CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-645

CHEMISTRY REVIEW(S)

NDA 20-645

Ammonul

(sodium phenylacetate and sodium benzoate) Injection

10% /10%

Ucyclcyd Pharma, a subsidiary of
Medicis Pharmaceutical Corporation

David Lewis, Ph.D. (drug substance)
Sheldon Markofsky, Ph.D. (drug product)

DIVISION OF METABOLISM and ENDOCRINE DRUG PRODUCTS

File: n20645Rev1i

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Chemistry Review Data Sheet

1. NDA 20-645

2. REVIEW #: 1

3. REVIEW DATE: 02-02-2005

4. REVIEWERS: David Lewis (drug substance)
   Sheldon Markofsky (drug product)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NDA (Original)	28-Feb-1998
Refuse to File Letter	30-April-1998
NDA (Resubmission)	29-June-2000
Refuse to File Letter	05-Oct-2000
NDA (Resubmission)	09-Aug-2004
IR Letter	22 Oct-2004
IR Letter	10-Jan-2005
Labeling Memo, in DFS (Labeling requests made to applicant by project Manager, Patricia Madara)	26-Jan-2005

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
NDA (Resubmission)	09-Aug-2004
Amendment[1]	09-Nov-2004
Amendment[2]	20-Dec-2004
Amendment[3]	05-Jan-2005
Amendment[4] (Labeling)	05-Jan-2005
Amendment[5]	17-Jan-2005
Amendment[6]	20-Jan-2005
Amendment[7]	21-Jan-2005
Amendment[8]	28-Jan-2005

1) The 11-9-04 amendment corrected an error in the formula used to calculate an impurity in sodium benzoate.
2) The 12-20-04 amendment provided responses to the Agency's 10-22-04 Information Request letter.
3) The 01-05-05 amendment provided compatibility and stability information for recommended infusion solutions of Ammonul with 10% dextrose and 10% Arginine HCl.
4) The 01-05-05 labeling amendment provided up-dated labeling information.
5) The 01-17-05 amendment provided responses to the Agency's 01-10-05 Information Request letter.
6) The 01-20-05 amendment provided sterility related information needed for the microbiology consult.
7) The 01-21-05 labeling amendment provided up-dated labeling information.
8) The 01-28-05 labeling amendment provided up-dated labeling information.

7. NAME & ADDRESS OF APPLICANT:

Name:	Medicis Pharmaceutical Corporation
Address:	8125 N. Hayden Road, Scottsdale AZ 85258
Representative:	R. Todd Plott, M.D. Vice President, Regulatory Affairs
Telephone:	602-808-8800

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Ammonul
b) Non-Proprietary Name (USAN): (sodium phenylacetate and sodium benzoate) Injection 10%/10%
c) Code Name/# (ONDC only): N/A
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Treatment of hyperammonemia in patients with urea cycle disorders

11. DOSAGE FORM: Injectable Solution

12. STRENGTH/POTENCY: 10% sodium phenylacetate and 10% sodium benzoate (in vials containing not less than 50-ml)

13. ROUTE OF ADMINISTRATION: IV Infusion

14. Rx/OTC DISPENSED: X Rx ___OT

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

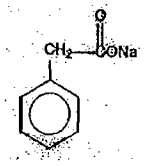
_____SPOTS product – Form Completed

__X__Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Sodium benzoate, NF (USAN), also known as benzoic acid, sodium salt. CAS Registry Number [532-32-1]. Molecular formula and weight: $C_7H_5NaO_2$, 144.1 g/mol. Structure:

Sodium phenylacetate, USP (USAN), also known as phenylacetic acid, sodium salt. CAS Registry Number [114-70-5]. Molecular formula and weight: C8H7NaO2, 158.1 g/mol. Structure:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	III	[redacted]	[redacted]	4	Adequate	N/A	N/A
	III			3	Adequate	5-19-04	N/A
	II			1	Adequate	1-12-05	N/A

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	17,123	sodium phenylacetate and sodium benzoate Injection 10%/10%

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable per EER	11-19-04	S. B. Markofsky
Pharm/Tox	Acceptable	12-8-04	Davis-Bruno
Biopharm			
LNC			
Methods Validation	Methods deemed adequate		S. B. Markofsky
DMETS	Acceptable	10-15-04	N. Roselle
EA	Acceptable	2-2-05	Markofsky (Chem. Rev. #1)
Microbiology	Acceptable	1-31-05	Langille

19. ORDER OF REVIEW : N/A (OGD Only)

The Executive Summary section

The Chemistry Review for NDA 20-645

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a Chemistry, Manufacturing, and Controls (CMC) point of view, this NDA can be **approved.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product and Drug Substances

1) Drug Product

The drug product, Ammonul, (sodium phenylacetate and sodium benzoate) Injection 10%/10% contains not less than 50-ml of this sterile aqueous–based-solution, which is packaged in single-use-glass-vials. These [redacted] vials, made from USP Type 1 [redacted] clear glass, are sealed with [redacted] stoppers and final capped [redacted] seals. The drug product is indicated for the treatment of hyperammonemia in patients with urea cycle disorders. [This life saving drug, for a rare class of genetic disorders, was given a high priority rating (3P)].

Although the applicant proposed a [redacted] expiry for Ammonul stored at room temperature [25 ^{0}C (77 ^{0}F) with excursions permitted to 15^0 – 30 ^{0}C (59^0 – 86 ^{0}F)], **we recommend a 24-month expiry.** The reasons we believe the stability data support a 24-month expiry are discussed in the **DRUG PRODUCT STABILITY** section of this review.

The applicant has satisfactorily addressed all of the CMC related issues, noted in the Information Request Letters of 22 Oct-2004 and 05-Jan-2005.

The Executive Summary section

2) Drug Substances

There are two drug substances in the drug product, sodium phenylacetate and sodium benzoate. Sodium phenylacetate, USP, is manufactured and supplied by [redacted] **CMC information regarding sodium phenylacetate is provided in DMF [redacted] which was last reviewed on 12-Jan-2005, and found adequate to support this NDA.** Sodium benzoate is manufactured by [redacted] and supplied by the [redacted] Sodium benzoate is not covered by a current DMF and is not manufactured under current drug GMP's. CMC information regarding sodium benzoate was provided directly to this NDA [redacted] substance specifications as per the USP]. Since sodium benzoate is a commonly utilized preservative in the pharmaceutical and food industries and because this very pure drug substance conforms to compendial specifications, this approach (to accept sodium benzoate not manufactured under cGMP and without a DMF) was agreed upon between the applicant and the FDA prior to NDA submission.

B. Description of How the Drug Product is Intended to be Used

In the treatment of hyperammonemia in patients with urea cycle disorders, the dose of Ammonul, administered by IV, is adjusted in each patient. Generally, Ammonul is administered as a loading dose infusion followed by maintenance infusion. The drug product must be diluted with sterile 10% Dextrose Injection before infusion. Ammonul infusion should be started as soon as the diagnosis of hyperammonemia is made. Treatment of hyperammonemia also requires caloric supplementation and restriction of dietary protein. During and after infusion of Ammonul, ongoing monitoring of neurological status, plasma ammonia levels, clinical laboratory values, and clinical responses are crucial to assess patient response and further treatment.

Infusion solutions, resulting from Ammonul being diluted with Dextrose Injection, 10%, are physically and chemically stable for up to 24 hours at room temperature. No compatibility information is available for the infusion solutions with other substances, except for Arginine HCl Injection (10%), which may be mixed into the same infusion container as Ammonul and Dextrose Injection, 10%.

C. Basis for Approvability or Not-Approval Recommendation

Satisfactory CMC information has been provided, and the cGMP compliance status is acceptable. Therefore, the application is approvable from a CMC point of view based on the following:

- The proposed drug product (formulation and method of manufacture) is the same as the drug product used in the clinical trials.

The Executive Summary section

- Both drug substances are satisfactorily manufactured to meet FDA guidelines for quality, purity and stability; and the appropriate in-process controls are adequate. The structures of sodium benzoate and sodium phenylacetate are adequately proved. Therefore, the drug substances are considered to be suitable for the drug product.

- There are adequate specifications and controls for the drug substances and the drug product.

- Ammonul has been shown to be adequately stable in the proposed packaging.

- The applicant has satisfactorily responded to the CMC related issues communicated to the firm in the Agency's Information Request Letters, dated 10-22-04 and 1-10-05.

III. Administrative

A. Reviewer's Signature

Sheldon Markofsky, Ph.D. (Chemistry Reviewer)

B. Endorsement Block (OGD only)

N/A

C. CC Block (OGD only)

N/A

40 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry- 1

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

/s/

Sheldon Markofsky
2/4/05 10:24:00 AM
CHEMIST

Mamta Gautam-Basak
2/4/05 10:34:48 AM
CHEMIST
Concur, recommended for approval from the CMC standpoint.