

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-645

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # 20-645 SUPPL # _____

Trade Name: Ammonul Generic Name (sodium phenylacetate/sodium benzoate) 10%/10%

Applicant Name Ucyclyd Pharma, a wholly owned subsidiary of Medicis Pharmaceutical Corp.
HFD # 510

Approval Date If Known February 10, 2005

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

- a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /**xx**/ NO /___/

If yes, what type? Specify, 505(b)(2),

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

YES /**xxx**/ NO /___/

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

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

d) Did the applicant request exclusivity?

YES /xxx/ NO /___/

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

The sponsor has indicated they hold the orphan designation for this drug product for treatment of episodic hyperammonemic encephalopathy. Therefore, it is assumed they are requesting exclusivity consistent with approval of an orphan drug product.

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /xxx/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /xxx/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

NDA# _____

NDA# _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /xxx/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 19-530 Ucephan

NDA# _____

NDA# _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

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

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

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

YES /xxx/ NO /___/

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

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

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

YES /xxx/ NO /___/

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

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

YES /___/ NO /xx/

The applicant submitted a listed of published references but made no specific statement that public data would not independently support the application. It is the opinion of the reviewing Medical Officer that public literature would NOT support the NDA.

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

YES /___/ NO /xxx/

If yes, explain:

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

YES /___/ NO /xxx/

If yes, explain:

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

Study entitled "Comprehensive Clinical Report"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the

if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 17,123 YES /**xxx**/ ! NO /___/ Explain: _____
! !
Investigation #2 !
IND # _____ YES /___/ ! NO /___/ Explain: _____

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

Investigation #1 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !

! !

! !
Investigation #2 !
YES /___/ Explain _____ ! NO /___/ Explain _____
! !

! !

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /**xxx**/

If yes, explain: _____

Pat Madara
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Date: *{See appended electronic signature page}*

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Date: *{See appended electronic signature page}*

Form OGD-011347 Revised 05/10/2004

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
2/22/05 08:26:09 AM

David Orloff
2/23/05 05:47:49 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-645 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: August 10, 2004 Action Date: February 10, 2005

HFD 510 Trade and generic names/dosage form: Ammonul (sodium phenylacetate and sodium benzoate) Inj., 10%/10%

Applicant: Ucyclyd Pharma, a wholly owned subsidiary of Medicis Pharmaceutical Therapeutic Class: 3041480

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

XX No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply.

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg 0.4025 mo. 0 yr. 0 Tanner Stage _____
Max _____ kg 109 mo. 0 yr. 18 Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

Patricia Madara

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA 20-645
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
2/18/05 01:48:42 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-645

INFORMATION REQUEST LETTER

Ucyclyd Pharma Inc.; a subsidiary of Medicis Pharmaceutical Corp.
Attention: R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258-2463

Dear Dr. Plott:

Please refer to your August 9, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ammonul (10% sodium phenylacetate, 10% sodium benzoate) Injection.

We also refer to your submissions dated November 9 and December 20, 2004.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For Drug Substances:

- The deficiencies in DMF [redacted] and requests for additional information about the drug substance, sodium phenylacetate, were communicated to [redacted] in a letter dated November 4, 2004, but responses from the DMF holder are still pending.

For Drug Product:

- 1) Your sampling plan in [redacted] should include the testing of more units in order to provide a statistically sound determination of [redacted] particulates. [See also USP <788> (Particulate Matter in Injections), Test Procedure]
- 2) Quality control document [redacted] for the acceptance of the glass vials does not include an inspection for defects or damage to the vials; and there is no inspection listed for visible impurities such as dirt and oil. These visual inspections, and the appropriate acceptance criteria, should be part of your acceptance tests for your vials.
- 3) Using the following or similar wording, provide the following post-approval stability commitments:

[redacted]
[redacted] The resulting stability data will be submitted in the Annual Report or in a format specified by the FDA.

- Medicis commits to complete the ongoing stability studies (through the expiration period) _____ according to their approved stability protocol.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Mamta Gautam-Basak, Ph.D.
Chemistry Team Leader II, for the
Division of Metabolic and Endocrine Drug Products
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mamta Gautam-Basak
1/10/05 02:25:58 PM
Information Request

CONSULTATION RESPONSE

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(ODS; HFD-420)**

DATE RECEIVED: August 30, 2004 DATE OF DOCUMENT: August 9, 2004	DUE DATE: October 30, 2004	ODS CONSULT #: 04-0245
TO: David Orloff, MD Director, Division of Metabolic and Endocrine Drug Products HFD-510		
THROUGH: Pat Madara Project Manager HFD-510		
PRODUCT NAME: Ammonul (Sodium Phenylacetate and Sodium Benzoate) Injection 10%/10% NDA: 20-645	NDA SPONSOR: Ucyclyd Pharma, a subsidiary of Medicis Pharmaceutical Corp	
SAFETY EVALUATOR: Nora Roselle, PharmD		
RECOMMENDATIONS: <ol style="list-style-type: none">1. DMETS has no objections to the use of the proprietary name, Ammonul. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.3. DDMAC had concerns regarding the proprietary name, Ammonul. However, after discussion with the review division, DDMAC "will not press the issue for this trade name."		
<hr/> <p>Carol Holquist, RPh Director, Division of Medication Errors and Technical Support Phone: (301) 827-3242 Fax: (301) 443-9664</p>		

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: October 15, 2004
NDA #: 20-645
NAME OF DRUG: Ammonul
(Sodium Phenylacetate and Sodium Benzoate) Injection
10%/10%
NDA HOLDER: Ucyclcyd Pharma, a subsidiary of Medicis Pharmaceutical Corp

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), to review the proprietary name, Ammonul, regarding potential name confusion with other proprietary and established drug names. Container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION

Ammonul is indicated as adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle. Ammonul is administered intravenously as a 90-minute loading dose infusion followed by a 24-hour maintenance dose infusion. Ammonul must be diluted with sterile Dextrose Injection, 10% before administration. The dilution and dosage of Ammonul are determined by weight for infants and young children, and by body surface area for larger patients, including older children, adolescents, and adults (see Table below). Ammonul will be supplied in 50 mL single-use glass vials.

Table 5. Dosage and Administration

Patient Population	Components of Infusion Solution			Dosage Provided		
	Ammonul	Arginine HCl Injection, 10%	Dextrose Injection, 10%	Sodium Phenylacetate	Sodium Benzoate	Arginine HCl
Neonates:						
CPS and OTC Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	2.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	2.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
AS and AL Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	6.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	6.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Infants and Young Children:						
CPS and OTC Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	2.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	2.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	200 mg/kg
AS and AL Deficiency						
Loading Dose (over 1.5 – 2 h)	2.5 mL/kg	6.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Maintenance Dose (over 24 h)*	2.5 mL/kg	6.0 mL/kg	= 25 mL/kg	250 mg/kg	250 mg/kg	600 mg/kg
Older Children and Adults:						
CPS and OTC Deficiency						
Loading Dose (over 1.5 – 2 h)	55 mL/m ²	2.0 mL/kg	= 25 mL/kg	5.5 g/m ²	5.5 g/m ²	200 mg/kg
Maintenance Dose (over 24 h)*	55 mL/m ²	2.0 mL/kg	= 25 mL/kg	5.5 g/m ²	5.5 g/m ²	200 mg/kg
AS and AL Deficiency						
Loading Dose (over 1.5 – 2 h)	55 mL/m ²	6.0 mL/kg	= 25 mL/kg	5.5 g/m ²	5.5 g/m ²	600 mg/kg
Maintenance Dose (over 24 h)*	55 mL/m ²	6.0 mL/kg	= 25 mL/kg	5.5 g/m ²	5.5 g/m ²	600 mg/kg

* Maintenance infusions may be continued at the same dose at the clinician's discretion.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts^{1,2} as well as several FDA databases³ for existing drug names which sound-alike or look-alike to Ammonul to a degree where potential confusion between drug names could occur under the usual clinical practice settings. The Saegis⁴ Pharma-In-Use database was searched for drug names with potential for confusion. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted⁵. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written studies (two inpatient) and one verbal prescription study, involving healthcare practitioners within FDA. These exercises were conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel Discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Ammonul. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC had concerns regarding the proprietary name, Ammonul. However, after discussion with the review division, DDMAC "will not press the issue for this trade name."
2. The Expert Panel Discussion (EPD) identified several proprietary names that were thought to have the potential for confusion with Ammonul. These products are listed in Table 1 (see page 4), along with the dosage forms available and usual FDA-approved dosage.

Appears This Way
On Original

¹ MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

² Facts and Comparisons, 2004, Facts and Comparisons, St. Louis, MO.

³ The Division of Medication Errors and Technical Support [DMETS] database of proprietary name consultation requests, Drugs@FDA, and the electronic online version of the FDA Orange Book.

⁴ Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

⁵ WWW location <http://www.uspto.gov/tmdb/index.html>.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage Form(s)	Usual adult dose*	Other
Ammonul	Sodium Phenylacetate and Sodium Benzoate Injection, 10%/10%	See Table on page 2.	
Amaryl	Glimepiride Tablets, 1 mg, 2 mg , 4 mg	<u>Initial:</u> 1 mg to 2 mg once daily given with breakfast or the first meal of the day <u>Maintenance:</u> 1 mg to 4 mg once daily to a maximum of 8 mg once daily	Sound-alike
Ammonium Lactate (established name, various brand name products)	Ammonium Lactate, 12% cream and lotion	Apply twice daily to affected skin areas and rub in thoroughly.	Look-alike
Ammonium Chloride	Ammonium Chloride Solution, 5 mEq/mL (20 mL vial)	<u>Intravenous Solution for Hypochloremia:</u> Estimation of an appropriate dose in mEq is based on the chloride deficit. A formula used for calculating the dosage is as follows: mEq chloride ion (as ammonium chloride) equals (chloride deficit in mEq/liter) multiplied by (0.2 x body weight in kilograms). Half of the dose should be administered initially and the patient's condition should be determined before subsequent doses are administered. <u>For urinary acidification:</u> 1.5 g IV every 6 hours, with a maximum dose of 6 g/day	Look-alike
Ammonium Molybdate	Ammonium Molybdate Injection, 25 mcg/mL (10 mL vial)	<u>Injection - Metabolically stable adults:</u> 20 mcg to 120 mcg/day <u>Deficiency state resulting from prolonged TPN support:</u> 163 mcg/day for 21 days	Look-alike
Ammonia Inhalant (OTC)	Ammonia in a crushable ampule	Hold the inhalant away from the face and squeeze it hard (crush) between your fingers; this will activate the dose package. Place the inhalant 4 inches from the nostrils until the patient awakens and no longer feels faint; or as directed by the doctor.	Look-alike

*Frequently used, not all-inclusive.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Ammonul were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary names to determine the degree of confusion of Ammonul with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). The exercises were conducted in an attempt to simulate the prescription ordering process. Two inpatient orders were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Ammonul (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, one inpatient order was recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTIONS	VERBAL PRESCRIPTIONS
Inpatient 1: <u>Ammonul 80ml IV over 72°</u>	Ammonul eighty milliliters. Give by IV over two hours.
Inpatient 2: <u>Ammonul 80ml IV over 2°</u>	

2. Results:

One respondent from the inpatient study interpreted the name to be Ammonia. Ammonia is packaged as an inhalation solution in a crushable ampule and used to treat or prevent fainting. Ammonia inhalant is an over-the-counter drug product. See Appendix A for the complete listing of interpretations from the verbal and written studies.

B. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proposed proprietary name Ammonul, the primary concerns raised were related to look-or sound-alike confusion with Amaryl and Ammonium Lactate. Similarly, upon further review, two additional drug names, Ammonium Chloride and Ammonium Molybdate, were also determined to have potential for confusion with Ammonul.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Ammonul. One respondent

from the inpatient study incorrectly interpreted the name to be, Ammonia, an inhalation solution used to treat or prevent fainting.

In addition, several panel members commented that the proposed name reminds them of or implies that the drug contains 'ammonia'. Ammonia inhalants, as mentioned above, is an inhalation solution and packaged in crushable ampules. It may be used, when available, to treat or prevent fainting. Ammonia inhalant is an OTC drug item and is often found in medical facilities and doctor's offices to be used as needed. Due to its OTC status, we believe that it is not as likely that it will be confused with the proposed proprietary name; an IV solution used for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

1. Amaryl (Glimepiride) was identified to have sound-alike potential with the proposed proprietary name, Ammonul. Amaryl is indicated for the treatment of diabetes. Amaryl is available as 1 mg, 2 mg, and 4 mg oral tablets. The usual initial dose of Amaryl is 1 mg to 2 mg once daily given with breakfast or the first meal of the day. The usual maintenance dose of Amaryl is 1 mg to 4 mg once daily up to a maximum of 8 mg once daily. Amaryl and Ammonul have sound-alike similarities in that each name begins with similar sounding letters ('Ama' vs. 'Ammo') and ends with the letter 'L'. However, there are many characteristics which help differentiate the two drugs. Amaryl and Ammonul have different dosage forms (tablet vs. injection), route of administration (oral vs. intravenous), doses (1 mg to 4 mg vs. dose based on weight [2.5 mL/kg or 55 mL/m²]), frequency of administration (once daily vs. loading dose infused over 1.5 to 2 hours or maintenance dose over 24 or more hours), and indication (diabetes vs. hyperammonemia). In addition, the two drugs have different strengths. Amaryl is a single ingredient product available in 1 mg, 2 mg, and 4 mg tablets. Ammonul, on the other hand, contains two active ingredients each with a 10% strength (100 mg/mL). Thus, even though the two names have sound-alike similarities, the above-mentioned differences will help minimize any risk for confusion and error between the two products.
2. Ammonium lactate was identified to have look-alike potential with the proposed proprietary name, Ammonul. Ammonium lactate is indicated for the treatment of ichthyosis vulgaris or xerosis of the skin. Ammonium lactate is available as a 12% cream and lotion. There are numerous brand name products which carry the established name, ammonium lactate (Amlactin, Lac-Hydrin, and LAClotion). Ammonium lactate is applied twice daily to affected skin areas. The "Ammonium" portion of the name has look-alike similarities to Ammonul in that the beginning of each name is identical ('Ammon') when scripted (see below). However, the two names are differentiated from one another due to the fact that the second half of the name, 'lactate', will most likely be written when prescribed. The two drugs have different dosage forms (cream/lotion vs. injection), route of administration (topical vs. intravenous), and indication (ichthyosis vulgaris or xerosis of the skin vs. hyperammonemia). While the strength of both products is expressed as a percentage, they vary numerically (12% vs. 10%/10%). The two medications do not have overlapping drug doses or frequency of administration; Ammonium lactate is applied as a small amount of cream/lotion to the affected skin areas twice daily and Ammonul is dosed based on weight [2.5 mL/kg or 55 mL/m²] and administered as an infusion over 1.5 to 2 hours (loading dose) or over 24+ hours (maintenance dose). In addition, it is unlikely that Ammonul will

be prescribed by its strength, as a prescribing dose will need to be identified in order for the drug to be properly compounded by the pharmacy prior to use. Thus, even though there are look-alike similarities, it is likely that the differences mentioned above will help differentiate one drug from the other.

Ammonium lactate *Ammonul*

3. Ammonium chloride was identified to have look-alike potential with the proposed proprietary name, Ammonul. Ammonium chloride is used to correct metabolic alkalosis resulting from chloride depletion following the use of diuretics, or following vomiting, gastric fistula drainage, or nasogastric suction. Ammonium chloride is available as a 5 mEq/mL intravenous solution. Estimation of an appropriate dose in milliequivalents (mEq) is based on the chloride deficit. A formula used for calculating the dosage is as follows: mEq chloride ion (as ammonium chloride) equals (chloride deficit in mEq/liter) multiplied by (0.2 x body weight in kilograms). Half of the dose should be administered initially and the patient's condition should be determined before subsequent doses are administered. For the treatment of urinary acidification, ammonium chloride is given as 1.5 g IV every 6 hours. For IV administration, 100 mEq or 200 mEq of ammonium chloride should be diluted to 500 or 1000 mL of NS injection. The diluted solution should be infused at a rate not to exceed 5 mL/minute. The "Ammonium" portion of the name has look-alike similarities to Ammonul in that the beginning of each name is identical ('Ammon') when scripted (see below). However, the two names are differentiated from one another due to the fact that the second half of the name, "chloride", will most likely be written when prescribed. The two drugs have an overlapping dosage form (injection) and route of administration (intravenous). In contrast, the two drugs have different strengths (5 mEq/mL vs. 10%/10%) and indications for use. In addition, the two medications do not have overlapping drug doses; Ammonium chloride is dosed based on individual calculated chloride depletion or as 1.5 g IV every 6 hours and Ammonul is dosed based on weight [2.5 mL/kg or 55 mL/m²]. Thus, even though there are some product and look-alike similarities, it is likely that the differences mentioned above will help differentiate one drug from the other.

ammonium chloride *Ammonul*

4. Ammonium molybdate was identified to have look-alike potential with the proposed proprietary name, Ammonul. Ammonium molybdate is trace metal used as part of intravenous nutritional therapy. Ammonium molybdate is available as a 25 mcg/mL injection (10 mL vials). For metabolically stable adults, ammonium molybdate is dosed as 20 mcg to 120 mcg daily. If treating a deficiency state resulting from prolonged TPN support, the dose of Ammonium molybdate is 163 mcg/day for 21 days. The "Ammonium" portion of the name has look-alike similarities to Ammonul in that the beginning of each name is identical ('Ammon') when scripted (see below). However, the two names are differentiated from one another due to the fact that the second half of the name, "molybdate", will most likely be written when prescribed. The two drugs do have an overlapping dosage form (injection) and route of administration (intravenous). Although, Ammonium molybdate and Ammonul have different strengths (25 mcg/mL vs. 10%/10%) and indications for use. In addition, the two medications do not have overlapping drug doses; Ammonium molybdate is dosed as 20 mcg to 120 mcg/day or 163 mcg/day (for 21 days) and Ammonul is

dosed based on weight [2.5 mL/kg or 55 mL/m²]). Thus, even though there are some product and look-alike similarities, it is likely that the differences mentioned above will help differentiate one drug from the other.

ammonium molybdate *Ammonul*

III. LABELING, PACKAGING, AND OTHER SAFETY RELATED CONCERNS:

DMETS reviewed the container labels, carton and insert labeling for Ammonul and has identified the following areas of possible improvement.

A. CONTAINER LABELS (50 mL Vial)

1. The proprietary and established names, and strength should be expressed as follows:

Ammonul
(Sodium Phenylacetate and Sodium Benzoate) Injection
10%/10%

or

Sodium Phenylacetate	10%
and Sodium Benzoate	10%
Injection	

2. From the black and white materials provided it is difficult to determine whether the proprietary and established names are the most prominent information on the label. Please revise accordingly. Additionally, ensure that the established name is at least ½ the size of the proprietary name as per 21 CFR 201.10(g)(2).
3. DMETS recommends the route of administration statement, "For IV use only", appear on the front display panel as per 21 CFR 201.100(b)(3).
4. Increase the prominence and bold the statement "Must be diluted before IV administration". It is important for practitioners to be alerted that the drug is concentrated and needs to be further diluted prior to use.

B. CARTON LABELING

See comments A1 – A4.

C. INSERT LABELING

1. In order to avoid confusion among prescribers, the package insert should include definitions of weight/age for neonates, infants, young children, older children and adults in the DOSAGE AND ADMINISTRATION table.
2. See comment A1.

IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name, Ammonul. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC had concerns regarding the proprietary name, Ammonul. However, after discussion with the review division, DDMAC "will not press the issue for this trade name."

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Nora Roselle, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nora L. Roselle
11/19/04 01:15:50 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
11/19/04 01:35:32 PM
DRUG SAFETY OFFICE REVIEWER



NDA 20-645

INFORMATION REQUEST LETTER

Medicis Pharmaceutical Corp
Attention: R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258

Dear Dr. Plott:

Please refer to your August 9, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ammonul (10% sodium phenylacetate/10% sodium benzoate) Injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

For Drug Substances:

1. Your data do not support an acceptance criterion of [REDACTED] Total Impurities in the sodium benzoate, NF, used in your drug product. Consequently, lower your acceptance specification for sodium benzoate, NF; or provide justification for the proposed [REDACTED] limit for Total Impurities.
2. Your acceptance criterion of [REDACTED] in sodium benzoate (drug substance) exceeds the qualification threshold of [REDACTED] for a drug that has a maximum daily dose above 2.0 g/day. [See ICH Guidance Q3A, Impurities in New Drug Substances.] Accordingly, lower the [REDACTED] limit in your acceptance specification for sodium benzoate, NF; or provide justification for your proposed limit of [REDACTED].
3. Provide certification that the [REDACTED] used to fabricate the content-contact portion of the drug substance container for sodium benzoate meets the current 21 CFR requirements for food contact safety.
4. DMF [REDACTED] for the drug substance, sodium phenylacetate, has been found deficient. The DMF holder will be informed of these deficiencies.
5. There are differences in [REDACTED] release specifications for sodium phenylacetate and your acceptance specifications for this drug substance. Accordingly, you should revise your acceptance criteria for sodium phenylacetate to be more in accord with [REDACTED] updated release specifications; and any differences that may remain should be justified.

For Drug Product:

1. Although you have an in-process control for the volume of the drug product in your containers, you should also provide a drug product specification for the volume of Ammonul in your vials, as, for example, by the method described in USP <1> (Volume in Container).
2. Provide a specific identification test (e.g. by IR) as part of your acceptance criteria for the stoppers used to seal your vials.
3. Your acceptance criterion of total peak area for Individual Unidentified Impurities exceeds the ICH Q3B(R) [Impurities in New Drug Products] guidelines of 0.15% for a drug that has a maximum daily dose above 2.0 g/day. Accordingly, you should revise your limit for Individual Unidentified Impurities in Ammonul.
4. Your batch data and stability studies show very low levels for Total Impurities in Ammonul. Consequently, your limit of Total Impurities in the drug product should be lowered in your specification for Ammonul. Alternatively, provide justification for the proposed limit for Total Impurities.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Mamta Gautam-Basak, Ph.D.
Chemistry Team Leader II for the
Division of Metabolic and Endocrine Drug
Products, HFD-510
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mamta Gautam-Basak
10/22/04 01:11:21 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 20-645

Medicis Pharmaceutical Corp.
Attention: R. Todd Plott, M.D.
Vice President, Clinical Research and Regulatory Affairs
8125 North Hayden Road
Scottsdale, AZ 85258

Dear Dr. Plott:

Please refer to your August 9, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ammonul (10% sodium phenylacetate/10% sodium benzoate) Injection.

We also refer to your submission dated August 16, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on October 9, 2004 in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 827-6416.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
10/8/04 01:54:41 PM
Signing for Kati Johnson

NDA 20-645

OCT 5 2000

Ucyclyd Pharma Inc.
Attention: Joseph Cooper
President
8125 North Hayden Rd.
Scottsdale, AZ 85258-2463

Dear Mr. Cooper:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ammonul (10% sodium phenylacetate and 10% sodium benzoate) Injection.

We have given your application a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

1. The efficacy of the drug infusion to lower plasma ammonia levels has not been appropriately evaluated. In order to evaluate the efficacy of the drug infusion to treat hyperammonemia, a comparison of plasma ammonia levels pre- and post-intravenous drug infusion is required. However, the application contains analyses that, in effect, confound any inference of efficacy of the intravenous drug infusion with that of other modalities used to treat hyperammonia, such as hemodialysis or peritoneal dialysis. In addition, the following data should not be included in the combined efficacy analysis:
 - a. ammonia levels from patients in whom no drug infusion data were available (i.e., drug dose and duration of administration were not known),
 - b. "baseline" ammonia levels that were normal (i.e., the patient was not hyperammonemic),
 - c. any "baseline" plasma ammonia level that was not a true baseline as it was not obtained immediately prior to the drug infusion, and
 - d. plasma ammonia levels from patients in whom there were significant protocol deviations, such as the amount of the bolus dose administered, the number of bolus doses administered, and failure to administer a bolus dose at all or to follow it with a sustaining infusion.

In addition, data were neither provided nor analyzed for the doses of the drugs administered

for the sustaining infusion.

2. Evaluation of the effect of the drug infusion on the time to resolution of hyperammonemic coma was not included in the application. This is a key analysis because the longer the duration of coma, the poorer the neurological outcome. There are case reports published by Saul Brusilow, MD, of Johns Hopkins University, relevant to this issue. As Johns Hopkins University was the principal investigative site, these data should be retrievable, at least for some patients, from hospital records. Specific data should be provided in the individual patient data listings to support the neurological outcome ratings.
3. Evaluation of the rapidity with which the infusion reverses acute hyperammonemic encephalopathy is not included in the application. This information should also be retrievable, at least for some patients, from Johns Hopkins University hospital records.
4. Our April 30, 1998, refusal to file letter requested that the data be sorted not only by enzyme deficiency, but also by neonatal onset versus late-onset. Within these groups, data should be sorted by rescue versus prospectively treated. The submitted information combines data from prospectively-treated patients with rescue patients.
5. Our April 30, 1998, refusal to file letter requested an analysis (mean \pm SD, median with range) of relevant laboratory parameters that could potentially be affected by the infusion, such as serum electrolytes, osmolarity, and acid-base status. This information is not included in the submission. In addition, the safety analysis performed is inadequate because it was not based on the dose of the drugs infused. Rather, safety data were analyzed irregardless of the bolus or sustaining-infusion dose. Therefore, a safety assessment cannot be made for the dose recommended in proposed labeling.
6. Our April 30, 1998, refusal to file letter made reference to the August 15, 1995, and January 10, 1997, pre-NDA meetings, as well as our December 19, 1995, letter for additional information relating to analysis of the database. We requested inclusion of information in the proposed labeling regarding appropriate use of hemodialysis versus drug infusion. This is a critical issue given that the ability of the drugs to bind waste nitrogen is limited and the longer the duration of hyperammonemic coma, the poorer the prognosis. Labeling should be based on analysis of the data relating to the degree of blood ammonia elevation and the severity and duration of encephalopathy. In addition, we requested submission of literature pertaining to the treatment of acute hyperammonemia with hemodialysis in patients with urea cycle disorders. Neither of these issues has been addressed in the submission.
7. Computation of the failure rate of the drug infusion to decrease hyperammonemia, thereby necessitating hemodialysis was requested, but was not provided.
8. We requested specific information be provided, such as neurological outcomes during hospitalization, including results of EEGs and CT or MRI scans. This information is provided in the narratives of the patients who died, but there is no information for the

survivors.

Within 30 days of the date of this letter, you may request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If, after the informal conference, you still do not agree with our conclusions, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(a)(3). If you do so, the application shall be filed over protest under 21 CFR 314.101(a)(2). The filing date will be 60 days after the date you requested the informal conference.

If you have any questions, call Maureen Hess, MPH, RD, Regulatory Health Project Manager, at (301) 827-6411.

Sincerely yours,

DGO 10-5-09

David G. Orloff, MD
Director
Division of Metabolic and Endocrine Drug
Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Cc:

NDA 20-645
HFD-510/Div. File
HFD-510/JTemeck/SMarkofsky/DWu/JElHage/HAhn/EGalliers
HFD-715/TSahlroot
HFD-160/PStinavage/PCooney
HFD-46/RBlay
HF-35/MHaffner
HFD-102/ADRA
HFD-094/DDMS
DISTRICT OFFICE

Drafted by: MHess/9.28.00

Initialed by: JTemeck/10.01.00/DOrloff/10.04.00/LRipper/10.05.00

Final: 10.05.00

NDA 20-645

Ucyclyd Pharma
Attention: Norbert L. Wiech, Ph.D.
President
500 McCormick Drive, Suite J
Glen Burnie, MD 21061

DF
APR 30 1998

Dear Dr. Wiech:

Please refer to your February 28, 1998, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for Ammonul (sodium benzoate/sodium phenylacetate) Injection, 10%.

We have given your NDA a preliminary review, and we find it is not sufficiently complete to merit review. Thus, it will not be filed as a new drug application within the meaning of section 505(b) of the Act.

We are refusing to file this NDA under 21 CFR 314.101(d)(3) for the following reasons:

- A. Information required under 21 CFR 314.50(d)(5) for the clinical technical section of the application is missing.
1. The majority of the submitted database is in raw form and has not been analyzed. In addition, the manner in which the very limited analyses were conducted provide little insight into the efficacy and safety of the product. A key issue is to determine the efficacy of the infusion as it correlates to the plasma ammonia level on admission and the duration of hyperammonemic coma. The submitted information does not address how rapidly the infusion reverses acute hyperammonemic encephalopathy.
 2. The data should be sorted not only by enzyme deficiency, but also by neonatal onset, rescue vs. prospectively treated; vs. late-onset patients. An analysis (mean \pm SD, median with range) of relevant laboratory parameters which could potentially be affected by the infusion, such as serum electrolytes, osmolarity and acid-base status, should be done.
 3. Please refer to the August 15, 1995, and January 10, 1997, pre-NDA meetings with you as well as our December 19, 1995, letter for additional information relating to the analysis of the database.

B. Information required under 21 CFR 314.50(d)(1) for the Chemistry, Manufacturing and Control (CMC) and Microbiology technical section of the application is missing.

1. An appropriate DMF for sodium benzoate (USP) has not been submitted. The manufacturer/supplier will need to submit this as well as providing an authorization letter permitting the FDA to cross-reference its Drug Master File (DMF) for this NDA on your behalf. Alternately, detailed information concerning (CMC) should be provided in the NDA.
2. The submission does not contain validation of the sterilization processes required to manufacture the drug product. Descriptions of the sterilization validation descriptions and data should be submitted as outlined in the November 1994, "Guidance for Industry for the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products." This guidance document is enclosed for your reference.

C. Information required under 21 CFR 314.50(d)(6) for the statistical technical section of the application is missing.

1. The statistical section should be a duplicate of the clinical section.
2. The primary efficacy measure of survival is mentioned, but results are not present in the overall summary of efficacy.
3. No description of statistical methods is included. For example, how were multiple episodes for a single patient handled?

D. Although the table of contents was resubmitted on March 16, 1998, it is still unclear and confusing, whereby it is difficult to locate information in the NDA.

We also offer the following comments and recommendations unrelated to our refusal to file decision that should be considered upon resubmission:

1. Detailed and certified CMC information is not present in DMF [redacted] for the key intermediate used in the manufacture of sodium phenylacetate.
2. The acceptance criteria for both drug substances does not include microbiology limits (bacterial count and bacterial endotoxins). While this information is not required in the submission, it is strongly recommended that such limits (specifications) be established.
3. It is not clear which tests will be performed by the various facilities involved in acceptance testing and the manufacturing and testing of the drug product.

NDA 20-645
page 4

Concurrences:

EGalliers/4.20.98/Jtemeck/4.20.98/Dorloff/4.20.98/SMarkofsky/4.20.98/DWu/4.21.98/Jmele/4.25.98/Enevius/4.24.98/PStinavage/4.21.98/Pcooney/4.21.98/

cc: NDA 20-645
HFD-510/Div. File
HFD-95/DDM-DIAB
HFD-510/JTemeck/DOrloff/SMarkofsky/DWu/RSteigerwalt/Hahn/Galliers
HFD-715/JMele/ENevius
HFD-160/PStinavage/PCooney
HF-35/MHaffner
DISTRICT OFFICE
HFD-820/JGibbs

drafted by: MHess/4.15.98/n20645 refuse to file.doc
final: 4/28/98

REFUSAL TO FILE (RF)

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # **20-645**

Supplement #

SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Ammonul Injection**

Generic Name: 10% sodium phenylacetate / 10% sodium benzoate

Strengths:

Applicant: Medicis Pharmaceutical Corp

Date of Application: August 9, 2004

Date of Receipt: August 10, 2004

Date clock started after UN:

Date of Filing Meeting: September 21, 2004

Filing Date: October 9, 2004

Action Goal Date (optional):

User Fee Goal Date: February 10, 05 (Priority)

Indication(s) requested: as adjunctive therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with deficiencies in enzymes of the urea cycle.

Type of Original NDA: (b)(1) _____ (b)(2) X

OR

Type of Supplement: (b)(1) _____ (b)(2) _____

NOTE:

(1) *If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.*

(2) *If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:*

____ NDA is a (b)(1) application OR ____ NDA is a (b)(2) application

Therapeutic Classification: S _____

P XX

Resubmission after withdrawal? _____

Resubmission after refuse to file? Yes

Chemical Classification: (1,2,3 etc.) 3

Other (orphan, OTC, etc.) Orphan

Form 3397 (User Fee Cover Sheet) submitted:

YES

User Fee Status:

Paid _____ Exempt (orphan, government) XX
Waived (e.g., small business, public health) _____

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx to OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling.*

If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? N/A
If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).
- Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.
- If yes, has OC/DMPQ been notified of the submission? N/A
- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
If no, explain:
- If an electronic NDA, does it follow the Guidance? YES
If an electronic NDA, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

All sections except for certifications, cover letter and 356h.
- If in Common Technical Document format, does it follow the guidance? N/A
- Is it an electronic CTD? N/A
If an electronic CTD, all certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format?

Additional comments:
- Patent information submitted on form FDA 3542a? YES

- Exclusivity requested? **NO**
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required. **Note: The sponsor holds the orphan designation for this drug/indication.***

- Correctly worded Debarment Certification included with authorized signature? **YES**
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? **YES**
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? **YES**

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? **YES**
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.

- List referenced IND numbers: **IND 17,123**

- End-of-Phase 2 Meeting(s)? **NO**
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? **January 10, 1997**
Date(s) September 30, 2003
If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? **YES**
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? **YES**
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? **N/A**
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? **N/A**

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? **N/A**

- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
If no, did applicant submit a complete environmental assessment? N/A
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES

ATTACHMENT

MEMO OF FILING MEETING

DATE:

BACKGROUND:

(Provide a brief background of the drug, e.g., it was already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	William Lubas, M.D.
Secondary Medical:	NN
Statistical:	NN
Pharmacology:	Karen Davis Bruno, Ph.D.
Statistical Pharmacology:	NN
Chemistry:	David Lewis, Ph.D.; Sheldon Markofsky, Ph.D.
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Jaya Vaidyanathan, Ph.D.
Microbiology, sterility:	Stephen Langille, Ph.D.
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	NN
Regulatory Project Management:	Patricia Madara
Other Consults:	DDMAC, ODS

Per reviewers, are all parts in English or English translation? **YES**
If no, explain:

CLINICAL FILE XX

- Clinical site inspection needed: **NO**
- Advisory Committee Meeting needed? YES, date if known _____ **NO**
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? **N/A**

CLINICAL MICROBIOLOGY **NN**

STATISTICS **NN**

BIOPHARMACEUTICS FILE XX

- Biopharm. inspection needed: **NO**

PHARMACOLOGY NA _____ FILE XX

- GLP inspection needed: **NO**

CHEMISTRY FILE XX

- Establishment(s) ready for inspection? **YES**
- Microbiology **YES**

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why:

XX The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

XX No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

Regulatory Project Manager, HFD-

Appendix A to NDA Regulatory Filing Review

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? **YES**

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
NDA 19-530, Ucephan (10% sodium phenylacetate/sodium benzoate) Oral Solution

3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? **YES** **NO**
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)?

YES **NO**

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? **YES**

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? **YES**
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? **NO**

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product?

NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? **YES** **NO**

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

This application provides for a change in dosage form, from Oral Solution to Injection.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). **NO**
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). **NO**
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). **NO**
10. Are there certifications for each of the patents listed for the listed drug(s)? **N/A**
There are no patents for the listed drug.

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

___ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.
(Paragraph I certification)

___ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)

___ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III
certification)

___ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by
the manufacture, use, or sale of the drug product for which the application is submitted.
(Paragraph IV certification)

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR
314.50(i)(1)(i)(A)(4)], the applicant must **subsequently** submit a signed certification stating
that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR
314.52(b)]. The applicant must also submit documentation showing that the NDA holder and
patent owner(s) received the notification [21 CFR 314.52(e)].*

XX 21 CFR 314.50(i)(1)(ii): No relevant patents.

___ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the
labeling for the drug product for which the applicant is seeking approval does not include any
indications that are covered by the use patent as described in the corresponding use code in the
Orange Book. Applicant must provide a statement that the method of use patent does not
claim any of the proposed indications. (Section viii statement)

___ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent
owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).

___ Written statement from patent owner that it consents to an immediate effective date upon
approval of the application.

12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?

NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

There is no marketing exclusivity for Ucephan, NDA 19530

YES

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

N/A

- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?

N/A

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

YES

- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

YES

- EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND # 17,123

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Patricia Madara
11/18/04 03:41:33 PM
CSO

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information

NDA 20-645	Efficacy Supplement Type SE-	Supplement Number
Drug: Ammonul (sodium phenylacetate/sodium benzoate)Inj 10% / 10%		Applicant: Ucyclyd Pharma, a wholly owned subsidiary of Medicis Pharmaceutical Corp
RPM: Pat Madara		HFD- 510 Phone # 301-827-6416
<p>Application Type: () 505(b)(1) (X) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p>() Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): NDA 19-530 Ucephan (sodium phenylacetate/sodium benzoate) 10% / 10% Oral solution
❖ Application Classifications:		
<ul style="list-style-type: none"> • Review priority • Chem class (NDAs only) • Other (e.g., orphan, OTC) 		() Standard (X) Priority 3 orphan
❖ User Fee Goal Dates		February 10, 2005
❖ Special programs (indicate all that apply)		(X) None Subpart H () 21 CFR 314.510 (accelerated approval) () 21 CFR 314.520 (restricted distribution) () Fast Track () Rolling Review () CMA Pilot 1 () CMA Pilot 2
❖ User Fee Information		
<ul style="list-style-type: none"> • User Fee • User Fee waiver 		() Paid UF ID number () Small business () Public health () Barrier-to-Innovation () Other (specify)
<ul style="list-style-type: none"> • User Fee exception 		(X) Orphan designation () No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) () Other (specify)
Application Integrity Policy (AIP)		
<ul style="list-style-type: none"> • Applicant is on the AIP 		() Yes (X) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? () Yes () No N/A

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? () Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	No
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ () No this applicant holds
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	November 18, 2004

(General Information)

Actions	
<ul style="list-style-type: none"> Proposed action 	(X) AP () TA () AE () NA
<ul style="list-style-type: none"> Previous actions (specify type and date for each action taken) 	RTF 10/5/2000; 4/30/1998
<ul style="list-style-type: none"> Status of advertising (approvals only) 	() Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
<ul style="list-style-type: none"> Press Office notified of action (approval only) 	() Yes (X) Not applicable
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
<ul style="list-style-type: none"> Division's proposed labeling (only if generated after latest applicant submission of labeling) 	February 10, 2005(package insert)
<ul style="list-style-type: none"> Most recent applicant-proposed labeling 	
<ul style="list-style-type: none"> Original applicant-proposed labeling 	
<ul style="list-style-type: none"> Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings) 	November 19, 2004 February 3, 2005
<ul style="list-style-type: none"> Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (immediate container & carton labels)	
<ul style="list-style-type: none"> Division proposed (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> Applicant proposed 	January 28, 2005
<ul style="list-style-type: none"> Reviews 	
❖ Post-marketing commitments	None required
<ul style="list-style-type: none"> Agency request for post-marketing commitments 	
<ul style="list-style-type: none"> Documentation of discussions and/or agreements relating to post-marketing commitments 	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	All included
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> EOP2 meeting (indicate date) 	
<ul style="list-style-type: none"> Pre-NDA meeting (indicate date) 	Mtg date: 10/30/03
<ul style="list-style-type: none"> Pre-Approval Safety Conference (indicate date; approvals only) 	
<ul style="list-style-type: none"> Other 	
❖ Advisory Committee Meeting	N/A
<ul style="list-style-type: none"> Date of Meeting 	
<ul style="list-style-type: none"> 48-hour alert 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	February 10, 2005
Clinical Information	
❖ Clinical review(s) (indicate date for each review)	February 10, 2005
❖ Microbiology (efficacy) review(s) (indicate date for each review)	
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	Part of clinical review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	N/A
❖ Biopharmaceutical review(s) (indicate date for each review)	January 26, 2005
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	Not needed
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) (indicate date for each review)	February 4, 2005
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	February 4, 2005
• Review & FONSI (indicate date of review)	NN
• Review & Environmental Impact Statement (indicate date of each review)	NN
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	January 31, 2005
❖ Facilities inspection (provide EER report)	Date completed: Nov 19, 2004 (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested NN () Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	December 8 2004
❖ Nonclinical inspection review summary	Not needed
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	Not needed
❖ CAC/ECAC report	Not needed

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

- (1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
- (2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
- (3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
- (4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).