

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-877**

**CHEMISTRY REVIEW(S)**



# **NDA 21-877**

**Arranon  
Nelarabine Injection, 50 mL  
(5 mg/mL)**

**Glaxosmithkline Inc.**

**Xiao-Hong Chen, Ph.D.  
HFD-150 Division of Oncology Drug Products**



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# Chemistry Review Data Sheet

1. NDA 21-877
2. REVIEW #1:
3. REVIEW DATE: September 6, 2005
4. REVIEWER: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents

Rolling Review Presubmissions Chemistry

Document Date

December 17, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Original NDA submission  
Amendment  
Amendment  
Amendment

Document Date

April 29, 2005  
July 29, 2005  
September 30, 2005  
October 4, 2005

7. NELARABINE & ADDRESS OF APPLICANT:

Nelarabine:

Glaxosmithkline Inc.

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Address:	One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101
Representative:	Ellen Cutler
Telephone:	(215) 751-4000

**8. DRUG PRODUCT NELARABINE/CODE/TYPE:**

- a) Proprietary Nelarabine: Arranon®
- b) Non-Proprietary Nelarabine (USAN): Nelarabine
- c) Code Nelarabine/# : 506U78
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: 1
  - Submission Priority: P

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

**10. PHARMACOL. CATEGORY:** T-cell acute lymphoblastic leukemia or T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens

**11. DOSAGE FORM:** Injection, Solution, Concentrate (709)

**12. STRENGTH/POTENCY:** 5 mg/ mL, (50 mL per vial)

**13. ROUTE OF ADMINISTRATION:** Intravenous (002)

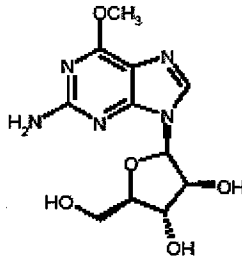
**14. Rx/OTC DISPENSED:**   X   Rx      OTC

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

         SPOTS product – Form Completed

X   Not a SPOTS product

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



Nelarabine	Nelarabine
Chemical Nelarabine	2-amino-9-β-D-arabinofuranosyl-6-methoxy-9H-purine
CAS number	121032-29-9
Molecular Weight	297.27
Molecular Formula	C <sub>11</sub> H <sub>15</sub> N <sub>5</sub> O <sub>5</sub>
Structural formula	See above

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
—	III		/ /	3	Adequate	10-26-2000	None
—	III		/ /	3	Adequate	6-1-2004	None

<sup>1</sup> 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

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7 – Other (explain under "Comments")

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

**B. Other Documents:**

IND 42,778	506U78	Submitted on Jun. 7, 1994.
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18. STATUS:

**ONDC:**

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	Acceptable	14-Dec-2004	Office of Compliance
Trade Nelarabine	Acceptable	28-Jul-2005	Nora Roselle, PharmD
Methods Validation	May be submitted post approval		
EA (Categorical exclusion)	Acceptable	29-Aug-2005	Xiao Hong Chen
Microbiology	Acceptable	7-Oct-2005	Stephen Langille

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Review for NDA 21-877

## The Executive Summary

### I. Recommendations

#### A. Recommendation and Conclusion on Approvability

From a CMC perspective, this application is recommended for approval. The applicant has satisfactorily addressed all CMC deficiencies. The Office of Compliance has provided an overall “acceptable” recommendation for this application.

We recommend that the following comment regarding shelf life be included in the approval letter:

An expiration-dating period of fifteen months for the drug product will be granted based on stability data provided.

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

N/A.

### II. Summary of Chemistry Assessments

#### A. Description of the Drug Product(s) and Drug Substance(s)

##### Drug Product

Arranon® (nelarabine) Injection, 5 mg/mL (previously 506U78) is indicated for the treatment of pediatric and adults patients with T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Arranon Injection is supplied as a clear, colorless, sterile solution in Type I, clear glass vials with a gray butyl rubber (latex-free) stopper and a red snap-off aluminum seal. Each vial contains 250 mg of nelarabine (5 gm nelarabine per mL) and the inactive ingredient sodium chloride (4.5 mg per mL) in 50 mL Water for Injection, USP.

The initial formulation of Nelarabine for Injection was \_\_\_\_\_ Each 50-mL glass vial contains 200 mg nelarabine. \_\_\_\_\_

\_\_\_\_\_ Nelarabine Injection, 5 mg/mL was subsequently developed as a ready-to-use liquid injectable dosage form. Excipients used to formulate Arranon® Injection are sodium chloride and Water for Injection (WFI). Stability study was conducted to evaluate the effects of \_\_\_\_\_

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on aqueous solutions of nelarabine. This study indicated that in aqueous solution, nelarabine is most stable between pH 5 and pH 7. Drug product manufacturing process is fairly straightforward due to the stable nature of nelarabine.

Nelarabine for Injection is manufactured by Glaxo Operations UK Limited at Barnard Castle, UK.

The for purity uses the same conditions as those of the for drug substance. It is capable of separating most of the impurities and other analytes such as nelarabine except impurity Batch data for four production batches, of the drug product were provided. Three of those batches were used in clinical studies and the fourth batch was used in stability study. All tests conform to specifications.

Stability studies were performed under ICH recommended storage conditions (long term 30°C/60%RH and accelerated 40°C/60%RH). primary stability data from four production batches of drug product manufactured at the, site were provided. In addition, site specific stability data from one batch of drug product manufactured at the commercial site, Barnard Castle, UK and up to of stability data for three batches of commercial drug product were provided. All stability data conform to the proposed specifications. Like drug substance, the drug product appears to be fairly stable under the long term storage conditions, and the stability trend appear to be comparable between the "primary" batches and commercial batches. Considering the differences in manufacturing process, site, and analytical method (for impurities) between the "primary" batches and the commercial batches, an expiration dating period of 15 months is granted.

**Drug Substance**

Nelarabine is a new molecular entity. It has been developed as a pro-drug of the deoxyguanosine analogue 9-β-D-arabinofuranosylguanine (ara-G). It is rapidly converted *in vivo* to ara-G and subsequently converted to the active 5'-triphosphate, ara-GTP. It is a cytotoxic agent belonging to the nucleoside analogue class of compounds. Nelarabine is a and it is an, with an aqueous solubility of over the pH range of 4–10. It has a molecular weight of 297.27

, which has been produced at all scales of manufacture. The median particle size volume diameter is typically in the range of, as determined by

Nelarabine drug substance is manufactured by the Wellcome Foundation Ltd. in Dartford, UK. The synthesis is a

The synthetic route has not been changed throughout

development with the exception of minor process modifications. Release data were provided for three commercial batches and three pilot batches of the drug substance. The impurity profiles among these batches appear to be comparable. All results conform to specifications.

Identified impurities were qualified by toxicology studies — studies were performed, and it was determined that the — to control drug related impurities in drug substance and drug product are stability indicating. The primary reference standard was prepared by the proposed process — and has a purity value of —.

The drug substance is stored in —. Stability studies were performed according to the ICH recommended storage conditions (long term 30°C/60%RH and accelerated 40°C/60%RH) and test schedules. — primary stability data for three drug substance batches manufactured at pilot scale and at pilot plant as well as — stability data for the first three commercial batches manufactured at commercial site were provided. In addition — months of supportive stability data for three batches manufactured at pilot site were also provided. All tests were within specifications. No significant changes or trend was observed. A — retest date has been established.

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

The recommended adult dose of Arranon® Injection is 1,500 mg/m<sup>2</sup> administered intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days. The recommended pediatric dose of Arranon® Injection is 650 mg/m<sup>2</sup> administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. The recommended duration of treatment has not been clearly established. In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity, or the patient became a candidate for bone marrow transplant.

**C. Basis for Approvability Recommendation**

The NDA is recommended for approval from the CMC perspective as the applicant has addressed all the deficiencies that were conveyed, and the Office of Compliance has provided an “acceptable” recommendation for this application.

**III. Administrative**

A. Reviewer’s Signature

B. Endorsement Block

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Chemist Name/Date: Xiao Hong Chen, Ph.D.  
Chemistry Team Leader Name/Date: Nallaperumal Chidambaram, Ph.D.  
Project Manager Name/Date: Sheila Ryan

C. CC Block

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75 Page(s) Withheld

§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

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

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Xiao Hong Chen  
10/24/2005 04:16:16 PM  
CHEMIST

Nallaperumal Chidambaram  
10/24/2005 04:46:04 PM  
CHEMIST