrate given as 20 g/day in 3 divided doses as tablets. (Note: Each study included one, four and six patients.) Plasma levels of phenylbutyrate (PBA), phenylacetate (PAA) and phenylacetylglutamine (PAG) were comparable to those observed in normal subjects. (Note: For normals who received a single oral dose of 2.5 g of sodium phenylbutyrate, C_{max} of PBA, PAA and PAG were approximately 0.7, 0.19 and 0.14 mM, respectively. For patients with cirrhosis, following a single oral dose of 2.5 g of sodium phenylbutyrate, C_{max} of PBA, PAA and PAG were approximately 0.7, 0.19 and 0.18 mM, respectively.) Approximately 50 to 75% of the administered sodium phenylbutyrate single dose was recovered in urine within 8 hrs as phenylacetylglutamine. After multiple doses, an average of 71% of the administered dose was excreted.

Patients with homozygous beta thalassemia were treated with multiple doses (the range of 18 or 20 g/day) of sodium phenylbutyrate. Trough plasma levels of phenylacetate were < 1.0mM and showed no progressive accumulation. Serial 24 hour urine collections showed a mean excretion of 75 ±13% (53-97%) of the administered sodium phenylbutyrate as urinary phenylacetylglutamine.

Pharmacokinetics of Phenylacetate

Information was provided where patients received a single iv bolus followed by a 14-day continuous iv infusion of phenylacetate. Phenylacetate displayed non-linear pharmacokinetics. There was an evidence for induction of clearance. Ninety-nine percent of phenylacetate elimination was accounted for by conversion to phenylacetylglutamine, which was excreted in the urine.

Assay:

Formulations:

The clinically tested tablets and powder with sodium phenylbutyrate were formulated, manufactured and packaged at The manufacturing site for the to-be-marketed tablets and powder formulations was changed to in July, 1994.

The tablet formulation is as follows:

Component	Amount per tablet
Sodium Phenylbutyrate, powder	500.00 mg
Colloidal Silicone Dioxide, NF	

The tablet formulation is as follows:

Component	Amount per tablet
Sodium Phenylbutyrate, powder	500.00 mg
Colloidal Silicone Dioxide, NF	
Magnesium Stearate, NF	

The formulation for the powder (94% wt/wt) is as follows:

Component	Amount
Sodium Phenylbutyrate, powder	940.0 mg (94.0%)
Colloidal Silicone Dioxide, NF	

Dissolution:
The dissolution tests were conducted in

Effect of paddle speed on percent released

Time(min)	
15	
30	
45	
60	98.3
90	
120	

Medium:

Effect of media on percent released

Time(min)	
15	
30	
45	
60	
90	
120	

Paddle speed:

The sponsor is proposing a dissolution method and specification as follows:

(1) Apparatus Type:
(2) Media: Water
(3) Speed of Rotatior.
(4) Recommended Dissolution Specification: Not less than in 45 min.

COMMENTS:

1. Additional dissolution related information is needed as covered below:

   a. A pH solubility profile of the drug.

   b. A complete assay description and assay validation i.e., sensitivity, linearity, % accuracy and precision (within and between runs) for the analysis of the drug in each dissolution medium.

   c. Individual dissolution profiles plus mean dissolution profiles (±SD) at .

   d. pH of medium before and after dissolution tests when is used as a medium.

   (Note: The items raised under Comment No.: (a and b) and (c) above were previously communicated to the sponsor on May 15, 1995 and July 25, 1995, respectively.)

2. Pharmacokinetic parameters such as C_{max}, T_{max}, terminal $t_{1/2}$ and clearance for sodium phenylbutyrate plus C_{max}, T_{max}, and terminal $t_{1/2}$ for phenylacetate need to be calculated from the bioequivalence study and inserted appropriately in the package insert.

3. It is recommended that analyses of pharmacokinetic parameters based on race be conducted and the results be inserted appropriately in the package insert.

LABELING COMMENTS:

1. A Pharmacokinetic subsection under the Clinical Pharmacology section of the package insert should be added. The following changes are recommended to be included.

Pharmacokinetic studies have not been conducted in the primary patient population (neonates, infants, and children) but pharmacokinetic data were obtained from normal adult subjects.

Absorption
Peak plasma levels of phenylbutyrate occur within one hour after a single oral dose with a C_{max} of (?) under fasting conditions. The effect of food on phenylbutyrate's absorption is unknown

Disposition and Metabolism
The overall disposition of sodium phenylbutyrate and its metabolites has not been fully characterized. However, it was found that sodium phenylbutyrate is metabolized to phenylacetate and subsequently to phenylacetylglutamine. Following oral administration, measurable plasma levels of phenylbutyrate and phenylacetate were found 15 and 30 minutes

after dosing, respectively and phenylacetylglutamine was found shortly thereafter. Information about terminal $t_{1/2}$ and clearance for sodium phenylbutyrate plus C_{max}, T_{max}, and terminal $t_{1/2}$ for phenylacetate needs to be inserted appropriately. The major sites for metabolism are the liver and kidney.

Excretion
A majority of the administered compound (approximately 80-100%) was excreted by the kidney within 24 hours as the conjugation product, phenylacetylglutamine. This suggests the production of between 0.10-0.13 grams of phenylacetylglutamine nitrogen for each 1 gram dose of phenylbutyrate.

Special Population
Gender: Significant gender differences were found in the pharmacokinetics of phenylbutyrate and phenylacetate but not for phenylacetylglutamine. The pharmacokinetic parameters, AUC and C_{max} for both plasma phenylbutyrate and phenylacetate were about 30% - 50% greater in females than in males. However, the clinical significance for this difference is not known.
Hepatic Insufficiency: Impaired hepatic function did not seem to affect the metabolism and excretion of sodium phenylbutyrate. This information, however, is obtained from unvalidated, uncontrolled case studies.

2. If the sponsor has any in-house data and/or literature pharmacokinetic information on Geriatrics, Pediatrics, Race, Renal insufficiency, and Drug-Drug Interactions, the information needs to be added under the Special Population part of the Pharmacokinetic subsection of the package insert's Clinical Pharmacology section.

9/14/95
Hae-Young Ahn, Ph.D.

RD initialed by J. Hunt 8/31/95
Biopharm Day (9/07/95, Collins, Malinowski, M. Chen, Fleischer, Hussain, Hunt, Troendle, Temeck)
FT initialed by J. Hunt 9/15/95

cc: NDA 20-572/3, HFD-510(Temeck and Spires), HFD-340(Vish), HFD-426(Fleischer), HFD-427 (Ahn and M. Chen), Chron, Drug, Review, FOI(HFD-19), Gender, Race

APPENDIX I

I. UNCONTROLLED STUDIES

Normal Subjects

Two male volunteers received 2.5 g of sodium phenylbutyrate orally as five 500 mg tablets. Blood samples were drawn for 8 hours and urine was collected up to 12 hours. Peak plasma levels of PBA were 0.625 mM and 0.702 mM at 0.5 hr. Peak plasma levels of PAA were 0.084 mM (1.5 hr) and 0.468 mM (3.5 hr). Peak concentrations of PAG were 0.158 mM (1.5 hr) and 0.128 mM (1.5 hr). For one subject, 85.6% of the sodium phenylbutyrate administered was recovered as PAG in the urine in 12 hour and for the other subject, 71.1% was recovered in 8 hour.

One male volunteer received a single oral dose of 5.0 g of sodium phenylbutyrate under fasting conditions. (Note:No statement whether it was given as tablets or powder.) Blood samples were drawn for 24 hours and Urine was collected up to 24 hours. Peak plasma level of PB was 0.696 mM at 1.5 hr and 2.5 hr after administration. Peak plasma levels of PAA were 0.232 mM measured at 3.5 hr postdosing. Peak concentrations of PAG were 0.328 mM measured at 3.5 hr postdosing. 91.5% of the sodium phenylbutyrate administered was recovered as PAG in urine for 24 hours.

Patients with urea cycle disorder

Seven hospitalized children received sodium phenylbutyrate and dosage level was 0.45 - 0.6 g/kg/d. The morning fasting levels (approximately 10 hours after the last dose) of PBA, PAA and PAG were measured. There were no detectable levels of PB or PAA. The mean plasma level (±SD) of PAG was 0.13 (+0.08) mM.

Patients with cirrhosis

One male patient received 2.5 g of sodium phenylbutyrate tablets under fasting conditions. The peak plasma level of PBA was 0.769 mM at 0.5 hr after administration. The peak plasma level of PAA were 0.188 mM measured at 4.0 hr postdosing. The peak concentration of PAG was 0.065 mM measured at 4.0 hr postdosing. 53.3 % of the sodium phenylbutyrate administered was recovered as PAG in urine for 8 hours.

Four male patients received 2.5 g of sodium phenylbutyrate orally as five 500 mg tablets while fasting. Peak plasma levels of PBA occurred 1 hour after administration and ranged from 0.529 to 1.03 mM. The mean peak plasma level of PAA was 0.197 (±0.179) mM measured between 2 and 5 hours postdosing. The mean peak concentration of PAG was 0.163 mM which occurred between 2 and 5 hours postdosing. About 74 % of the sodium phenylbutyrate administered was recovered as PAG in urine for 8 hours.

Six male patients with portal hypertension received 20g/day of sodium phenylbutyrate as tablets in three divided doses for three consecutive days. On day 1, mean peak plasma level of PB was 1.547 (±0.630) mM. The mean peak plasma levels of PAA and PAG were 0.896 (±0.558) mM and 1.012 (±0.666) mM, respectively. On day 3, the mean peak plasma level of PBA was 1.219 (±0.450) mM. Mean peak plasma levels of PAA and PAG were 1.728 (±1.183) mM

FIRM:UCYCLYD
TRADE NAME:BUPHENYL POWDER
GENERIC NAME:SODIUM PHENYLBUTYRATE

and 1.517 (±1.086) mM, respectively. An average of 70.8% of the phenylbutyrate administered over three days was recovered as PAG in urine and an average of only 1% of the phenylbutyrate administered over three days was recovered as unconjugated phenylacetate in urine.

Patients with Hemoglobinopathies
Eight patients were administered the range of 18 and 20 g/day of sodium phenylbutyrate in three divided doses for several days. Peak daytime plasma levels of PBA, PAA and PAG ranged between 0.60 - 1.70 mmol/L, 0.50 - 1.50 mmol/L and 0.56 - 2.67 mmol/L, respectively. Twenty four hour urine collections showed a mean of 76 ± 13% (54 - 97%) of the molar amount administered sodium phenylbutyrate excreted as urinary PAG.

II. BIOEQUIVALENCE (Study No.:139-01-10753)

Objectives:
1. To compare the absorption and pharmacokinetics of phenylbutyrate from two test sodium phenylbutyrate formulations (tablets and powder) with a reference formulation following single-dose administration to healthy male and female volunteers.
2. To compare the pharmacokinetic behavior of phenylacetate between the test and reference formulations.
3. To compare the pharmacokinetic behavior of phenylacetylglutamine between the test and reference formulations.
4. To compare the pharmacokinetic behavior of phenylbutyrate, phenylacetate and phenylacetylglutamine between the male and female subjects.

Study Design: A random, three-period crossover design with 7 days washout period.
Populations: Twenty four subjects were recruited but 21 subjects (11 female and 10 male) completed the study. At each of the three study periods, subjects received 5 g of sodium phenylbutyrate tablets (Lot No. F-032-022) manufactured by sodium phenylbutyrate tablets (Lot No. 23210694) manufactured by the or sodium phenylbutyrate powder (Lot No. 28110694) manufactured by the . The tablet formulations were administered with 300 mL of water. The powder formulation was dissolved in 150 mL of apple juice and administered. Volunteers fasted for at least 10 hours prior to drug administration until five hours postdose.

Assay: method was used and found to be acceptable.

Results:

Table 1. Mean (%CV) plasma phenylbutyrate pharmacokinetic data

	Tablet	Powder	Tablet
AUC_{0-t} (μg.hr/mL)	577.3 (31)	493.8 (28)	586.0 (25)
$AUC_{0-\infty}$ (μg.hr/mL)	609.8 (31)	525.6 (28)	631.4 (27)
C_{max} (μg/mL)	218.0 (25)	195.2 (25)	240.1 (21)
T_{max} (hr)	1.35 (49)	1.0 (35)	1.20 (37)

Table 2. Mean (%CV) plasma phenylacetate pharmacokinetic data

	Tablet	Powder	Tablet
AUC_{0-t} (μg.hr/mL)	210.6 (47)	187.6 (41)	231.2 (52)
$AUC_{0-\infty}$ (μg.hr/mL)	224.0 (44)	207.5 (37)	248.7 (48)
C_{max} (μg/mL)	48.5 (39)	45.3 (36)	53.7 (45)
T_{max} (hr)	3.74 (22)	3.55 (18)	3.74 (19)

Table 3. Mean (%CV) plasma phenylacetylglutamine pharmacokinetic data

	Tablet	Powder	Tablet
AUC_{0-t} (μg.hr/mL)	306.0 (25)	267.7 (24)	301.4 (20)
$AUC_{0-\infty}$ (μg.hr/mL)	393.8 (22)	344.3 (21)	398.1 (18)
C_{max} (μg/mL)	68.5 (20)	62.8 (17)	69.2 (26)
T_{max} (hr)	3.43 (14)	3.23 (13)	3.40 (21)

The study showed the two tablet formulations to be bioequivalent, using the Agency's Two One-Sided Tests Procedures (90% confidence interval) for log-transformed AUC0-t, AUC0-∞ and Cmax. The powder formulation was bioequivalent to the tablet formulation, except for phenylbutyrate Cmax (90% CI: 76% to 86%).

Table 4. Average bioequivalence of tablets and tablets using Two One-Sided Tests Procedures on log-transformed data

	phenylbutyrate		phenylacetate		phenylacetylglutamine	
	Ratio of means	90% CI	Ratio of means	90% CI	Ratio of means	90% CI
AUC_{0-t} (μg.hr/mL)	97	94 - 101	93	87 - 99	101	97 - 105
$AUC_{0-\infty}$ (μg.hr/mL)	96	93 - 99	92	87 - 97	99	95 - 102
C_{max} (μg/mL)	90	84 - 96	92	86 - 99	100	94 - 108

Table 5. Average bioequivalence of powder and tablets using Two One-Sided Tests Procedures on log-transformed data

	phenylbutyrate		phenylacetate		phenylacetylglutamine	
	Ratio of means	90% CI	Ratio of means	90% CI	Ratio of means	90% CI
AUC_{0-t} (μg.hr/mL)	84	81 - 87	87	82 - 93	89	85 - 92
$AUC_{0-\infty}$ (μg.hr/mL)	84	81 - 86	90	85 - 95	89	86 - 93
C_{max} (μg/mL)	81	76 - 86	90	84 - 97	92	86 - 98

ANOVA analyses showed that there were statistically significant gender differences for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} in the pharmacokinetics of phenylbutyrate and phenylacetate, but not for phenylacetylglutamine.

Table 6. Mean (%CV) plasma pharmacokinetic parameters by sex

	phenylbutyrate		phenylacetate		phenylacetylglutamine	
	male	female	male	female	male	female
AUC_{0-t} (μg.hr/mL)	480.1 (33)	622.1 (18)	154.4 (36)	245.8 (32)	282.7 (23)	297.7 (23)
$AUC_{0-\infty}$ (μg.hr/mL)	515.6 (35)	661.0 (19)	170.1 (36)	264.2 (28)	359.5 (17)	401.2 (21)
C_{max} (μg/mL)	192.5 (20)	242.6 (16)	39.2 (30)	55.1 (28)	36.4 (19)	66.9 (18)
T_{max} (hr)	1.18 (24)	1.21 (32)	3.62 (13)	3.73 (14)	3.25 (15)	3.43 (10)
Half-life (hr)	0.78 (45)	0.82 (24)	1.20 (18)	1.26 (18)	2.12 (26)	2.66 (23)

Conclusion:

The study showed the two tablet formulations (the clinical trial formulation and the to-be-marketed formulation) to be bioequivalent for phenylbutyrate, phenylacetate and phenylacetylglutamine. It was also found that the clinical trial tablet formulation and the clinical trial powder formulation (the to-be-marketed powder formulation) were bioequivalent based on pharmacokinetics of phenylacetate which is an active moiety.

Statistical gender differences were found in the pharmacokinetics of phenylbutyrate and phenylacetate, but not for phenylacetylglutamine.

Pharmacologist Review

NDAs 20-572 and 20,573 4/23/96
Ammonapse tablets and powder
Ucyclyd Pharma, Inc

Pharmacology Review of Neurotoxicity Data

I have reviewed the literature on phenylacetate neurotoxicity in animals and the following paragraph should be added to the end of the precautions section of the labeling.

Neurotoxicity of phenylacetate in animals
When given subcutaneously to rat pups, phenylacetate caused decreased proliferation and increased loss of neurons and reduced CNS myelin. There was retardation of cerebral synapse maturation and reduced numbers of functioning nerve terminals in the cerebrum with a net effect of impaired brain growth. Prenatal exposure of rat pups to phenylacetate produced lesions in layer 5 cortical pyramidal cells; dendritic spines were longer and thinner than normal and reduced in number.

A Jordan 4/23

Alex Jordan, PhD

NDA 20-572; 20-573
HFD-510
AJordan

NDA 20-572 / 21-573 January 18, 1996

Ucyclyd Pharma, Inc.
Baltimore, MD

Submission: 2/17/95

Pharmacology Review of NDA

Drug: Ammonapse (sodium phenylbutyrate), tablet

Indication: Adjunctive therapy for the chronic management of patients with urea cycle disorders.

The sponsor submitted no toxicology and limited pharmacology. The drug is under investigation in the Division of Oncology and the pharm/tox review is appended. The active metabolite, phenylacetate is an approved drug (Ucephan)

Pharmacology:

Phenylbutyrate is converted to phenylacetate by beta-oxidation in mammalian liver and kidney. In higher primates, phenylacetate is conjugated in the liver and kidney with glutamine to form phenylacetylglutamine which serves as a substitute vehicle for waste nitrogen excretion.

Human pK data show that after administration of a 5 g tablet, the AUC (to infinity) for phenylbutyrate was 610 ug.hr/ml; phenylacetate was 224 ug.hr/ml and phenylacetylglutamine was 394 ug.hr/ml. These data show that although phenylbutyrate may be a prodrug, significant systemic concentrations are reached following tablet administration.

Urea cycle disorder (UCD) is a rare disease (approximately 150-200 patients currently under treatment) characterized by the partial or complete absence of one of the following enzymes of the urea cycle; carbamylphosphate synthetase; argininosuccinic acid synthetase; ornithine transcarbamylase. Because of the enzyme deficiency, urea synthesis (and nitrogen removal) is inhibited. Without treatment, the disease is fatal to newborns. Adults can be maintained with low protein diets, etc but hyperammonemia can be fatal.

Evaluation:

The sponsor provided no animal safety data on phenylbutyrate and none are required. The clinical safety data are sufficient to support the safety of this drug for the treatment of this indication.

Labelling: Label is satisfactory.

Conclusion: Pharmacology recommends approval of Ammonapse for the treatment of urea cycle

disorders.

A Jordan 1/18

Alex Jordan, PhD

ATTACHMENT

NDA 20-572 NDA + 20-[illegible]
HFD-510 (2)
AJordan
CSO

Chemist Review

DIVISION OF Metabolism and Endocrine DRUG PRODUCTS
Review of Chemistry, Manufacturing, and Controls

NDA#: 20-573 **CHEM.REVIEW #:** 3 **REVIEW DATE:** 4-29-96

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	2-15-95	2-17-96	2-22-95
Amendments	2-13-96	2-15-96	
	2-22-96	2-23-96	
	3-7-96	3-8-96	
	4-1-96	4-2-96	
	4-8-96	4-9-96	
	4-12-96	4-15-96	
	4-24-96	4-24-96	
	4-25-96	4-26-96	

NAME & ADDRESS OF APPLICANT:

Ucyclyd Pharma, Inc.
10819 Gilroy Road
Suite 100
Hunt Valley MD 21031
Tel.: 410-584-8188

DRUG PRODUCT NAME:

Proprietary: Ammonapse Powder
Nonproprietary: Sodium Phenylbutyrate [USAN] (Powder)
Code Name/#: CAS-1716-12-7
Chem. type/Ther. Class: 1 PV

PHARMACOL.CATEGORY/INDICATION:

Treatment for hyperammonemia, a condition in which ammonia accumulates in the body because nitrogen compounds can not be converted to urea.

DOSAGE FORM: Powder (Oral)

STRENGTHS: 500 g of sodium phenylbutyrate/bottle
250 g of sodium phenylbutyrate/bottle

ROUTE OF ADMINISTRATION: Oral
DISPENSED: ___X___ Rx _____ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT.:

Sodium Phenylbutyrate, $C_{10}H_{11}O_2Na$, Mol Wt = 186.18
Structure: See Review # 1

SUPPORTING DOCUMENTS: NDA 20-573

RELATED DOCUMENTS: NDA 20-572

CONSULTS:

REMARKS/COMMENTS:

The amendment, dated 2-13-96 provides information on the many deficiencies delineated in Review # 1.

The amendment of 3-7-96 provides up-dated information on the drug product for In-Process Control Tests, Regulatory Specifications, the Container Closure system, Stability and Labeling.

The 4-1-96 amendment is a response to the deficiencies noted in the Agency's letter to the applicant, dated 2-16-96.

The 4-8-96 amendment provides revised labeling.

The amendments of 2-22-96, 4-12-96, and 4-25-96 provide Environmental Assessment information.

In response to our Facsimile transmission of 4-23-96, the amendment, dated 4-24-96, corrects minor deficiencies (mostly typographical errors) with respect to Regulatory Specifications, In-Process Specifications, Stability (forms), and Labeling.

CONCLUSIONS & RECOMMENDATIONS:

The application is approvable, from a Chemistry point of view. The following comment should be communicated to the applicant:

Please insert the word "level" before the words "teaspoon" and "tablespoon" in those sections of the physician's and patient's package inserts which describe how the drug should be dispensed.

Requested - FAX Ltr 4/30/96

cc:
Orig. NDA 20-573
HFD-510/Division File
HFD-510/Sheldon Markofsky/4-29-96
HFD-510/J. Short(CSO)
HFD-510/S. Moore(Team Leader)
HFD-510/Y-Y. Chiu

Sheldon Markofsky 4-29-96
Sheldon Markofsky, Review Chemist

R/D Init by: Team Leader

filename: n20573.31

Stephen Moore 4/29/96

APR 11 1996 546

REQUEST FOR TRADEMARK REVIEW

To: Labeling and Nomenclature Committee
Attention: Dan Boring , Chair, HFD-530 NLRC 200 HFD-530

From: Division of Metabolism and Endocrine D. P./ HFD-510
Attention: Sheldon Markofsky Phone: (301) 443-3520

Date: 2-5-96

Subject: Request for Assessment of a Trademark for a Proposed Drug Product

Proposed Trademark (s): **NDA #: 20-573**

Company Name: Ucyclyd Pharma Inc.

Established name, including dosage form: Sodium Phenylbutyrate Powder (Oral)

Other trademarks by the same firm for companion products: Ammonapse Powder (Oral)

Indications for Use (may be a summary if proposed statement is lengthy):
Treatment of hyperammonemia, a condition in which ammonia accumulates in the body because nitrogen compounds can not be converted into urea.

Initial comments from the submitter (concerns, observations, etc.):
The name "Ammonapse" has been approved by the Labeling and Nomenclature Committee, but the applicant desires to change the name (see attached) .

NDA 20-573, for this orphan drug, has been given an "approvable" status by the Agency. The applicant has been requested to submit additional chemistry information.

filename: n20572t

NOTE: *Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.*

Rev Oct. 1993

Consult #546 (HFD-510)

sodium phenylbutyrate oral powder

The Committee had no overwhelming objections to the use of

however, it was noted that ceph is widely associated with cephalosporins and the trademarks with the syllable -CEPH had a potential for confusion with cephalosporin products. was unacceptable due to its similarity with conjugated estrogens and its use of -ASE as a syllable. The USAN council has adopted -ASE as a stem syllable for enzymatic products and it's use should be discourged in non-enzyme applications. was unacceptable due to its similarity to a marketed product containing urea.

R W Boring 4/4/96, Chair

CDER Labeling and Nomenclature Committee

APR 2 9 1996

ENVIRONMENTAL ASSESSMENT

AND

FINDING OF NO SIGNIFICANT IMPACT

FOR

SODIUM PHENYLBUTYRATE POWDER

NDA 20-573

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

DIVISION OF METABOLISM AND ENDOCRINE
DRUG PRODUCTS (HFD-510)

FINDING OF NO SIGNIFICANT IMPACT

NDA 20-573

Sodium Phenylbuyrate Powder

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 sodium phenylbutyrate powder, Ucyclyd Pharma, Inc. has prepared an abbreviated environmental assessment in accordance with 21 CFR 25.31a(b)(3) (attached) which evaluates the potential environmental impacts of the manufacture, use and disposal of the product.

Sodium phenylbutyrate is a synthetic drug which will be administered orally in the treatment of patients with urea cycle disorders. The product has Orphan Drug status.

The drug substance will be manufactured by a contract manufacturer whose identity is classified as confidential business information. The drug product will be manufactured by [redacted]. The finished drug product will be used in hospitals, clinics and by patients in their homes.

Sodium phenylbutyrate may enter the environment from excretion by patients, from disposal of pharmaceutical waste or from emissions from manufacturing sites. Due to the small, dispersed patient population and metabolism of the drug product to a naturally occurring compound, environmental effects from use are not expected.

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 will be sent to licensed disposal companies. At U.S. hospitals and clinics, empty or partially empty packages will be disposed according to hospital/clinic 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, while 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.

4/28/96
DATE

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

4/29/96
DATE

CONCURRED
Roger L. Williams, M.D.
Deputy Center Director for Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment: Environmental Assessment

END

BT

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