

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-877**

**ADMINISTRATIVE**  
**DOCUMENTS/CORRESPONDENCE**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

21-877

NAME OF APPLICANT / NDA HOLDER

SmithKline Beecham Corporation (d.b.a.  
GlaxoSmithKline)

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)  
ARRANON

ACTIVE INGREDIENT(S)  
nelarabine

STRENGTH(S)  
5 mg/ml

DOSAGE FORM  
IV Injection

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

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**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number  
5,747,472

b. Issue Date of Patent  
5/5/1998

c. Expiration Date of Patent  
2/20/2013

d. Name of Patent Owner  
SmithKline Beecham Corporation

Address (of Patent Owner)

One Franklin Plaza  
PO 7929

City/State

Philadelphia, Pennsylvania

ZIP Code  
19101

FAX Number (if available)  
919-483-7988

Telephone Number  
919-483-8247

E-Mail Address (if available)  
john.l.lemanowicz@gsk.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number (as listed in the patent) 2 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
 ARRANON is indicated for the treatment of patients with [\*T-cell acute lymphoblastic leukemia and] T-cell lymphoblastic lymphoma whose disease has not responded to or has progressed despite treatment with at least two other chemotherapy regimens. (\* The subject matter of the label indication in brackets is not within the scope of claim 2.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

**Date Signed**

*John L. Lemanowicz*

*3/24/05*

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**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

**Name**

John L. Lemanowicz  
Senior Patent Counsel  
GlaxoSmithKline

**Address**

Five Moore Drive

**City/State**

Research Triangle Park, NC

**ZIP Code**

27709-3398

**Telephone Number**

919-483-8247

**FAX Number (if available)**

919-483-7988

**E-Mail Address (if available)**

john.l.lemanowicz@gsk.com

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Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

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*For Each Patent That Claims a Drug Substance  
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NDA NUMBER

21-887

NAME OF APPLICANT / NDA HOLDER

SmithKline Beecham Corporation (d.b.a.  
GlaxoSmithKline)

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

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5 mg/ml

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**1. GENERAL**

a. United States Patent Number  
5,821,236

b. Issue Date of Patent  
10/13/1998

c. Expiration Date of Patent  
2/20/2013

d. Name of Patent Owner  
SmithKline Beecham Corporation

Address (of Patent Owner)

One Franklin Plaza  
PO 7929

City/State

Philadelphia, Pennsylvania

ZIP Code

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Address (of agent or representative named in 1.e.)

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No

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2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?
1	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.) ARRANON is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia [*and T-cell lymphoblastic lymphoma] whose disease has not responded to or has progressed despite treatment with at least two other chemotherapy regimens. (* The subject matter of the label indication in brackets is not within the scope of claim 1.)
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**5. No Relevant Patents**

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3/24/05

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NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

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**1. GENERAL**

a. United States Patent Number  
5,492,897

b. Issue Date of Patent  
2/20/1996

c. Expiration Date of Patent  
2/20/2013

d. Name of Patent Owner  
SmithKline Beecham Corporation

Address (of Patent Owner)

One Franklin Plaza  
PO Box 7929

City/State

Philadelphia, Pennsylvania

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2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

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4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

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Name

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a. United States Patent Number

5,424,295

b. Issue Date of Patent

6/13/1995

c. Expiration Date of Patent

6/13/2012

d. Name of Patent Owner

SmithKline Beecham Corporation

Address (of Patent Owner)

One Franklin Plaza  
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2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No

2.6 Does the patent claim only an intermediate?  Yes  No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No

3.2 Does the patent claim only an intermediate?  Yes  No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



3/24/05

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

**Check applicable box and provide information below.**

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

John L. Lemanowicz  
Senior Patent Counsel  
GlaxoSmithKline

Address

Five Moore Drive

City/State

Research Triangle Park, NC

ZIP Code

27709-3398

Telephone Number

919-483-8247

FAX Number (if available)

919-483-7988

E-Mail Address (if available)

john.l.lemanowicz@gsk.com

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

## EXCLUSIVITY SUMMARY

NDA # 21-877

SUPPL #

HFD # 150

Trade Name Arranon for Injection

Generic Name nelarabine

Applicant Name GlaxoSmithKline

Approval Date, If Known

### 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 questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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  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  NO

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

5

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

YES  NO

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

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  NO

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

NDA#

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 NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

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

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

YES  NO

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

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

YES  NO

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

YES  NO

If yes, explain:

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

YES  NO

If yes, explain:

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

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 safety of a previously approved drug, answer "no.")

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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

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

Investigation #1	YES <input type="checkbox"/>	NO <input type="checkbox"/>
Investigation #2	YES <input type="checkbox"/>	NO <input type="checkbox"/>

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



Investigation #2

!

YES

!

! NO

Explain:

! 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

If yes, explain:

---

Name of person completing form: Sheila Ryan, Pharm.D.  
Title: Regulatory Project Manager  
Date: 9-26-05

Name of Office/Division Director signing form: Robert L. Justice, M.D.  
Title: Acting Director, DDOP

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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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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Robert Justice  
10/27/2005 06:44:56 PM

# PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 21-877 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 4-29-05 Action Due Date: 10-29-05

HFD 150 Trade and generic names/dosage form: ARRANON (nelarabine) for Injection

Applicant: GlaxoSmithKline Therapeutic Class: 1

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): 2

Indication #1: T-cell acute lymphoblastic leukemia (T-ALL) whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens

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

Yes: Please proceed to Section A.

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 for a 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 \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ 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:

{See appended electronic signature page}

\_\_\_\_\_  
Sheila Ryan, Pharm.D.  
Regulatory Project Manager

cc: NDA 21-877  
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

**Attachment A**

(This attachment is to be completed for those applications with multiple indications only.)

**Indication #2: patients with T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens**

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

Yes: Please proceed to Section A.

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 \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

*If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.*

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Sheila Ryan, Pharm.D.  
Regulatory Project Manager

cc: NDA 21-877  
HFD-960/ Grace Carmouze

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

(revised 10-14-03)

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

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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/

-----  
Sheila Ryan

9/29/2005 12:41:20 PM

**CONFIDENTIAL**

1.3.3 Debarment Certification

NDA 21-877  
ARRANON™ (nelarabine) Injection  
Original Submission: New Drug Application

**DEBARMENT CERTIFICATION**

GlaxoSmithKline 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.



30 MAR 2005

Charles E. Mueller  
Director, North America Clinical Compliance  
Worldwide Regulatory Compliance

Date

✓ AC  
2/15/05  
1/15/05

## NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-877	Efficacy Supplement Type SE- N/A	Supplement Number N/A
Drug: Arranon® (nelarabine) Injection 5 mg/mL		Applicant: GlaxoSmithKline
RPM: Sheila Ryan, Pharm.D./Nicholette Hemingway, MPH	HFD-150	Phone # 301-796-1365
<p>Application Type: ( <input checked="" type="checkbox"/> ) 505(b)(1) ( ) 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><b>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.</b></p> <p>( ) Confirmed and/or corrected</p>	<p>Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p>	
<b>❖ Application Classifications:</b>		
• Review priority	( ) Standard ( <input checked="" type="checkbox"/> ) Priority	
• Chem class (NDAs only)	1	
• Other (e.g., orphan, OTC)	Orphan	
User Fee Goal Dates	10-29-05	
Special programs (indicate all that apply)	( ) None Subpart H ( <input checked="" type="checkbox"/> ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( <input checked="" type="checkbox"/> ) Fast Track ( <input checked="" type="checkbox"/> ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2	
<b>❖ User Fee Information</b>		
• User Fee	( ) Paid UF ID number	
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)	
• User Fee exception	( <input checked="" type="checkbox"/> ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)	
<b>❖ Application Integrity Policy (AIP)</b>		
• Applicant is on the AIP	( ) Yes ( <input checked="" type="checkbox"/> ) No	

<ul style="list-style-type: none"> <li>This application is on the AIP</li> </ul>	( ) Yes ( X ) No
<ul style="list-style-type: none"> <li>Exception for review (Center Director's memo)</li> </ul>	N/A
<ul style="list-style-type: none"> <li>OC clearance for approval</li> </ul>	N/A
Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	( X ) Verified
❖ Patent	
<ul style="list-style-type: none"> <li>Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.</li> </ul>	( X ) Verified
<ul style="list-style-type: none"> <li>Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) ( ) Verified
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).</i></li> <li>[505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.</li> </ul> <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).</p> <p><i>If "Yes," skip to question (4) below. If "No," continue with question (2).</i></p> <p>(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?</p> <p><i>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).</i></p> <p><i>If "No," continue with question (3).</i></p> <p>(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?</p>	( ) N/A (no paragraph IV certification) ( ) Verified
	( ) Yes ( ) No
	( ) Yes ( ) No
	( ) 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," 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

*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"> <li>• Exclusivity summary</li> <li>• 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.)</li> </ul>	No
<ul style="list-style-type: none"> <li>• 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.</li> </ul>	<input type="checkbox"/> Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	9-29-05
• Most recent applicant-proposed labeling	10-12-05
• Original applicant-proposed labeling	4-29-05
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DDMAC: 8-30-05 DMETS: 9-22-05 DSRCS: 7-28-05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	NA
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	No changes
• Applicant proposed	4-29-05
• Reviews	DMETS: 9-22-05
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	9-19-05
• Documentation of discussions and/or agreements relating to post-marketing commitments	9-26-05
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	11-24-03 and 6-30-04
• Pre-NDA meeting (indicate date)	6-23-04 (CMC) 9-22-04 2-18-05
• Pre-Approval Safety Conference (indicate date; approvals only)	9-20-05 (no minutes generated)
• Other	Filing Meeting: 6-20-05
❖ Advisory Committee Meeting	
• Date of Meeting	9-14-05
• 48-hour alert	NA
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	8-17-05

<b>Summary Reviews</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) <i>(indicate date for each review)</i>	MOR TL 10-5-05
<b>Clinical Information</b>	
❖ Clinical review(s) <i>(indicate date for each review)</i>	10-5-05
❖ Microbiology (efficacy) review(s) <i>(indicate date for each review)</i>	10-7-05
❖ Safety Update review(s) <i>(indicate date or location if incorporated in another review)</i>	Copied from MOR
❖ Risk Management Plan review(s) <i>(indicate date/location if incorporated in another rev)</i>	9-16-05
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	9-29-05
❖ Demographic Worksheet <i>(NME approvals only)</i>	NA
❖ Statistical review(s) <i>(indicate date for each review)</i>	9-27-05
❖ Biopharmaceutical review(s) <i>(indicate date for each review)</i>	9-26-05
❖ Controlled Substance Staff review(s) and recommendation for scheduling <i>(indicate date for each review)</i>	NA
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	9-23-05
• Bioequivalence studies	NA
<b>CMC Information</b>	
❖ CMC review(s) <i>(indicate date for each review)</i>	
❖ Environmental Assessment	
• Categorical Exclusion <i>(indicate review date)</i>	
• Review & FONSI <i>(indicate date of review)</i>	
• Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Microbiology (validation of sterilization & product sterility) review(s) <i>(indicate date for each review)</i>	NA
❖ Facilities inspection (provide EER report)	Date completed: 8-1-05 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (X) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	
❖ Nonclinical inspection review summary	
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	
❖ CAC/ECAC report	

### Appendix A to NDA/Efficacy Supplement Action Package Checklist

1 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).

# FOOD AND DRUG ADMINISTRATION OFFICE OF ONCOLOGY DRUG PRODUCTS



## DIVISION OF DRUG ONCOLOGY PRODUCTS

5901-B Ammendale Road  
Beltsville, Maryland 20705-1266

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PHONE: (301)796-1365 FAX: (301) 796-9845

TO: Ellen Cutler, GSK  
Fax: 610-787-7062

FROM: Nichollette Y. Hemingway, Project Manager  
Phone: (301) 796-1365

Total number of pages, including cover sheet 2

Date: 11-16-05

COMMENTS: Re: your NDA 21-877 for Arranon (nelarabine), we have the following request for information from our pharm/tox review team. Please respond as soon as possible.

### COMMENT:

Please identify the literature citations that support the following statement at their earliest convenience.

"Adenosine deaminase demethylates Nelarabine to form the active compound."

Please call me at the above number if you have any questions.

Thanks,  
Nicholette

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/s/

-----  
Nicholette Hemingway  
11/16/2005 04:00:49 PM  
CSO

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH  
DIVISION OF DRUG ONCOLOGY PRODUCTS  
OFFICE OF ONCOLOGY DRUG PRODUCTS

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FAX TO: Ellen Cutler

Telephone No.: 610-787-3733 Facsimile No.: 610-787-7063

FROM: Nichollette Hemingway

Telephone No.: (301) 796-2330 Incoming Facsimile No.: (301) 796-9845

DATE: 10/28/05

MESSAGE:

Approval letter for ADA 21-877

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

       § 552(b)(5) Deliberative Process

  /   § 552(b)(5) Draft Labeling

Division Director Summary Review of a New Drug Application

NDA: 21-877

Drug: Arranon® (nelarabine) Injection

Applicant: GlaxoSmithKline

Date: October 27, 2005

This NDA was received on April 29, 2005 and seeks approval of nelarabine for the following indication: "ARRANON is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. This use is based on the induction of complete responses. Randomized trials demonstrating increased survival or other clinical benefit have not been conducted."

Nelarabine is a pro-drug of ara-G a cytotoxic deoxyguanosine analogue. Nelarabine is rapidly demethylated by adenosine deaminase to form ara-G which is then phosphorylated intracellularly to ara-GTP. The mechanism of action is thought to be due to incorporation of ara-GTP into DNA with resultant cell death. In vitro, T-cells are more sensitive than B-cells.

Nelarabine was evaluated in two open-label, single-arm, multicenter studies, one in pediatric patients and one in adults. The following summary of safety and efficacy is excerpted from the proposed labeling.

Efficacy and Safety in Pediatric Patients

The pediatric study was conducted by the Children's Oncology Group (COG P9673). The study included patients 21 years of age and younger, who had relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four patients, 39 of whom had received two or more prior induction regimens, were treated with 650 mg/m<sup>2</sup>/day of ARRANON administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days (Table 1). Patients who experienced signs or symptoms of grade 2 or greater neurologic toxicity on therapy were to be discontinued from further therapy with ARRANON.

**Table 1. Pediatric Clinical Study - Patient Allocation**

<b>Patient Population</b>	<b>N</b>
Patients treated at 650 mg/m <sup>2</sup> /day x 5 days every 21 days.	84
Patients with T-ALL or T-LBL with two or more prior induction treated at 650 mg/m <sup>2</sup> /day x 5 days every 21 days.	39
Patients with T-ALL or T-LBL with one prior induction treated at 650 mg/m <sup>2</sup> /day x 5 days every 21 days.	31

The 84 patients ranged in age from 2.5-21.7 years (overall mean, 11.9 years), 52% were 3 to 12 years of age and most were male (74%) and Caucasian (62%). The majority (77%) of patients had a diagnosis of T-ALL.

Complete response (CR) was defined as bone marrow blast counts  $\leq 5\%$ , no other evidence of disease, and full recovery of peripheral blood counts. Complete response without full hematologic recovery (CR\*) was also assessed as a meaningful outcome in this heavily pretreated population. Duration of response is reported from date of response to date of relapse, and may include subsequent stem cell transplant. Efficacy results are shown in Table 2.

**Table 2. Efficacy Results in Patients 21 Years of Age and Younger at Diagnosis With  $\geq 2$  Prior Inductions Treated with 650 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days**

	N = 39
CR plus CR* % (n) [95% CI]	23% (9) [11%, 39%]
CR % (n) [95% CI]	13% (5) [4%, 27%]
CR* % (n) [95% CI]	10% (4) [3%, 24%]
Duration of CR plus CR* (range in weeks) <sup>1</sup>	3.3 to 9.3
Median overall survival (weeks) [95% CI]	13.1 [8.7, 17.4]

CR = Complete response

CR\* = Complete response without hematologic recovery

<sup>1</sup> Does not include 5 patients who were transplanted or had subsequent systemic chemotherapy (duration of response in these 5 patients was 4.7 to 42.1 weeks).

The mean number of days on therapy was 46 days (range of 7 to 129 days). Median time to CR plus CR\* was 3.4 weeks (95% CI: 3.0, 3.7).

For the pediatric patients who received 1 prior induction, the CR plus CR\* rate was 48% (15/31) and the CR rate was 42% (13/31).

The safety profile for children is based on data from 84 pediatric patients in the COG P9673 study who were treated with the recommended dose and schedule. The most common adverse events in pediatric patients, regardless of causality, were hematologic disorders (anemia, leukopenia, neutropenia, and thrombocytopenia). Of the non-hematologic adverse events in pediatric patients, the most frequent events reported were headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting. The most common adverse events by System Organ Class, regardless of causality, including severe or life threatening events (NCI Common Toxicity Criteria grade 3 or grade 4) and fatal events (grade 5) are shown in Table 4.

**Table 4. Most Commonly Reported ( $\geq 5\%$  Overall) Adverse Events Regardless of Causality in Pediatric Patients Treated with 650 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days**

System Organ Class Preferred Term	Percentage of Patients: 650 mg/m <sup>2</sup> ; N = 84		
	Toxicity Grade		
	Grade 3 %	Grade 4+ %	All Grades %
<b>Blood and Lymphatic System Disorders</b>			
Anemia	45	10	95
Neutropenia	17	62	94
Thrombocytopenia	27	32	88
Leukopenia	14	7	38
<b>Hepatobiliary Disorders</b>			
Transaminases increased	4	0	12
Blood albumin decreased	5	1	10
Blood bilirubin increased	7	2	10
<b>Metabolic/Laboratory</b>			
Blood potassium decreased	4	2	11
Blood calcium decreased	1	1	8
Blood creatinine increased	0	0	6
Blood glucose decreased	4	0	6
Blood magnesium decreased	2	0	6
<b>Nervous System Disorders (see Table 6)</b>			
<b>Gastrointestinal Disorders</b>			
Vomiting	0	0	10
<b>General Disorders &amp; Administration Site Conditions</b>			
Asthenia	1	0	6
<b>Infections &amp; Infestations</b>			
Infection	2	1	5

Grade 4+ = Grade 4 and Grade 5

Three (3) patients had a fatal event. Fatal events included neutropenia and pyrexia (n = 1), status epilepticus/seizure (n = 1), and fungal pneumonia (n = 1). The status epilepticus was thought to be related to treatment with ARRANON. All other fatal events were unrelated to treatment with ARRANON.

The most common neurologic adverse events ( $\geq 2\%$ ), regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 6.

**Table 6: Neurologic Adverse Events (≥2%) Regardless of Causality in Pediatric Patients Treated with 650 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 1 Hour Daily for 5 Consecutive Days Repeated Every 21 Days**

Nervous System Disorders Preferred Term	Percentage of Patients; N = 84				
	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Headache	8	2	4	2	17
Peripheral neurologic disorders, any event	1	4	7	0	12
Peripheral neuropathy	0	4	2	0	6
Peripheral motor neuropathy	1	0	2	0	4
Peripheral sensory neuropathy	0	0	6	0	6
Somnolence	1	4	1	1	7
Hypoesthesia	1	1	4	0	6
Seizures	0	0	0	6	6
Convulsions	0	0	0	3	4
Grand mal convulsions	0	0	0	1	1
Status epilepticus	0	0	0	1	1
Motor dysfunction	1	1	1	0	4
Nervous system disorder	1	2	0	0	4
Paresthesia	0	2	1	0	4
Tremor	1	2	0	0	4
Ataxia	1	0	1	0	2

Grade 4+ = Grade 4 and Grade 5

One (1) patient had a fatal neurologic event, status epilepticus. This event was thought to be related to treatment with ARRANON.

The other grade 3 event in pediatric patients, regardless of causality, was hypertonia reported in 1 patient (1%). The additional grade 4+ events, regardless of causality, were 3<sup>rd</sup> nerve paralysis, and 6<sup>th</sup> nerve paralysis, each reported in 1 patient (1%).

The other neurologic adverse events, regardless of causality, reported as grade 1, 2, or unknown in pediatric patients were dysarthria, encephalopathy, hydrocephalus, hyporeflexia, lethargy, mental impairment, paralysis, and sensory loss, each reported in 1 patient (1%).

#### Efficacy and Safety in Adult Patients

A study in adults was conducted by the Cancer and Leukemia Group B. This study included 39 patients, 28 who had T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) that had relapsed following or was refractory to at

least two prior induction regimens. ARRANON 1,500 mg/m<sup>2</sup> was administered intravenously over 2 hours on days 1, 3 and 5 repeated every 21 days. Patients who experienced signs or symptoms of grade 2 or greater neurologic toxicity on therapy were to be discontinued from further therapy with ARRANON. Seventeen patients had a diagnosis of T-ALL and 11 had a diagnosis of T-LBL. For patients with  $\geq 2$  prior inductions, the age range was 16-65 years (mean 34 years) and most patients were male (82%) and Caucasian (61%). Patients with central nervous system (CNS) disease were not eligible.

Complete response (CR) was defined as bone marrow blast counts  $\leq 5\%$ , no other evidence of disease, and full recovery of peripheral blood counts. Complete response without complete hematologic recovery (CR\*) was also assessed. The results of the study for patients who had received  $\geq 2$  prior inductions are shown in Table 3.

**Table 3. Efficacy Results in Adult Patients With  $\geq 2$  Prior Inductions Treated with 1,500 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days**

	N = 28
CR plus CR* % (n) [95%CI]	21% (6) [8%, 41%]
CR % (n) [95%CI]	18% (5) [6%, 37%]
CR* % (n) [95%CI]	4% (1) [0%, 18%]
Duration of CR plus CR* (range in weeks) <sup>1</sup>	4 to 195+
Median overall survival (weeks) [95% CI]	20.6 weeks [10.4, 36.4]

CR = Complete response

CR\* = Complete response without hematologic recovery

<sup>1</sup> Does not include 1 patient who was transplanted (duration of response was 156+ weeks).

The mean number of days on therapy was 56 days (range of 10 to 136 days). Time to CR plus CR\* ranged from 2.9 to 11.7 weeks.

For patients who received 1 prior induction, the CR plus CR\* rate was 27% (3/11) and the CR rate was 18% (2/11).

The safety profile is based on data from 103 adult patients enrolled and treated in the CALGB study and in an adult chronic lymphocytic leukemia study (PGAA2003) who were treated with the recommended dose and schedule. The most common adverse events in adults, regardless of causality, were fatigue; gastrointestinal (GI) disorders (nausea, diarrhea, vomiting, and constipation); hematologic disorders (anemia, neutropenia, and thrombocytopenia); respiratory disorders (cough and dyspnea); nervous system disorders (somnolence and dizziness); and pyrexia.

The most common adverse events by System Organ Class, regardless of causality, including severe or life threatening events (NCI Common Toxicity Criteria grade 3 or grade 4) and fatal events (grade 5) are shown in Table 5.

**Table 5: Most Commonly Reported ( $\geq 5\%$  Overall) Adverse Events Regardless of Causality in Adult Patients Treated with 1,500 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days**

System Organ Class Preferred Term	Percentage of Patients; N = 103		
	Toxicity Grade		
	Grade 3 %	Grade 4+ %	All Grades %
<b>Blood and Lymphatic System Disorders</b>			
Anemia	20	14	99
Thrombocytopenia	37	22	86
Neutropenia	14	49	81
Febrile neutropenia	9	1	12
<b>Cardiac Disorders</b>			
Sinus tachycardia	1	0	8
<b>Gastrointestinal Disorders</b>			
Nausea	0	0	41
Diarrhea	1	0	22
Vomiting	1	0	22
Constipation	1	0	21
Abdominal pain	1	0	9
Stomatitis	1	0	8
Abdominal distension	0	0	6
<b>General Disorders and Administration Site Conditions</b>			
Fatigue	10	2	50
Pyrexia	5	0	23
Asthenia	0	1	17
Edema, peripheral	0	0	15
Edema	0	0	11
Pain	3	0	11
Rigors	0	0	8
Gait, abnormal	0	0	6
Chest pain	0	0	5
Non-cardiac chest pain	0	1	5
<b>Infections</b>			
Infection	2	1	9
Pneumonia	4	1	8

System Organ Class Preferred Term	Percentage of Patients; N = 103		
	Toxicity Grade		
	Grade 3 %	Grade 4+ %	All Grades %
Sinusitis	1	0	7
<b>Hepatobiliary Disorders</b>			
AST increased	1	1	6
<b>Metabolism and Nutrition Disorders</b>			
Anorexia	0	0	9
Dehydration	3	1	7
Hyperglycemia	1	0	6
<b>Musculoskeletal and Connective Tissue Disorders</b>			
Myalgia	1	0	13
Arthralgia	1	0	9
Back pain	0	0	8
Muscular weakness	5	0	8
Pain in extremity	1	0	7
<b>Nervous System Disorders (see Table 7)</b>			
<b>Psychiatric Disorders</b>			
Confusional state	2	0	8
Insomnia	0	0	7
Depression	1	0	6
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>			
Cough	0	0	25
Dyspnea	4	2	20
Pleural effusion	5	1	10
Epistaxis	0	0	8
Dyspnea, exertional	0	0	7
Wheezing	0	0	5
<b>Vascular Disorders</b>			
Petechiae	2	0	12
Hypotension	1	1	8

Grade 4+ = Grade 4 and Grade 5

Five (5) patients had a fatal event. Fatal events included hypotension (n = 1), respiratory arrest (n = 1), pleural effusion/pneumothorax (n = 1), pneumonia (n = 1), and cerebral hemorrhage/coma/leukoencephalopathy (n = 1). The cerebral hemorrhage/coma/leukoencephalopathy was thought to be related to treatment with ARRANON. All other fatal events were unrelated to treatment with ARRANON.

The most common neurologic adverse events ( $\geq 2\%$ ), regardless of causality, including all grades (NCI Common Toxicity Criteria) are shown in Table 7.

**Table 7: Neurologic Adverse Events ( $\geq 2\%$ ) Regardless of Causality in Adult Patients Treated with 1,500 mg/m<sup>2</sup> of ARRANON Administered Intravenously Over 2 Hours on Days 1, 3, and 5 Repeated Every 21 Days**

System Organ Class Preferred Term	Percentage of Patients; N =103				
	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %	All Grades %
Somnolence	20	3	0	0	23
Dizziness	14	8	0	0	21
Peripheral neurologic disorders, any event	8	12	2	0	21
Neuropathy	0	4	0	0	4
Peripheral neuropathy	2	2	1	0	5
Peripheral motor neuropathy	3	3	1	0	7
Peripheral sensory neuropathy	7	6	0	0	13
Hypoesthesia	5	10	2	0	17
Headache	11	3	1	0	15
Paresthesia	11	4	0	0	15
Ataxia	1	6	2	0	9
Depressed level of consciousness	4	1	0	1	6
Tremor	2	3	0	0	5
Amnesia	2	1	0	0	3
Dysgeusia	2	1	0	0	3
Balance disorder	1	1	0	0	2
Sensory loss	0	2	0	0	2

One (1) patient had a fatal neurologic event, cerebral hemorrhage/coma/leukoencephalopathy.

This event was thought to be related to treatment with ARRANON.

Most nervous system events in the adult patients were evaluated as grade 1 or 2. The additional grade 3 events in adult patients, regardless of causality, were aphasia, convulsion, hemiparesis, and loss of consciousness, each reported in 1 patient (1%). The additional grade 4 events, regardless of causality, were cerebral hemorrhage, coma, intracranial hemorrhage, leukoencephalopathy, and metabolic encephalopathy, each reported in one patient (1%).

The other neurologic adverse events, regardless of causality, reported as grade 1, 2, or unknown in adult patients were abnormal coordination, burning sensation, disturbance in attention, dysarthria, hyporeflexia, neuropathic pain, nystagmus, peroneal nerve palsy, sciatica, sensory disturbance, sinus headache, and speech disorder, each reported in one patient (1%). Blurred vision was also reported in 4% of adult patients.

There have also been reports of events associated with demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome. There was a single report of biopsy confirmed progressive multifocal leukoencephalopathy

#### Medical Officer Review

The Medical Officer Review by Martin H. Cohen, M.D., concluded that “Nelarabine is active as evidenced by the observed CR and CR\* rates. CR and CR\* are surrogate endpoints considered reasonably likely to predict clinical benefit in the treatment of pediatric and adult T- cell ALL/T- cell LBL.” The review states that “The medical and statistical reviewers recommend accelerated approval.”

Dr. Cohen had the following comment on the required phase 4 commitment:

Pursue design of a phase III trial with the Children’s Oncology Group to demonstrate nelarabine clinical benefit (phase 4 commitment)). This protocol has been designed and is undergoing review by the NCI. A request for a Special Protocol Assessment (SPA) will be submitted prior to initiation of the study. The final (CTEP approved) protocol will be available November 2005.

#### Clinical Team Leader Review

The Clinical Team Leader Review by John R. Johnson, M.D., concluded and recommended the following:

CR plus CR\* rates are 23% in children and 21% in adults in patients with relapsed or refractory T cell ALL or T cell LBL after two or more prior induction regimens. Interpretation of CR or CR\* duration, time to progression and survival is impaired because some patients had Transplant or other systemic chemotherapy prior to progression. The CR + CR\* rates are a reasonably likely surrogate for clinical benefit.

Toxicity is similar to other treatments used in this patient population. Like other drugs of this class, such as fludarabine and Cytarabine, Nelarabine has neurotoxicity. Nelarabine neurotoxicity is manageable with careful monitoring. Nelarabine toxicity is acceptable in this patient population considering the CR plus CR\* rate and lack of effective available alternative therapy.

Accelerated approval of this NDA under Subpart H for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens is recommended.

## Statistical Review and Evaluation

The Statistical Review and Evaluation by Tristan Massie, Ph.D. made the following conclusions and recommendations:

Since the studies submitted to support this application were open label, uncontrolled, and non-randomized no valid statistical comparisons could be made. Clinical judgment is needed to assess the efficacy of this drug.

## Oncologic Drugs Advisory Committee

This application was presented to the Oncologic Drugs Advisory Committee on September 14, 2005. The committee's votes on four questions are provided below.

1. In pediatric patients with  $\geq 2$  prior inductions 9 of 39 (23%) of patients had CR or CR\*. Four of 9 CR or CR\* patients who did not have their CR or CR\* duration confounded by subsequent Transplant or other Systemic chemotherapy had CR or CR\* durations of 3.3, 3.6, 6.1 and 9.3 weeks.

Are these results reasonably likely to predict clinical benefit in this setting?

The committee voted 11 yes and 1 no.

2. In adult patients with  $\geq 2$  prior inductions 6 of 28 (21% of patients had CR or CR\*. Five of 6 CR or CR\* patients who did not have their CR or CR\* duration confounded by subsequent Transplant or other Systemic chemotherapy had CR or CR\* durations of 4, 15, 19, 30 and 195+ weeks.

Are these results reasonably likely to predict clinical benefit in this setting?

The committee voted 12 yes and 0 no.

3. Is the benefit/risk favorable?

No vote was taken.

4. Should this NDA be granted accelerated approval?

For pediatric patients? The committee voted 11 yes and 1 no.

For adult patients? The committee voted 12 yes and 0 no.

## Phase 4 Confirmatory Study

COG AALL0434, the proposed Phase 4 study to confirm clinical benefit, is a randomized, multi-center, cooperative group trial (COG). The draft study design was presented at the Oncologic Drugs Advisory Committee meeting. It will accrue 640 patients with T-ALL,

ages 1-30 years. It will utilize the modified BFM regimen. Intermediate and high risk patients will be randomized to a regimen with or without nelarabine and to high-dose methotrexate or to escalating IV methotrexate. The primary endpoint is event-free survival at 4 years. The safety phase will evaluate the first 20 consecutive high risk patients.

As submitted on September 26, 2005 and committed to on October 25, 2005, the anticipated timelines for the Phase III COG Study (AALL0434) as discussed with the NCI and the COG are as follows:

First patient enrolled ..... April 2006  
End of safety phase ..... 4Q 2009  
Complete accrual ..... 4Q 2012  
Complete 3- year follow- up... 4Q 2015  
Availability of study report... 4Q 2016

#### Clinical Inspection Summary

The Division of Scientific Investigation's overall assessment of findings and general recommendations are summarized below:

The inspections of \_\_\_\_\_ and Dr. Camitta did not identify any significant observations. The inspection of Dr. DeAngelo identified two discrepancies between the CRFs and sponsor's data listings. The review division should examine the sponsor's method for determining the date of study withdrawal for protocol CALGB 1980. Overall, the data appear reliable.

#### Clinical Pharmacology/Biopharmaceutics Review

The Clinical Pharmacology/Biopharmaceutics Review by Sophia Abraham, Ph.D. stated that

NDA 21- 877 filed for ARRANON (Nelarabine) Injection is acceptable from the Clinical Pharmacology and Biopharmaceutics perspectives. Please forward the Clinical Pharmacology Labeling Recommendations (Pages 53-58 of this review) and the following Comment to the Applicant.

Adenosine deaminase (ADA) activity is required for the formation of the active species of nelarabine. \_\_\_\_\_ adenosine deaminase may reduce the effectiveness of this drug in some patients. Please correlate the pharmacokinetic results of the phase 1 studies with the results of the ADA genetic screening and submit this report to the FDA.

The labeling recommendations were incorporated into the latest version of the package insert.

### Chemistry Review

The Chemistry Review by Xiao-Hong Chen, Ph.D., had the following 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.

### Product Quality Microbiology Review

The microbiology review by Stephen Langille, Ph.D. stated that "NDA 21-877 is recommended for approval from the standpoint of product quality microbiology."

### Pharmacology/Toxicology Review and Evaluation

The Pharmacology/Toxicology Review and Evaluation by W. David McGuinn, Jr., Ph.D., stated that "I find no pharmacological or toxicological issues that would prevent the approval of Nelarabine for the proposed medical indication." No additional non-clinical studies were recommended. Recommendations on labeling were communicated to the applicant and were incorporated into the package insert.

The tertiary review by Kenneth L. Hastings, Dr.P.H., stated that "I have reviewed the information and proposed product label for ARRANON® (nelarabine) Injection and concur that this product is approvable based on submitted pharmacology/ toxicology data. The label is adequate with respect to nonclinical issues and requires no changes."

### DSRCS Consult on the PPI

A consult on the proposed Information for Patients and Caregivers was requested of the Division of Surveillance, Research, and Communication Support. The consultation from Jeanine Best, M.S.N., R.N., P.N.P provided revised Patient Labeling which was sent to the applicant. The applicant agreed to the revised Patient Labeling.

### DDMAC Consultation on the Draft Labeling

A DDMAC consultation on the draft labeling by Joseph A. Grillo was completed on August 30, 2005 and the comments were considered during the labeling negotiations.

### DMETS Consultation

A consultation from the Division of Medication Errors and Technical Support, Office of Drug Safety was completed on September 22, 2005. The recommendations are as follows.

1. DMETS has no objections to the use of the proprietary name, Arranon. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval 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 in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Arranon acceptable from a promotional perspective.

The DMETS label and labeling recommendations were communicated to the applicant. Revised labeling was submitted. The revised labels were acceptable to the CMC reviewers.

### ODS Review of Proposed Risk Management Plan

A consultation regarding a proposed risk management plan was completed by Susan Lu, R.Ph., on September 15, 2005. The conclusions were as follows.

ODS has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RMP to minimize risk would be normally associated. In summary, the information in the product labeling and routine pharmacovigilance practices proposed by GSK appear reasonable in communicating the risk of neurotoxicity of nelarabine. ODS plans to closely monitor postmarketing adverse event reports of severe neurotoxicity associated with nelarabine.

### Recommended Regulatory Action

I concur that the application should be granted accelerated approval for the proposed indication and agree with the concept of the proposed Phase 4 study to confirm clinical benefit. Although the Phase 4 study is not ongoing, it will be submitted for a Special Protocol Assessment in November 2005 and will begin accrual in April 2006.

Robert L. Justice, M.D., M.S.  
Acting Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

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/s/

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Robert Justice  
10/27/2005 06:41:21 PM  
MEDICAL OFFICER

**MEMORANDUM**

Oct. 27, 2005

TO: File

FROM: Kenneth L. Hastings, Dr.P.H., D.A.B.T.

SUBJECT: NDA 21-877

I have reviewed the information and proposed product label for ARRANON® (nelarabine) Injection and concur that this product is approvable based on submitted pharmacology/toxicology data. The label is adequate with respect to nonclinical issues and requires no changes.

---

Kenneth L. Hastings, Dr.P.H., D.A.B.T.

Associate Director for Pharmacology and Toxicology  
Office of Drug Evaluations II & III

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/s/

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Kenneth Hastings  
10/27/2005 04:04:59 PM  
PHARMACOLOGIST

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2 **OFFICE OF ONCOLOGY DRUG PRODUCTS**  
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8 **Beltsville, Maryland 20705-1266**  
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15 immediately notify us by telephone and return it to us at the above address by mail. Thank you.  
16

17 **PHONE: (301)796-1365 FAX: (301) 796-9845**

18  
19 **TO: Ellen Cutler, GSK**

20 **Fax: 610-917-4100**

21  
22 **FROM: Nicholette Y. Hemingway, Project Manager**

23 **Phone: (301) 796-1365**

24  
25 **Total number of pages, including cover sheet 22**

26  
27 **Date: 10-26-05**

28  
29 **COMMENTS:** Re: your NDA 21-877 for Arranon (nelarabine), we have the following comments  
30 regarding proposed labeling changes that need to be addressed as soon as possible. Please respond  
31 by 12 PM October 27, 2005.

32 Nicholette

33  
34  
35

**COMMENTS:**

**APPEARS THIS WAY  
ON ORIGINAL**

**APPEARS THIS WAY  
ON ORIGINAL**

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

\_\_\_\_\_ § 552(b)(5) Deliberative Process

✓  
\_\_\_\_\_ § 552(b)(5) Draft Labeling

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/s/

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Nicholette Hemingway  
10/26/2005 03:28:32 PM  
CSO

October 25, 2005

Robert Justice, M.D., Acting Director  
Division of Oncology Drug Products  
Center for Drug Evaluation and Research  
Attn: Document Control Room  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**Re: NDA 21-877; ARRANON® (nelarabine) Injection  
General Correspondence: Phase IV Commitment**

Dear Dr. Justice:

Reference is made to NDA 21-877 for Arranon (nelarabine) Injection submitted April 29, 2005 for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Reference is also made to our September 26, 2005 submission whereby GSK provided a detailed overview of the timelines for the proposed Phase III study of Arranon in the frontline treatment of patients with T-ALL to be conducted by the Children's Oncology Group (COG). This study would be conducted as a postmarketing study to verify and describe the clinical benefit of Arranon if approved under Subpart H, 21 CFR 314.510. Additional reference is made to an October 25 voice message from Nicholette Hemingway requesting written confirmation of our commitment to conduct the study described in our letter. This submission provides written confirmation of GSK's commitment to conduct the following postmarketing study.

GSK agrees to conduct COG AALL0434: "Intensified methotrexate, Compound 506U78 and Augmented BFM Therapy for Children and Young Adults with Newly Diagnosed T-cell Acute Lymphoblastic Leukemia."

The anticipated timelines for the Phase III COG study (AALL0434) as discussed with the NCI and COG are as follows:

First patient enrolled ..... April 2006  
End of safety phase ..... 4Q 2009  
Complete accrual ..... 4Q 2012  
Complete 3-year follow-up... 4Q 2015

Robert Justice, M.D.

October 25, 2005

Page 2

Availability of study report... 4Q 2016

As discussed at our February 18, 2005 pre-NDA meeting, we plan to submit a request for a Special Protocol Assessment (SPA) prior to initiation of the study. The final (CTEP approved) protocol will be available November 2005.

Additionally, GSK agrees to annually report the status of the required postmarketing commitment in accordance with 21 CFR 314.81(b)(2)(vii).

If you should have any additional comments concerning this submission, please contact me by telephone at 610-787-3733 or by facsimile at 610-787-7062.

Sincerely,

Ellen S. Cutler  
Senior Director  
Regulatory Affairs

**FOOD AND DRUG ADMINISTRATION  
OFFICE OF ONCOLOGY DRUG PRODUCTS**



**DIVISION OF DRUG ONCOLOGY PRODUCTS**

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**PHONE: (301)796-1365 FAX: (301) 796-9845**

**TO: Ellen Cutler, GSK**  
**Fax: 610-917-4100**

**FROM: Nicholette Y. Hemingway, Project Manager**  
**Phone: (301) 796-1365**

**Total number of pages, including cover sheet 4**

**Date: 10-24-05**

**COMMENTS:** Re: your NDA 21-877 for Arranon (nelarabine), we have the following comments regarding revised patient information that need to be addressed as soon as possible.

**COMMENTS:**

7 Page(s) Withheld

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       § 552(b)(5) Deliberative Process

✓  
       § 552(b)(5) Draft Labeling

Please provide this information by 12PM October 25, 2005.

Please call me at the above number if you have any questions.

Thanks,  
Nicholette

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/s/

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Nicholette Hemingway  
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17 **PHONE: (301)796-1365 FAX: (301) 796-9845**

18  
19 **TO: Ellen Cutler, GSK**  
20 **Fax: 610-787-7062**

21  
22 **FROM: Nicholette Y. Hemingway, Project Manager**  
23 **Phone: (301) 796-1365**

24  
25 **Total number of pages, including cover sheet 20**

26  
27 **Date: 10-24-05**

28  
29 **COMMENTS:** Re: your NDA 21-877 for Arranon (nelarabine), we have the following proposed  
30 labeling changes from our review team that need to be addressed as soon as possible.  
31

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/s/

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Nicholette Hemingway  
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PHONE: (301)594-5750 FAX: (301) 594-0499

TO: Ellen Cutler, GSK  
Fax: 610-787-7062

FROM: Nicholette Y. Hemingway, Project Manager  
Phone: (301) 594-5750

Total number of pages, including cover sheet 2

Date: 9-28-05

COMMENTS: Re: your NDA 21-877 for Arranon (nelarabine), we have the following deficiencies from our chemistry review team that need to be addressed as soon as possible.

### DEFICIENCIES:

#### Drug Substance:

1. It appears that you do not have sufficient batch data or manufacturing experience to justify for eliminating \_\_\_\_\_ testing. This test should be included in the drug substance release specifications.
2. Batch analysis data for \_\_\_\_\_ ranges from \_\_\_\_\_. The acceptance limit of \_\_\_\_\_ appears to be too broad and should be tightened.
3. Please provide updated release specifications.
4. It is not acceptable that stability testing for annual batches of nelarabine drug substance follows a reduced stability testing protocol (\_\_\_\_\_).

months). Proposal for reduced stability testing should be submitted in a prior approval supplement with sufficient data and manufacturing history.

**Drug Product:**

5. The proposed specification of NGT —, w/w for — is too broad and should be tightened based on toxicology and batch data.
6. Specification for Any Other Impurity should also be tightened to NMT 0.1% per ICH Q3B Guidelines.
7. Please provide updated release specifications.
8. It is not acceptable that stability testing for annual batches of nelarabine drug product follows a reduced stability testing protocol ( — months). Proposal for reduced stability testing should be submitted in a prior approval supplement with sufficient data and manufacturing history.
9. Please submit real time in-use stability data to support your claim that Nelarabine Injection, 5 mg/mL was compatible and stable for up to 8 hours in the proposed diluent and PVC infusion bags.

**Comments:**

1. Based on provided primary and supportive drug substance stability data, a retest period of — can be established.
2. The proposed drug product shelf life of — at 25°C (77°F) is not acceptable, due to the differences in specifications, analytical methods, manufacturing sites and packaging used for the proposed commercial product and for primary stability batches. Based on provided primary and supportive drug product stability data, an expiration dating period of — can be considered.

Please provide this information by COB September 30, 2005.

Please call me at the above number if you have any questions.

Thanks,  
Nicholette

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/s/

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Nicholette Hemingway  
9/28/2005 11:56:05 AM  
CSO

September 26, 2005



GlaxoSmithKline

Robert Justice, M.D., Acting Director  
Division of Oncology Drug Products  
Center for Drug Evaluation and Research  
Attn: Document Control Room  
Food and Drug Administration  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

**GlaxoSmithKline**  
2301 Renaissance Boulevard  
P.O. Box 61540  
King of Prussia, PA  
19406-2772  
Tel. 610 787 7000  
Fax. 610 787 7777  
www.gsk.com

**Re: NDA 21-877; ARRANON® (nelarabine) Injection  
Response to FDA Request: Phase IV Commitment**

Dear Dr. Justice:

Reference is made to NDA 21-877 for Arranon (nelarabine) Injection submitted April 29, 2005 for the treatment of patients with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Reference is also made to a September 19, 2005 request from Dr. Sheila Ryan to provide a detailed overview of the timelines for the proposed Phase III study of Arranon in the frontline treatment of patients with T-ALL or T-LBL to be conducted by the Children's Oncology Group (COG) and to provide the synopses for any other studies under consideration.

The purpose of this submission is to provide a response to the information requested.

1. Anticipated Timelines for the Phase III COG Study (AALL0434) as discussed with the NCI and the COG are as follows:

First patient enrolled ..... April 2006  
End of safety phase ..... 4Q 2009  
Complete accrual ..... 4Q 2012  
Complete 3-year follow-up... 4Q 2015  
Availability of study report... 4Q 2016

As discussed at our February 18, 2005 pre-NDA meeting, we plan to submit a request for a Special Protocol Assessment (SPA) prior to initiation of the study. The final (CTEP approved) protocol will be available November 2005. A draft protocol from the COG (prior to CTEP approval) will be available shortly and could be provided to you in advance of the SPA submission. A detailed list of any revisions to the draft protocol

could also be included at the time of the SPA request. Please let me know if you would like to start the review the draft protocol or wait for the final protocol next month.

2. Other Studies Under Consideration

We have not been able to identify other potential clinical trials that isolate the contribution of Arranon, have endpoints suitable for conversion to regular approval, and can be achieved in any shorter time frame than the currently proposed AALL0434 study. We have considered

Arranon has shown the greatest activity in patients with immature T-cell malignancies, so there is concern about conducting a confirmatory trial in patients with malignancies other than T-ALL/T-LBL. Randomized studies are only acceptable in the front-line setting for these patients. Most patients with relapsed or refractory disease will receive a stem cell transplant or additional chemotherapy after achieving remission. A very small percent would not, making it difficult to enroll in a timely manner a sufficient number of patients whose response is uncomplicated by other therapies.

Please contact me by telephone at (610) 787-3733 or by facsimile at (610) 787-7062 if you have any questions or clarification is needed.

Sincerely,



Ellen S. Cutler  
Senior Director  
Regulatory Affairs



**MEMORANDUM**      **DEPARTMENT OF HEALTH AND HUMAN SERVICES**  
**PUBLIC HEALTH SERVICE**  
**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

---

**DATE:** September 15, 2005

**TO:** Robert Justice, MD, Acting Director  
Division of Drug Oncology Products, HFD-150

**THROUGH:** Office of Drug Safety (ODS)  
Mary Dempsey, Project Management Officer, HFD-400

**FROM:** Division of Drug Risk Evaluation (DDRE)  
Susan Lu, R.Ph., Safety Evaluator Team Leader, HFD-430

**DRUG:** Arranon® (nelarabine) for Injection

**NDA #:** 21-877

**SPONSOR:** GlaxoSmithKline (GSK)

**SUBJECT:** ODS Review of Proposed Risk Management Plan (RMP) submitted  
April 29, 2005

**PID #:** D050520

The Office of Drug Safety (ODS) has reviewed the proposed Risk Communication Strategy for nelarabine as submitted on April 29, 2005 and concludes that this RMP does not appear to differ substantially from routine risk management measures, such as FDA-approved professional labeling and routine post-marketing surveillance.

Arranon® (nelarabine), a pro-drug of ara-G, is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy agents.

Dose limiting neurologic adverse events were observed early in the development of nelarabine and included grade 3 and 4 neurotoxicity affecting both central and peripheral nervous systems. Neurologic adverse events have included somnolence, confusion, convulsions, ataxia, paresthesias and hypoesthesia. Severe neurologic toxicity can present as coma, status epilepticus, craniospinal demyelination and Guillain Barre-like syndrome.

These events may be irreversible and can be fatal. Increasing nelarabine daily dose and increasing patient age (especially >65 years) were generally observed with increasing rate of neurological events.

The sponsor states that like other nucleoside analogs, nelarabine has been associated with hematologic and neurologic toxicity and that data indicates the safety profile can be acceptable when patients are carefully observed for onset of neurotoxicity and when nelarabine is administered according to recommended doses.

GSK has proposed to manage the risk of nelarabine associated neurologic events through

- 1) Communicating neurologic risks through product labeling in a boxed warning, Warnings section, Adverse Events section, Information for Patient section and Dosage and Administration section
- 2) Educational programs and awareness sessions directed to physicians and associated health-care professional involved in the treatment of the indicated patient population
- 3) Good pharmacovigilance practices by GSK to collect, evaluate, and report safety concerns
- 4) Reporting of additional safety information from ongoing clinical trials, including multi-agent trials.<sup>2</sup>

On August 16, 2005 Susan Lu conferred with Bob Justice (Acting Director DDOP) and Marty Cohen (M.O.) about the proposed RMP for nelarabine. They both concurred that the product labeling sufficiently addresses the risk of neurotoxicity and that a RMP is not needed. A separate Patient Package Insert (PPI) consult was performed by the ODS Division of Surveillance, Research and Communication Support (DSRCS).

ODS has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RMP to minimize risk would be normally associated. In summary, the information in the product labeling and routine pharmacovigilance practices proposed by GSK appear reasonable in communicating the risk of neurotoxicity of nelarabine. ODS plans to closely monitor postmarketing adverse event reports of severe neurotoxicity associated with nelarabine.

Should the review division wish ODS to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

---

Mary Dempsey, Project Management Officer  
Office of Drug Safety, HFD-400

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/s/

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Mary Dempsey  
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DRUG SAFETY OFFICE REVIEWER

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       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler--GSK

From: Sheila Ryan, PharmD

Fax: 610-787-7062

Fax: 301-594-0498

Phone: 610-787-3733

Phone: 301-594-5771

Pages, including cover sheet:

Date: September 9, 2005

Re: NDA 21-877 for Arranon® (nelarabine) Injection

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● Dear Ellen,

Please refer to your NDA 21-877 for Arranon (nelarabine) Injection. This facsimile contains comments regarding the proprietary name for this application from the Division of Medication Errors and Technical Support (DMETS). Also, this facsimile contains comments regarding the carton and container labels for this product.

Please contact me should you have any questions.

Thank you,

Sheila Ryan, Pharm.D.  
Regulatory Project Manager

**PROPRIETARY NAME COMMENTS:**

1. DMETS has no objections to the use of the proprietary name, Arranon. 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. DDMAC finds the proprietary name Arranon acceptable from a promotional perspective.

**LABELING COMMENTS:**

DMETS recommends implementation of the following label and labeling revisions to minimize potential errors with the use of this product.

**A. GENERAL COMMENTS**

1. Center the established name (i.e., Nelarabine Injection) so that it is presented directly under the proprietary name in order to increase readability.
2. Increase the size of the established name so that it is at least one-half the size of the proprietary name.
3. Increase the prominence of the route of administration in order to ensure the medication is administered correctly.
4. In order to inform healthcare practitioners of the total drug content in each vial as well as the concentration, revise the statement of strength to read \_\_\_\_\_
5. The container label, nor the carton and package insert labeling contain any information and/or directions with regard to dilution or administration of this product. Please include this information in detail in the package insert, and list this information on the carton labeling and container label (if space allows).

**B. CONTAINER LABEL**

1. See General Comments A-1 through A-6.
2. Relocate the statement, \_\_\_\_\_ to the side panel, in order to increase the prominence of the total drug content and concentration.
3. Include a usual dosage statement that reads, “\_\_\_\_\_”

C. CARTON LABELING

1. See General Comments A-1 through A-3 and comment B-2.
2. Revise the usual dosage statement to read, ' —

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/s/

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Sheila Ryan  
9/9/2005 03:00:12 PM  
CSO

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler

From: Sheila Ryan, PharmD

Fax: 610-787-7062

Fax: 301-594-0498

Phone: 610-787-3733

Phone: 301-594-5771

Pages, including cover sheet: 2

Date: September 1, 2005

Re: NDA 21-877 Nelarabine telecon date

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●Ellen,

In response to your August 17, 2005 request for a teleconference for Arranon (nelarabine) Injection, we have a tentative date of September 6, 2005 at 12:00 PM EST. I have attached the FDA invitees for the meeting. Please confirm this date as soon as possible.

Please contact me should you have any questions.

Thank you,

Sheila Ryan  
Regulatory Project Manager

**ATTENDEES:**

Robert Justice, M.D., Acting Division Director  
John Johnson, M.D., Clinical Team Leader  
Martin Cohen, M.D., Clinical Reviewer  
Rajeshwari Sridhara, Ph.D., Biostatistical Team Leader  
Tristan Massie, Ph.D., Biostatistical Reviewer

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/s/

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Sheila Ryan  
9/1/2005 10:26:40 AM

4 Page(s) Withheld

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

       § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

**CONSULTATION RESPONSE**

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

<b>DATE RECEIVED:</b> August 12, 2005	<b>DESIRED COMPLETION DATE:</b> September 30, 2005	<b>ODS CONSULT #:</b> 04-0288-1
<b>DATE OF DOCUMENT:</b> April 29, 2005	<b>PDUFA DATE:</b> October 28, 2005	

**TO:** Robert Justice, MD  
Acting Director, Division of Drug Oncology Products  
HFD-150

**THROUGH:** Sheila Ryan  
Project Manager, Division of Drug Oncology Products  
HFD-150

<b>PRODUCT NAME:</b> Arranon (Nelarabine Injection) 250 mg/50 mL	<b>NDA SPONSOR:</b> GlaxoSmithKline
<b>NDA#:</b> 21-877	

**SAFETY EVALUATOR:** Felicia Duffy, RN

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Arranon. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval 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 in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Arranon acceptable from a promotional perspective.

Denise P. Toyer, PharmD Deputy Director Division of Medication Errors and Technical Support Office of Drug Safety	Carol Holquist, RPh Director Division of Medication Errors and Technical Support Office of Drug Safety Phone: (301) 827-3242      Fax: (301) 443-9664
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**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** August 29, 2005  
**NDA #:** 21-877  
**NAME OF DRUG:** Arranon (Nelarabine Injection) 250 mg/50 mL  
**NDA HOLDER:** GlaxoSmithKline

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Drug Oncology Products (HFD-150), for re-review of the proprietary name, "Arranon", regarding potential name confusion with other proprietary or established drug names as well as pending names. The proposed proprietary name, Arranon, was found acceptable by DMETS in a review dated January 3, 2005 (ODS consult #04-0288). Container labels, carton, and insert labeling were provided for review and comment at this time.

**PRODUCT INFORMATION**

Arranon is a chemotherapeutic agent indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two other chemotherapy regimens. The usual adult dose of Arranon is 1500 mg/m<sup>2</sup> intravenously over two hours on days 1, 3 and 5 repeated every 21 days. The usual pediatric dose is 650 mg/m<sup>2</sup> intravenously over one hour daily for 5 consecutive days repeated every 21 days. Arranon will be supplied in vials containing 250 mg nelarabine in 50 mL Water for Injection, USP. Cartons will be available with 1 vial or 6 vials.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup> as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Arranon to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use

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<sup>1</sup> MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)

database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Arranon. 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 finds the proposed proprietary name, Arranon, acceptable from a promotional perspective.
2. The Expert Panel identified two additional proprietary names that were thought to have the potential for confusion with Arranon. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

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

Product Name	Dosage form(s), Established name	Usual adult dose	Other
Arranon	Nelarabine Injection: 250 mg/50 mL	Adult Dose: 1500 mg/m <sup>2</sup> intravenously over two hours on days 1, 3, and 5 and repeated every 21 days Pediatric Dose: 650 mg/m <sup>2</sup> intravenously over one hour daily for 5 consecutive days repeated every 21 days	
Omacor	Omega-3-Acid Ethyl Esters Capsule: 1 gram	4 grams/day (taken as a single dose or as a twice daily divided dose).	LA
Amicar	Aminocaproic Acid Tablet: 500 mg Syrup: 1.25 gm/5 mL Injection: 250 mg/mL	Adults: <u>Intravenous therapy:</u> Give 4 to 5 grams in 250 mL of diluent by infusion during the first hour, followed by continuous infusion at the rate of 1 gram/hr in 50 mL of diluent. Continue for 8 hours or until bleeding is controlled. <u>Oral therapy:</u> 5 grams by mouth given the first hour, followed by 1 gram (tablets) or 1.25 grams (syrup) per hour. Continue for 8 hours or until bleeding is controlled. Pediatrics: 100 mg/kg or 3 grams/m <sup>2</sup> IV as a loading dose, followed by 33.3 mg/kg/hr or 1 gram/m <sup>2</sup> /hour IV continuous infusion, not to exceed 18 grams/m <sup>2</sup> /day IV.	LA
*Frequently used, not all-inclusive. **L/A (look-alike), S/A (sound-alike)			

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 Arranon were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

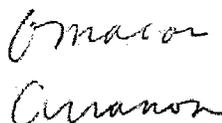
Prescription studies were not repeated because they were conducted during the initial review (see ODS consult #04-0288, section IIC).

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Arranon, the primary concerns related to look-alike and sound-alike confusion with Omacor and Amicar.

1. Omacor can look similar to Arranon when scripted. Omacor is indicated as an adjunct to diet to reduce very high ( $\geq 500$  mg/dL) triglyceride levels in adults. The first letter 'O' can look similar to the letter 'A' when scripted (see below). Additionally, the double letter 'r' in Arranon can appear orthographically similar to the letter 'm' in Omacor. The last two letters of each name ('-or' vs. '-on') may look the same if the endings trail off. Omacor and Arranon may share an overlapping dose of 2 grams if a patient has a body surface area of  $1.3 \text{ m}^2$  at a dose of  $1500 \text{ mg/m}^2$ . In order for this to occur, the patient would need to be 5'0" and weigh 90 pounds. Although it possible for an adult to meet these criteria, the patient would be small and petite in stature. Additionally, an Omacor 2 gram dose would be given twice a day whereas a 2 gram Arranon dose would be given as a one-time order on days 1, 3, and 5. Differentiating product characteristics include indication for use (elevated triglycerides vs. leukemia/lymphoma), strength (1 gram vs. 250 mg/50 mL), usual dose (4 grams vs.  $1500 \text{ mg/m}^2$  and  $650 \text{ mg/m}^2$ ), dosing frequency (once daily or twice daily vs. days 1, 3 and 5 repeated every 21 days), route of administration (oral vs. intravenous), and dosage form (capsule vs. injection). Although some orthographic similarities exist, the differentiating product characteristics decrease the potential of medication errors between Omacor and Arranon.

Omacor / Arranon



Omacor  
Arranon

2. Amicar and Arranon can look similar when scripted. Amicar is useful in enhancing hemostasis when fibrinolysis contributes to bleeding. Fibrinolytic bleeding may frequently be associated with surgical complication following heart surgery, hematological disorders, acute and life-threatening abruption placenta, hepatic cirrhosis, and neoplastic disease such as carcinoma of the prostate, lung, stomach, and cervix. The beginnings of each name can

look similar when scripted ('Am' vs. 'Arr') (see page 5). Furthermore, each name is close in length (6 letters vs. 7 letters). Additionally, the endings can also look similar when scripted ('-ar' vs. '-on'). Amicar and Arranon share an overlapping numeral in the strength (250 mg/mL vs. 250 mg/50 mL), route of administration (intravenous), dosage form (injection), and prescriber population (hematology/oncology). The potential exists for an overlap in dose (4 grams); however, for this to occur, the patient would be 325 pounds and 7'1". This scenario is highly unlikely for a cancer patient whose disease has not responded to or has relapsed following treatment with at least two chemotherapeutic agents. The likelihood of the pediatric dose of Amicar and Arranon to overlap would appear only in an extreme case. For example, in order for the dose of a 2 year-old male (10.4 kg and 36") receiving Arranon, to overlap with an Amicar pediatric dose, the child receiving Amicar would have to be a premature infant (1.1 kg and 17"). This case is not likely to occur. The differentiating product characteristics between Amicar and Arranon include indication for use (hemostasis vs. leukemia/lymphoma), usual dose (4-5 grams or 3 grams/m<sup>2</sup> vs. 1500 mg/m<sup>2</sup> or 650 mg/m<sup>2</sup>), dosing regimen (over 8 hours or until the bleeding stops or 3 grams/m<sup>2</sup> IV as a loading dose, followed 1 gram/m<sup>2</sup>/hour IV continuous infusion vs. over 2 hours on days 1, 3, and 5 every 21 days or over 1 hour daily for 5 days repeated every 21 days). Although Amicar and Arranon share orthographic similarities and overlapping product characteristics, the likelihood of dose overlapping is minimal. Thus, the potential for confusion is also minimized.

Amicar / Arranon

*Amicar*  
*Arranon*

**III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:**

In the review of the container labels, carton and insert labeling of Arranon, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which may minimize potential user error.

**A. CONTAINER LABEL**

1. Ensure the size of the established name is at least one-half the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. The route of administration is small and difficult to read. Revise the route of administration statement to read, ~~intravenous~~ Increase the prominence of this statement in order to ensure the medication is administered correctly.

3. In order to inform healthcare practitioners of the total drug content in each vial as well as the concentration, revise the statement of strength to read. \_\_\_\_\_
4. Include the net quantity on the container label as it has been omitted. Ensure that the net quantity is presented away from the product strength in order to avoid confusion.
5. It is unclear if Arranon should be diluted prior to administration. The container label, nor the carton and package insert labeling contain any information and/or directions with regard to dilution or administration of this product. However, the stability subsection of the Dosage and Administration section states that "Nelarabine is stable \_\_\_\_\_ for up to 8 hours at up to 30°C." Please clarify if whether or not this product should be diluted in order to ensure proper administration. If the product must be further diluted prior to administration, this information should appear in the package insert, and on the carton labeling and container label.
6. Include a usual dosage statement that reads, " \_\_\_\_\_"
7. Relocate the \_\_\_\_\_ statement to the side panel to allow for space to increase the prominence of the strength and concentration.

#### B. CARTON LABELING

See comments A1 through A3, A5, and A6.

#### C. PACKAGE INSERT

See comment A5.

#### IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Arranon. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name and its associated labels and labeling must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product. We would be willing to revisit these issues of the Division another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Arranon acceptable from a promotional perspective

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 Diane Smith, Project Manager, at 301-827-1998.

---

Felicia Duffy, RN  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

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

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/s/

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Felicia Duffy  
9/21/2005 02:15:32 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
9/21/2005 02:55:56 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
9/22/2005 11:56:24 AM  
DRUG SAFETY OFFICE REVIEWER

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** July 28, 2005

**TO:** Richard Pazdur, M.D., Director  
Division of Oncologic Drug Products  
HFD-150

**VIA:** Sheila Ryan, Regulatory Health Project Manager  
Division of Oncologic Drug Products  
HFD-150

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCS Review of Patient Labeling for Arranon (nelarabine Injection), NDA 21-877

The patient labeling which follows is the revised Patient Labeling for Arranon (nelarabine Injection), NDA 21-877. We have simplified the wording, made it consistent with the PI, removed other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications, not to provide detailed information about the condition), and put it in the format that we are recommending for all patient information, although this format is not required for voluntary patient labeling (PPIs). Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor on April 29, 2005. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI

Comments to the review Division are bolded, italicized, and underlined. We can provide marked-up and clean copies of the revised document in Word if requested by the review division. Please let us know if you have any questions.

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**Tell the doctor about all health conditions you or your child have, including if you or your child:**

- **have any nervous system problems**
- **have kidney problems**
- **are pregnant or plan to become pregnant.** ARRANON may harm an unborn baby. You should use effective birth control to avoid getting pregnant. Talk with your doctor about your choices.
- **are breast feeding.** It is not known whether ARRANON passes through breast milk. You should not breast feed during treatment with ARRANON.

**Tell the doctor about all the medicines you or your child take, including prescription and nonprescription medicines, vitamins, and herbal supplements.**

**How is ARRANON given?**

- ARRANON is an I.V. medicine. This means it is given through a tube in your vein.

**What should I or my child avoid during ARRANON treatment?**

- **You or your child should not drive or operate dangerous machines.** ARRANON may cause sleepiness.
- **You or your child should not receive vaccines made with live germs during treatment with ARRANON.**

**What are the possible side effects of ARRANON?**

ARRANON may cause serious nervous system problems. See "What is the most important information I should know about ARRANON?"

**ARRANON may also cause:**

- **Decreased blood counts** such as low red blood cells, low white blood cells, and low platelets. Call the doctor right away if you or your child:
  - is more tired than usual, pale, or has trouble breathing
  - has a fever or other signs of an infection
  - bruises easy or has any unusual bleedingBlood tests should be done regularly to check blood counts.
- **stomach area problems** such as nausea, vomiting, diarrhea, and constipation.
- headache
- sleepiness
- blurry eyesight

**[DSRCS Comment: List other pertinent SEs.]**

These are not all the side effects with ARRANON. Ask your doctor or pharmacist for more information.

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/s/

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Jeanine Best  
7/28/05 02:25:52 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
7/28/05 04:12:14 PM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

**From:** Ryan, Sheila  
**Sent:** Friday, July 22, 2005 4:35 PM  
**To:** 'ellen.s.cutler@gsk.com'  
**Subject:** NDA 21-877  
Elaine

Please refer to NDA 21-877 for Arranon (nelarabine) Injection). Please also refer to your facsimile dated July 19, 2005. The following is the Division's response to this submission.

Your proposal for improved presentation of hematologic AE's is adequate.

Your proposal for improved presentation of neurologic AE's is also adequate, as long as all component MedDRA terms are listed in the label text or as subheadings in the AE table.

Please let me know if you have any questions.

Thank you,  
Sheila

Sheila Ryan, PharmD  
Regulatory Project Manager  
Division of Drug Oncology Products  
Phone: 301-594-5771  
Fax: 301-594-0498  
Email: ryans@cderr.fda.gov

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## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler--GSK

From: Sheila Ryan, PharmD

Fax: 610-787-7062

Fax: 301-594-0498

Phone: 610-787-3733

Phone: 301-594-5771

Pages, including cover sheet: 3

Date: July 8, 2005

Re: NDA 21-877 information request

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●Ellen,

Please refer to your New Drug Application for Arranon (nelarabine) Injection. Included in this facsimile are information requests from the review team. Please provide the requested information as soon as possible to facilitate our review of this application.

Please contact me should you have any questions.

Thank you,

Sheila Ryan  
Regulatory Project Manager

1. Please submit a dataset similar to the “pkpd.xpt” dataset submitted on April 29, 2005, with the following additional information appended.

- a. Add the data from subjects in the Phase 2 studies to the pkpd.xpt dataset. Use “NA” values and/or other flag variables for any data items that were not measured in the Phase 2 studies.

*Please note that the remaining requests in this facsimile apply to both the Phase 1 and Phase 2 datasets.*

- b. Add the following columns to the dataset:

Peripheral Neuropathy  
Guillain-Barré-like syndrome  
Seizure  
Pain in extremities  
Neutropenia  
Dizziness  
Ataxia

In these columns, please report the measured severity of the first occurrence of the adverse event when (if) it occurred in that subject. Please use separate flag variables to distinguish between incidences in which the adverse event occurred but the severity is unknown versus incidences in which the adverse event did not occur in that particular subject.

- c. Add the following columns:

Time of Peripheral Neuropathy  
Time of Guillain-Barré-like syndrome  
Time of Seizure  
Time of Pain in extremities  
Time of Neutropenia  
Time of Dizziness  
Time of Ataxia

In these columns, please report the time that the first incident of the particular adverse event occurred. Report the time in hours since the first dose of drug was administered.

2. Please submit the raw concentration-time data for each subject, as well as each subject’s adverse event data associated with the time of its observation for all Phase 1 and Phase 2 studies. For example, please submit a dataset in SAS Transport file format with the following columns of information:

ptid	Study number
subject	Unique Patient Identifier
trt	Prescribed treatment

trtgrpmg	Dose prescribed in mg
trtgrpm2	Prescribed treatment in mg/m <sup>2</sup>
tmtstdt	Treatment start date
tmtsttm	Time of treatment start
date	Date of PK and/or PD measurement on this line in dataset
time	Time of PK and/or PD measurement on this line in dataset
regimen	Dosing regimen
day	Day
course	Course
doseday	Dose day / cycle
Infusion.Duration	Infusion duration – numeric value
time.sfd	Time in hours since first dose of drug given to this patient
analyt	Analyte (e.g. "506U78" "ara-G" "ara-GTP")
Concentration	Concentration of analyte (e.g. Nelarabine, Ara-G,Ara-GTP)
AE.name	Adverse event recorded from the following list: (Peripheral Neuropathy,Guillain-Barré-like syndrome, Seizure, Pain in extremities, Neutropenia, Dizziness, Ataxia)
AE.severity	Severity of AE
actdsday	Number of doses in each cycle
cycl.dos	Total dose / cycle
age	Numeric value of age
agecat	Category of age (i.e. pediatric, adult >65 year)
cdx	Disease/clinical diagnosis
wtkg	Weight in kg
htcm	Height in cm
sexn	Sex numeric: 1=Male; 0=Female
race	Category of race
clcrgrp	Creatinine CL category
clcr	Creatinine clearance – numeric value
dmbsa	Body Surface Area
tmax	Time of maximum concentration
cmax	Maximum concentration
auct	AUC at tlast
aucinf	AUC with extrapolation
vss	Volume at steady state

Use flag variables to indicate values which are missing or haven't been measured.

- Please provide the computer code (e.g. SAS code) that was used to perform the analysis of the pkpd.xpt dataset (submitted on April 29, 2005).

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/s/

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Sheila Ryan  
7/8/05 01:26:26 PM  
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**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # 21-877                      Supplement # N/A                      Efficacy Supplement Type SE- N/A

Trade Name: ARRANON Injection  
Established Name: nelarabine  
Strengths: 5 mg/mL

Applicant: GlaxoSmithKline  
Agent for Applicant: N/A

Date of Application: 4-29-05  
Date of Receipt: 4-29-05  
Date clock started after UN: N/A  
Date of Filing Meeting: 6-20-05  
Filing Date: 6-28-05  
Action Goal Date (optional):

User Fee Goal Date: 10-29-05

Indication(s) requested: treatment of adult and pediatric patients with T-cell lymphoblastic leukemia (T-LBL) or T-cell lymphoblastic lymphoma (T-LBL) whose disease has no responded to or has relapsed following treatment with at least 2 chemotherapy regimens

Type of Original NDA:                      (b)(1)                       (b)(2)   
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   
Resubmission after withdrawal?                                            Resubmission after refuse to file?   
Chemical Classification: (1,2,3 etc.)                      1  
Other (orphan, OTC, etc.)                      orphan

Form 3397 (User Fee Cover Sheet) submitted:                      YES                       NO

User Fee Status:                      Paid                       Exempt (orphan, government)   
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

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

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? YES  NO   
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES  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)]? YES  NO

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)? YES  NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A  YES  NO   
**If an electronic NDA, all forms and certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format? all

Additional comments: All forms and certifications were submitted in paper with original signatures.

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A  YES  NO

- Is it an electronic CTD (eCTD)? N/A  YES  NO   
**If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments: NDA eCTD hybrid submission

- Patent information submitted on form FDA 3542a? YES  NO

- Exclusivity requested? YES, 7 Years NO   
**NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.**

- Correctly worded Debarment Certification included with authorized signature? YES  NO

**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  NO   
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)  
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y  NO
- PDUFA and Action Goal dates correct in COMIS? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: 42,778
- End-of-Phase 2 Meeting(s)? Date(s) 11-24-03, 6-30-04 NO   
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 9-27-04, 2-18-05 NO   
If yes, distribute minutes before filing meeting.

**Project Management**

- Was electronic "Content of Labeling" submitted? YES  NO   
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?  
YES  NO
- Risk Management Plan consulted to ODS/IO? N/A  YES  NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y  NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?  
N/A  YES  NO

**If Rx-to-OTC Switch application:**

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A  YES  NO
- Has DOTCDP been notified of the OTC switch application? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  
YES  NO

**Chemistry**

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

**APPEARS THIS WAY  
ON ORIGINAL**

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 6-20-05

**BACKGROUND:** GlaxoSmithKline submitted the Non-clinical and Quality (CMC) portions of this rolling NDA for this new molecular entity in December 2004. The clinical section of the application was submitted on April 29, 2005. This submission completed the application and started the review clock. The proposed indication is for the treatment of adult and pediatric patients with T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Nelarabine received Fast Track Designation on October 19, 2003 for treatment of T-cell malignancies and Orphan Drug Designation on August 10, 2004 for treatment of ALL and LBL.

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

**ATTENDEES:**

Richard Pazdur, M.D., Director  
John Johnson, M.D., Clinical Team Leader  
Rajeshwari Sridhara, Ph.D., Statistical Team Leader  
Tristan Massie, Ph.D., Statistical Reviewer  
Nallaperumal Chidabaram, Ph.D., Chemistry Team Leader  
Xiao Hong Chen, Ph.D., Chemistry Reviewer  
David Morse, Ph.D., Pharm/Tox Reviewer  
William D. McGuinn, Ph.D., Pharm/Tox Reviewer  
Sophia Abraham, Ph.D., Clin Pharm/Biopharmaceutics Reviewer  
Mary Mease, R.Ph., Division of Scientific Investigations  
Sheila Ryan, Pharm.D., Regulatory Project Manager

**ASSIGNED REVIEWERS (including those not present at filing meeting) :**

<b><u>Discipline</u></b>	<b><u>Reviewer</u></b>
Medical:	Cohen/Johnson
Secondary Medical:	N/A
Statistical:	Massie/Sridhara
Pharmacology:	McGuinn/Morse
Statistical Pharmacology:	N/A
Chemistry:	Chen,X/Chidambaram
Environmental Assessment (if needed):	TBD
Biopharmaceutical:	Abraham/Booth
Microbiology, sterility:	Langille
Microbiology, clinical (for antimicrobial products only):	N/A
DSI:	Mease
Regulatory Project Management:	Ryan
Other Consults:	Grillo (DDMAC), Lu (ODS)

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

YES  NO

CLINICAL

FILE

REFUSE TO FILE

- Clinical site inspection needed?

YES  NO

- Advisory Committee Meeting needed?

YES, date if known

9/13 or  
9/14/05

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

YES

NO

CLINICAL MICROBIOLOGY

N/A

FILE

REFUSE TO FILE

STATISTICS

N/A

FILE

REFUSE TO FILE

BIOPHARMACEUTICS

FILE

REFUSE TO FILE

- Biopharm. inspection needed?

YES

NO

PHARMACOLOGY

N/A

FILE

REFUSE TO FILE

- GLP inspection needed?

YES

NO

CHEMISTRY

FILE

REFUSE TO FILE

- Establishment(s) ready for inspection?
- Microbiology

YES

NO

YES

NO

**ELECTRONIC SUBMISSION:**

Any comments: NDA eCTD hybrid submission.

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

The application is unsuitable for filing. Explain why:

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

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 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.  Convey document filing issues/no filing issues to applicant by Day 74.
4. Complete consults to ODS/IO riskMAP. Completed by SR, 6-24-05.
5. Complete consult to ODS/DDRE for pre-approval safety conference. Completed by SR, 6-24-05
6. Complete consult to ODS/DSRCS for patient package insert. Completed by SR, 6-24-05.
7. Schedule labeling meetings for end of September/early October. Completed by SR, 6-20-05.
8. Notify company of possible ODAC meeting on September 13-14, 2005. Completed by SR, 6-05.

Sheila Ryan, Pharm.D.  
Regulatory Project Manager, HFD-150

## 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  NO

*If "No," skip to question 3.*

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
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? YES  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  NO

*(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  NO   
(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, YES  NO   
ORP?

*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? YES  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").
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)). YES  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)). YES  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). YES  NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES  NO
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)  
Patent number(s):

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

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

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)  
Patent number(s):

**NOTE:** *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)].*

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)  
Patent number(s):

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).  
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.  
Patent number(s):

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?  
YES  NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES  NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A  YES  NO

• 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  YES  NO

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  NO

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

YES  NO

- EITHER

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

IND# \_\_\_\_\_ NO

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?

YES  NO

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

YES  NO

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this page is the manifestation of the electronic signature.**  
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/s/

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Sheila Ryan  
6/28/05 01:47:59 PM  
CSO



**FILING COMMUNICATION**

NDA 21-877

SmithKline Beecham Corporation d/b/a GlaxoSmithKline  
Attention: Ellen Cutler  
Senior Director, Oncology Regulatory Affairs  
230 Renaissance Boulevard  
PO Box 61540  
King of Prussia, PA 19406

Dear Ms. Cutler:

Please refer to your April 29, 2005 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ARRANON® (nelarabine) Injection, 5 mg/mL.

We also refer to your submissions dated December 17, 2004 and April 14, 2005.

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 June 28, 2005 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 Sheila Ryan, Pharm.D., Regulatory Project Manager, at (301) 594-5771.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
Center for Drug Evaluation and Research

-----  
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this page is the manifestation of the electronic signature.**  
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/s/

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Dotti Pease  
6/27/05 12:05:46 PM  
Signing for Richard Pazdur, M.D.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-877

SmithKline Beecham Corporation d/b/a GlaxoSmithKline  
Attention: Ellen Cutler  
Senior Director, Oncology Regulatory Affairs  
230 Renaissance Boulevard  
PO Box 61540  
King of Prussia, PA 19406

Dear Ms. Cutler:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	ARRANON® (nelarabine) Injection 5 mg/mL
Review Priority Classification:	Priority (P)
Date of Application:	April 29, 2005
Date of Receipt:	April 29, 2005
Our Reference Number:	NDA 21-877

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on June 28, 2005 in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be October 29, 2005

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this

NDA 21-877

Page 2

application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Central Document Room (CDR)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

If your submission only contains paper, send it to one of the following address:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Oncology Drug Products  
Attention: Division Document Room, 3067  
5600 Fishers Lane  
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Oncology Drug Products, HFD-150  
Attention: Document Room 3067  
1451 Rockville Pike  
Rockville, Maryland 20852

If you have any questions, call Sheila Ryan, Pharm.D., Regulatory Project Manager, at (301) 594-5771

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I  
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.**  
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/s/

-----  
Dotti Pease  
6/27/05 12:01:38 PM  
Signing for Richard Pazdur, M.D.

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler--GSK

From: Sheila Ryan, PharmD

Fax: 610-787-7062

Fax: 301-594-0498

Phone: 610-787-3733

Phone: 301-594-5771

Pages, including cover sheet: 1

Date: May 10, 2005

Re: NDA 21-877 clinical information request

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

●Ellen,

Please refer to your New Drug Application for Arranon (nelarabine) Injection. Please provide the following information as soon as possible to facilitate our review of this application.

1. What is study PGAA2003? Please provide a description of this study.
2. Where can the primary bone marrow and lesion data for studies 2001 and 2002 be found within the application?

Please contact me should you have any questions.

Thank you,

Sheila Ryan  
Regulatory Project Manager

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

/s/

-----  
Sheila Ryan

5/10/05 02:52:37 PM

CSO

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler--GSK

From: Sheila Ryan, PharmD

Fax: 610-787-7062

Fax: 301-594-0498

Phone: 610-787-3733

Phone: 301-594-5771

Pages, including cover sheet: 2

Date: May 10, 2005

Re: NDA presentation for Arranon® (nelarabine) Injection

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● Dear Ellen,

Please refer to your NDA 21-877 for Arranon (nelarabine) Injection. We have tentatively scheduled your NDA presentation regarding this application for June 14, 2005 at 2:00 pm EST. The presentation will take place at the Woodmont Office Complex II (WOCII) located at 1451 Rockville Pike, Rockville, MD. Please confirm this date with me by facsimile or phone as soon as possible.

This presentation is expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA. In addition to providing an overview of the NDA, you should present your reasons for why the Division or the Office of Drug Evaluation I should approve this NDA.

I have also attached the anticipated FDA attendees for the presentation. Please provide me with a list of attendees from your company and 25 copies of the presentation prior to the presentation date.

Please contact me should you have any questions.

Thank you,

Sheila Ryan, Pharm.D.  
Regulatory Project Manager

May 10, 2005

**Anticipated Attendees:**

Richard Pazdur, MD, Division Director, Division of Oncology Drug Products (DODP)  
Robert Justice, MD, Acting Deputy Director, DODP  
John Johnson, MD, Medical Team Leader, DODP  
Martin Cohen, MD, Medical Reviewer, DODP  
Nallaperumal Chidambaram, PhD, Chemistry Team Leader, DODP  
Xiao Hong Chen, PhD, Chemistry Reviewer, DODP  
David Morse, PhD, Pharmacology Team Leader, DODP  
William McGuinn, PhD, Pharmacology Reviewer, DODP  
Brian Booth, PhD, Acting Biopharmaceutics Team Leader, DODP  
Sophia Abraham, PhD, Biopharmaceutics Reviewer, DODP  
Rajeshwari Sridhara, PhD, Statistical Team Leader, DODP  
Ning Li, PhD, Statistical Reviewer, DODP  
David Hussong, PhD, Microbiology Team Leader, DODP  
Sheila Ryan, PharmD, Project Manager, DODP

**In addition, the following people have been invited to attend:**

Robert Temple, MD, Director, Office of Drug Evaluation I  
Karen Weiss, MD, Director, Office of Drug Evaluation VI  
Joseph Grillo, PharmD, Division of Drug Marketing, Advertising, and Communication  
David Gan, MD, DrPH, Division of Scientific Investigation  
Leslie Ball, MD, Division of Scientific Investigation  
Ele Ibarra-Pratt, Division of Scientific Investigation  
Robert Kang, Office of Drug Safety  
Susan Lu, Office of Drug Safety  
Robert Pratt, Office of Drug Safety  
Jennie Chang, Office of Drug Safety

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler

From: Sheila Ryan, PharmD

Fax: 610-787-7062

Fax: 301-594-0498

Phone: 610-787-3733

Phone: 301-594-5771

Pages, including cover sheet: 7

Date: March 15, 2005

Re: IND 42,778 pre-NDA minutes

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

●Ellen,

Attached are the finalized FDA minutes for the pre-NDA meeting for nelarabine that occurred on February 18, 2005.

Please contact me should you have any questions.

Thank you,

Sheila Ryan  
Regulatory Project Manager

## INDUSTRY MEETING MINUTES

**MEETING DATE:** February 18, 2005      **TIME:** 12:00 PM      **LOCATION:** WOCII/E

**IND:** 42,778

**Meeting Request Submission Date:** December 16, 2004 (sn174)

**FDA Response Date:** December 22, 2004

**Briefing Document Submission Date:** January 20, 2005 (sn176)

**Additional information Submission Date:** February 16, 2005 (sn178)

**DRUG:** Nelarabine (506U78)

**SPONSOR:** GlaxoSmithKline (GSK)

**TYPE of MEETING:**

Pre-NDA meeting

**INDICATION:**

For the treatment of pediatric and adult 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 2 chemotherapy regimens.

**FDA PARTICIPANTS:**

Grant Williams, M.D.	-	Deputy Director
Lilia Talarico, M.D.	-	Associate Director
John Johnson, M.D.	-	Clinical Team Leader
Martin Cohen, M.D.	-	Clinical Reviewer
Ramzi Dagher, M.D.	-	Clinical Team Leader
Ann Farrell, M.D.	-	Clinical Team Leader
Brian Booth, Ph.D.	-	Acting Clinical Pharmacology/Biopharmaceutics Team Leader (internal meeting only)
Sophia Abraham, Ph.D.	-	Clinical Pharmacology/Biopharmaceutics Reviewer
Rajeshwari Sridhara, Ph.D.	-	Biostatistics Team Leader
Yong-Cheng Wang, Ph.D.	-	Biostatistics Reviewer
Susan Lu, Pharm.D.	-	Safety Evaluator, Office of Drug Safety (internal meeting only)
Mary Dempsey	-	Project Manager, Office of Drug Safety (internal meeting only)
Sheila Ryan, Pharm.D.	-	Regulatory Project Manager

**INDUSTRY PARTICIPANTS:**

Ohad Amit, Ph.D.	-	Associate Director, Biomedical Data Sciences
Michelle Casey, Ph.D.	-	Senior Statistician, Biomedical Data Sciences
Elaine Cutler	-	Senior Director, Regulatory Affairs
Christopher Abissi, M.D.	-	Director, Global Clinical Safety & Pharmacovigilance
Peter Ho, M.D., Ph.D.	-	VP, Discovery Medicine and Clinical Pharmacology, Oncology
Tom Lampkin, Pharm.D.	-	Director, Medicines Development Center, Clinical Oncology
Paolo Paoletti, M.D.	-	Sr VP, Medicines Development Center, Clinical Oncology
Mark Russo, M.D., Ph.D.	-	Group Director, Medicines Development Center, Clinical Oncology
Robert Watson	-	VP, Regulatory Affairs, Oncology
Anthony Murgo, M.D.	-	Associate Branch Chief, Investigation Drug Branch, DCTD, National Cancer Institute
Malcom Smith, M.D., Ph.D.	-	Associate Branch Chief, Clinical Investigations Branch, CTEP, DCTD, National Cancer Institute
William Carroll	-	Head, ALL Committee, Children's Oncology Group

**MEETING OBJECTIVE:**

To obtain FDA guidance on the proposed regulatory plan for the submission of the nelarabine NDA and to discuss the risk management plan for nelarabine.

**BACKGROUND:**

GlaxoSmithKline (GSK) has collaborated closely with the National Cancer Institute (NCI) during the clinical development program for nelarabine. This development program includes an on-going pilot Phase 2 trial (AALL00P2) conducted by the Children's Oncology Group (COG) which is enrolling pediatric patients with newly diagnosed T-ALL who receive nelarabine in addition to a modified BFM multi-agent regimen. A planned Phase 3 study (AALL0434) study to be conducted by the COG will evaluate event free survival at four years of a multi-regimen (hemi-augmented BFRM) with and without nelarabine. Additional clinical trials conducted with nelarabine include: Phase 1 study in combination with fludarabine and Phase 2 single agent studies in patients with chronic lymphocytic leukemia, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, and non-T-cell ALL.

The sponsor has met with the Agency previously in November 2003 and June 2004 to discuss the development plan for nelarabine. The sponsor has requested this meeting to receive further guidance on the development plan, including the AALL0434 study, and to obtain guidance on the company's proposed risk management plan for this product. The Agency met internally on February 11, 2005. Agency responses were sent to the sponsor on February 14, 2005. The

sponsor decided to proceed with the meeting to receive clarification of these responses.  
*Meeting discussion is in italics.*

## **SPONSOR QUESTIONS WITH FDA RESPONSES AND DECISIONS REACHED:**

### **Clinical**

1. Does the Agency concur with our plan to submit the NDA for traditional (full) approval on the basis of complete remission rate, duration of remission and survival data presented in Sections 2.1.1 and 2.2.1 and further rationale provided in Section 3 that demonstrates that nelarabine provides evidence of clinical benefit?

#### **FDA RESPONSE: No**

**It is unlikely that the submitted phase II studies will be sufficient for full approval. Response duration and survival are confounded by significant numbers of patients receiving transplants while on study.**

**Whether the data would support accelerated approval is a review issue.**

2. Please discuss/advise on potential Phase 4 commitments.

#### **FDA RESPONSE:**

•

- **Design and completion of a controlled clinical study(ies) to verify and describe the clinical benefit of nelarabine in adult and pediatric T-ALL, T-LBL. Timelines for study start, completion and submission of the study report should be submitted as soon as possible (see question 3).**

3. Do you agree that positive results from the proposed Phase 3 study (AALL0434) described in Section 4 and Appendix 5:

#### **FDA RESPONSE:**

**Please provide a treatment schema for this proposed study. It is difficult from the study description in the briefing document to ascertain whether or not it will be possible to isolate nelarabine's contribution to the treatment result.**

***This proposed randomized study (AALL0434) should be submitted as a SPA in order for the FDA to evaluate its role in the development plan.***

**Safety**

4. Does the Agency agree that the proposed strategy described in Section 3.2.1 of the briefing document is adequate to communicate the potential risks of nelarabine to physicians and associated health-care professionals?

**FDA RESPONSE:** This will be a review issue and require further discussion with you.

**ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:**

1. You should collect pharmacokinetic data using optimal sparse sampling in your proposed Phase 3 Study AALL0434 to adequately characterize the disposition of nelarabine and its metabolite, Ara-G in pediatric patients. Pharmacokinetic information obtained from these pediatric patients should be used to examine exposure-response relationships for measures of efficacy and toxicity.
2. You should conduct *in vitro* human liver microsomal studies to determine whether CYP P450 enzymes are involved in drug metabolism and determine the potential of nelarabine to inhibit and/or induce these enzymes. We refer you to the FDA published Guidance for Industry, Drug Metabolism/ Drug Interaction Studies in the Drug Development Process: Studies in Vitro (<http://www.fda.gov/cder/guidance/clin3.pdf>).
3. Please provide a better description of the renal and hepatic studies that have been performed (Study CALGB69803).

**ADDITIONAL CLINICAL COMMENTS:**

1. Please submit the safety data on all patients studied. Specially submit all safety data on children receiving doses above 650 mg/m<sup>2</sup>.

**ADDITIONAL REGULATORY COMMENTS:**

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing

an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "Guidance for Industry: Financial Disclosure by Clinical Investigators" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

3. Demographics

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATE GORY	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG	NUMBER EXPOSED TO STUDY DRUG
Gen- der	Males	All Females	Females >50
Age:	0-≤1 Mo.	>1 Mo. ≤ 2 Year	>2- <12
	12-16	17-64	≥65
Race:	White	Black	Asian
	Other		

**ACTION ITEMS:**

1. GSK will submit Study AALL0434 as a special protocol assessment for Agency review.

*The meeting concluded at approximately 12:45 PM.*

There were no resolved issues.

3-9-05

Sheila Ryan, Pharm.D.  
Project Manager

Concurrence Chair: 3-11-05

John Johnson, M.D.  
Clinical Team Leader

-----  
**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/

-----  
Sheila Ryan  
3/15/05 12:21:40 PM  
sent via fax.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

IND 42,778

Glaxo Group Limited d/b/a GlaxoSmithKline  
2301 Renaissance Boulevard  
PO Box 61540  
King of Prussia, PA 19406

Attention: Ellen Cutler  
Senior Director, Regulatory Affairs

Dear Ms. Cutler:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (the Act) for nelarabine (506U78) for Injection.

We also refer to our October 19, 2003 letter granting fast track designation for nelarabine for injection for treating adult and pediatric patients with T-cell malignancies (acute lymphoblastic leukemia, ALL and lymphoblastic lymphoma, LBL).

We also refer to your December 6, 2004 request for step-wise submission of sections of the New Drug Application (NDA) for this product. Additionally, we refer to our discussion of your proposal during the preNDA teleconference on September 22, 2004.

We have reviewed your request and have concluded that the proposed plan for step-wise submission of sections of the NDA is acceptable.

If you pursue a clinical development program that does not support use of nelarabine for the treatment of patients with T-cell ALL or T-cell LBL, the application will not be reviewed under the fast track drug development program and submission of sections of the NDA will not be permitted under this program.

If you have any questions, call Maureen Pelosi, Regulatory Project Manager, at 301 594-5778.

Sincerely,

*{See appended electronic signature page}*

Richard Pazdur, M.D.  
Director  
Division of Oncology Drug Products  
Office of Drug Evaluation I

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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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Dotti Pease  
12/17/04 09:51:14 AM

11 Page(s) Withheld

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

✓ § 552(b)(5) Deliberative Process

       § 552(b)(5) Draft Labeling

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Ellen Cutler

From: Maureen Pelosi

Fax: 610-787-7062

Fax: 301-827-4590

Phone: 610-787-3733

Phone: 301-594-5778

Pages, including cover sheet: 16

Date: 18 OCT 04

Re: Finalized Meeting Minutes

Urgent

For Review

Please Comment

Please Reply

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● Dear Ellen,

Attached are the finalized meeting minutes from our September 22, 2004 teleconference for 506U78. The minutes have an electronic signature on the last page.

Please phone me if I may be of further assistance,

Maureen A. Pelosi

Senior Regulatory Project Manager

## Teleconference Minutes

**MEETING DATE:** September 22, 2004 **TIME:** 1 PM **LOCATION:** Conference Rm B

**IND: 42,778**

Meeting Request Submission Date: 7/22/04 Serial #166 (MR)  
Briefing Document Submission Date: 8/18/04, Serial #167 (MP)  
Supplemental Document Date: 9/21/04, Serial #168 (MS)  
Meeting Granted Fax: 7/23/04

**DRUG:** 506U78 / Nelarabine (pro-drug, ara G, a nucleoside analog class of drug)

**SPONSOR/APPLICANT:** GlaxoSmithKline

### TYPE of MEETING:

1. **preNDA**
2. **Proposed Indication:** "NELARABINE FOR INJECTION is indicated for the treatment of — patients with — (acute lymphoblastic leukemia and lymphoblastic lymphoma) whose disease has not responded to or whose disease has relapsed following treatment with at least two — chemotherapy regimens."
3. **Fast Track** granted 10/19/03 and **Orphan status** granted on 8/10/04

### FDA PARTICIPANTS:

**FDA:** Grant Williams, MD, Deputy Director  
John Johnson, MD, Team Leader  
Martin Cohen, MD, Reviewer  
Rajeshwari Sridhara, PhD, Acting Biometrics Team Leader  
YongChen Wang, PhD, Biometrics Reviewer  
Julian Canizares, OIM  
Peter Vaccari, Orphan Drug  
Maureen Pelosi, RPh, Project Manager

### INDUSTRY PARTICIPANTS: GlaxoSmithKline

**Isaac Hammond, M.D.** Director, Global Clin Safety & Pharmacovigilance  
**Ohad Amit, Ph.D.** Associate Director, Biometrics and Data Sciences  
**Andrew Beelen, M.D.** Dir, Clinical Pharmacology & Discovery Medicine  
**Michelle Casey, Ph.D.** Senior Statistician, Biometrics and Data Sciences  
**Peter Ho, M.D., Ph.D.** VP, Oncology, Clin Pharm & Clin Development  
**Roxanne Jewell, Ph.D.** Principal Clin Pharmacokineticist, Clin Pharm & Discovery Med.  
**Tom Lampkin, PharmD.** Director, Oncology, Clin Dev & Medical Affairs  
**Mark Russo, M.D., Ph.D.** Group Director, Oncology, Clin Dev & Medical Affairs  
**Robert Watson, B.Sc.** Vice President, Regulatory Affairs - Oncology  
**Ellen Cutler,** Regulatory Affairs  
**Jane Finlay** Project Management

### GSK Invitees:

**Malcolm Smith, M.D., Ph.D.** Associate Branch Chief, Clinical Investigations Branch, CTEP, DCTD, National Cancer Institute

**MEETING OBJECTIVES:**

1. To answer specific questions contained in the meeting package.
2. To agree on content and format for the CTD
3. To provide an overview of the submission

**BACKGROUND: Proposed NDA Submission**

**Pivotal and Supportive Trials**

**Table 1 Pivotal Trials for the Submission**

<b>Study Title</b>	<b>Sponsor</b>	<b>Study Status</b>	<b>Type of Report</b>
<b>COG P9673 (PGAA2001):</b> A Phase II Study of Compound 506U78 in Patients with Refractory T-Cell Malignancies	DCTD, NCI (IND 52,611)	Completed	GSK Clinical Study Report
<b>CALGB19801 (PGAA2002):</b> A Phase II Study of 506U78 in Patients with Refractory Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma	DCTD, NCI (IND 52,611)	Completed	GSK Clinical Study Report

**APPEARS THIS WAY  
ON ORIGINAL**

**Table 2 Supportive Trials for the Submission**

<b>Study Title</b>	<b>Sponsor</b>	<b>Study Status</b>	<b>Type of Report</b>
<b>PGAA1001:</b> A Phase I Study of 2-Amino-9- $\beta$ -D-Arabinofuranosyl-6-Methoxy-9H-Purine (Compound 506) in Children and Adults with Refractory Hematologic Malignancies	GSK (IND 42,778)	Completed	GSK Clinical Study Report
<b>PGAA1002:</b> A Phase I Study of 506U78 Administered as a Two Hour Infusion Daily for 3 Consecutive Days in Adult Patients and as a Two Hour Infusion Daily Over 5 Consecutive Days in Pediatric Patients with Refractory Hematologic Malignancies	GSK (IND 42,778)	Completed	GSK Clinical Study Report
<b>PGAA1003:</b> A Phase I Study of 506U78 Administered as a Two Hour Infusion on a Day 1, 3, and 5 Schedule in Patients with Refractory Hematologic Malignancies	GSK (IND 42,778)	Completed	GSK Clinical Study Report
<b>PGAA1005:</b> Pilot Study of the Pharmacodynamic Investigation of Treatment with GW506U Combined with Fludarabine in Refractory Leukemics	GSK (IND 42,778)	Completed	GSK Clinical Study Report
<b>PGAA2003:</b> A Multicenter Study to Assess the Efficacy of 506U78 in Patients with Chronic Lymphocytic Leukemia Who Have Previously Failed Fludarabine Therapy	GSK (IND 42,778)	Completed	GSK Clinical Study Report

continued

**APPEARS THIS WAY  
ON ORIGINAL**

**Proposed Supportive Trials for the Submission (continued)**

Study Title	Sponsor	Study Status	Type of Report
<b>CALGB69803:</b> A phase I study of Compound 506U78 (NSC# 686673) in patients with hematologic malignancies and renal or hepatic impairment	DCTD, NCI (IND 52,611)	Closed	Study Summary
<b>MDACC 86:</b> A phase II study of 506U78 (NSC #686673) in patients with previously treated cutaneous T-cell lymphoma	DCTD, NCI (IND 52,611)	Closed	Study Summary
<b>COG AALL00P2:</b> The use of modified BFM +/- Compound 506U78 (NSC #686673) in an intensive chemotherapy regimen for the treatment of T-cell leukaemia leukaemia	DCTD, NCI (IND 52,611)	Ongoing	Status Report
<b>MDACC 430:</b> A phase II study of 506U78 (NSC #686673) for patients with relapsed or refractory indolent B-cell or peripheral T-cell lymphoma	DCTD, NCI (IND 52,611)	Ongoing	Status Report
<b>SWOG S0010:</b> A phase II trial of 506U78 (IND 52611) in patients with relapsed or refractory non T-cell acute lymphoblastic leukaemia leukaemia (ALL)	DCTD, NCI (IND 52,611)	Ongoing	Status Report
<b>CALGB59901:</b> A phase II study of 506U78 (NSC #686673, IND#52611) in patients with previously systemically untreated cutaneous T-cell lymphoma (CTCL) or with refractory or relapsed non-cutaneous peripheral T-cell lymphoma (PTCL)	DCTD, NCI (IND 52,611)	Ongoing	Status Report
<b>TRC9701:</b> Compound 506U78 (NSC #686673) in patients with refractory T-cell ALL or T-cell lymphoblastic lymphoma	DCTD, NCI (IND 52,611)	Ongoing	Status Report
<b>Compassionate Use Program (Special Exceptions Protocols)</b>	DCTD, NCI (IND 52,611)	Ongoing	Status Report

**APPEARS THIS WAY  
ON ORIGINAL**

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

**Content and Format**

1. We propose to submit full study reports for the two pivotal studies [COG 9673 (PGAA2001) and CALGB19801 (PGAA2002)] plus five GSK sponsored studies (Module 5, 5.3). Results of the additional NCI sponsored studies will be reported in summary reports (one-two page summaries), and ongoing studies will be reported in status reports (data as provided by NCI).

In addition to the full study reports and individual study summaries, two reports will be included in 5.3.5.3, Reports of Analyses of Data from More Than One Study. These are PK/PD Meta-Analysis and Analysis of Safety Data for Characterization of Neurological Events. The latter will also be summarized in the Summary of Clinical Safety (Module Section 2.7.4).

Do you agree with this proposal?

**FDA RESPONSE: Yes**

2. Case narratives will be provided for deaths and other Serious Adverse Events from all studies. The data cut-off date for SAEs from all sources will be the date of the database lock for the last pivotal study.

The four month safety update will provide additional SAEs and data from other sources for the period from the original data cut-off date through the date of the NDA submission with clinical data (March 2005).

Do you agree with this proposal?

**FDA RESPONSE:**

**Yes, but please also include deaths as well as SAEs.**

GSK clarified that the four month safety update will include case narratives for deaths and SAEs from the original data cut-off date through the date of the NDA submission.

3. Case narratives will be provided for all patients who achieved a CR or PR in the efficacy analyses from PGAA2002 and from Strata 1 and 2 in PGAA2001, as discussed in the communications for the June 30, 2004 teleconference. Do you agree?

**FDA RESPONSE: YES**

4. We propose to submit case report forms for deaths and discontinuations due to adverse events from the two pivotal studies PGAA2001 and PGAA2002 (Module 5.3.7.1). Do you agree?

**FDA RESPONSE:**

**CRFs should be submitted for all patients with Grade 3 or greater non-hematologic toxicity or deaths within 30 days of last Nelarabine dose. These should be submitted for all Glaxo studies.**

GSK explained that in addition to the pivotal studies, CRFs for deaths, discontinuations due to adverse events, and all patients with Grade 3 or greater non-hematologic toxicity or death within 30 days of last nelarabine dose will be provided for all GSK-sponsored trials which include the following trials:

**PGAA1001:** A Phase I Study of 2-Amino-9- $\beta$ -D-Arabinofuranosyl-6-Methoxy-9H-Purine (Compound 506) in Children and Adults with Refractory Hematologic Malignancies

**PGAA1002:** A Phase I Study of 506U78 Administered as a Two Hour Infusion Daily for 3 Consecutive Days in Adult Patients and as a Two Hour Infusion Daily Over 5 Consecutive Days in Pediatric Patients with Refractory Hematologic Malignancies

**PGAA1003:** A Phase I Study of 506U78 Administered as a Two Hour Infusion on a Day 1, 3, and 5 Schedule in Patients with Refractory Hematologic Malignancies

**PGAA1005:** Pilot Study of the Pharmacodynamic Investigation of Treatment with GW506U Combined with Fludarabine in Refractory Leukemias

**PGAA2003:** A Multicenter Study to Assess the Efficacy of 506U78 in Patients with Chronic Lymphocytic Leukemia Who Have Previously Failed Fludarabine Therapy (Phase II)

5. Based on the discussion June 30, GSK is seeking to obtain additional information on the subset of patients who underwent stem cell transplantation. The plans for gathering that data are described in more detail in the briefing document (Sections 6.2.1, 6.2.2, 7.3.1). We plan to submit the information in a separate report or revised case narratives when available. Do you agree with this proposal?

**FDA RESPONSE:**

**This information must be submitted with the clinical submission if it is to be considered a reviewable unit.**

6. Financial Disclosure - GlaxoSmithKline has determined that the two pivotal studies [COG P9673 (PGAA2001) and CALGB19801 (PGAA2002)] are covered studies under 21CFR Part 54. Both studies were conducted by cooperative groups under an IND held by the National Cancer Institute, which thus served as the regulatory sponsor. GlaxoSmithKline's provision of financial support to the studies was relatively limited. GlaxoSmithKline only provided the investigational drug to support the COG P9673. GlaxoSmithKline provided the investigational drug and a grant to the CALGB foundation at the beginning of CALGB study. More recently, after the studies ended, GlaxoSmithKline provided a grant to the cooperative groups to facilitate collection and clarification of data for the NDA.

The Cancer Therapy Evaluation Program (CTEP) collects financial disclosure information annually for all NCI-registered investigators. The forms are maintained by the Pharmaceutical Management Branch of NCI.

In lieu of GlaxoSmithKline including in Form 3454 (Certification: Financial Interests and Arrangements of Clinical Investigators) and, if applicable, Forms FDA 3455 (Disclosure Financial Interests and arrangements of Clinical Investigators) information pertinent to these two studies, we propose to provide a letter from NCI stating that the financial disclosure information for all investigators in the pivotal studies is maintained by NCI and is available upon request.

Is this proposal acceptable as a means of addressing 21CFR 314.50(k) for financial disclosure?

**FDA RESPONSE : NO**

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 "*Guidance for Industry: Financial Disclosure By Clinical Investigators*" (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

During the telecon, GSK stated that they are currently in discussion with the NCI to determine how to obtain the required documentation. We will provide a proposal to address the requirement for collection of this information upon further evaluation of the available documentation. This may require a teleconference at a later date to discuss the plans.

7. GSK intends to provide complete electronic datasets for the two pivotal trials as well as PGAA2003. In addition we plan to provide datasets supporting the analyses in the Clinical Safety Summary and electronic datasets for the pharmacokinetic data from the Phase I studies. Is this acceptable to the Division?

**FDA RESPONSE: Yes**

**Also, please provide SAS Programs, datasets, and SAS Transport Files for efficacy and safety analysis and for the PK data.**

GSK replied that datasets for efficacy and safety analyses and PK data will be provided as SAS Transport Files. In addition they will provide annotated CRFs and data definition tables. GSK does not plan to provide SAS programs as part of the electronic submission, however, we can discuss this issue further to ensure the needs of the agency are met.

It was agreed that for the two pivotal trials GSK would send the main efficacy and safety analysis programs.

**APPEARS THIS WAY  
ON ORIGINAL**

**Administrative**

1. Does the Division believe it is of value to have a small team of GSK staff available to meet with the reviewers soon after submission to facilitate the use of the electronic submission and discuss the CTD format?

**FDA RESPONSE:** Generally this is not necessary, but we will notify you if it is needed after submission..

**NDA/sNDA Presentations to CDER's Division of Oncology**

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Do you anticipate the need for any paper review copies of any of the components of this NDA?

**FDA RESPONSE:**

**We would appreciate copies of the Study Reports for the two pivotal studies.**

GSK proposed to submit paper copies of the core study reports. The core report consists of Sections 1 through 15 as described in the ICH E3 Guideline for Industry: Structure and Content of clinical Study Reports. Appendices and annexes will be available upon request. Is this acceptable? Please specify number of copies requested.

**FDA would like to have 4 copies to start.**

**General**

1. Based on the preliminary results provided in the Briefing Document and the proposed content of the application, do you agree that the Application will be acceptable for review?

**FDA RESPONSE :**

**The FDA can make no commitment on whether or not the application will be filed until we have seen the NDA.**

2. The proposed indication of nelarabine is for the treatment of \_\_\_\_\_ patients with 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.

Does the Agency agree that the data to be provided in this Application will support this indication?

**FDA RESPONSE :**

**This is a review issue.**

**In the absence of comparative studies, it is important to support the safety and efficacy of Nelarabine by submission and evaluation in the NDA of published information on results with other treatments for this patient population**

3. Nelarabine has Fast Track designation, and GSK plans to submit the NDA as a rolling submission. We plan to submit the Nonclinical and the Quality [chemistry, manufacturing and controls (CMC)] sections in December 2004.

The Nonclinical sections will include Module Section 2.4 Nonclinical Overview, Section 2.6 Nonclinical Summary, and Module 4 – Nonclinical Study Reports and References.

The Quality section will include Module Section 2.3 Quality Overall Summary and complete Module 3. Based on discussions subsequent to the June 23, 2004, FDA teleconference, the stability data will be updated during review, in March 2005.

The remaining Modules (1, 2, and 5) will be submitted in March 2005.

Is this proposed schedule acceptable to the Agency?

**FDA RESPONSE: Yes**

4. Could the Division please comment on the possibility for a priority review for NDA for nelarabine?

**FDA RESPONSE :**

**No. Review priority is not determined until the NDA is received.**

5. Can the Division comment on the likelihood for an Advisory Committee Review?

**FDA RESPONSE:**

**If questions arise, ODAC review is likely.**

**APPEARS THIS WAY  
ON ORIGINAL**

**Comments from ODS:**

- If the sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert (PI) or patient package insert (PPI)) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a Risk Minimization Action Plan (RiskMAP).

- If the NDA/BLA application includes RiskMAPs or pharmacovigilance plans and will be submitted in the Common Technical Document format, please submit as follows:

**RiskMAPs**

2.5.5 Overview of Safety with appropriate cross references to section  
2.7.4 Summary of Clinical Safety  
and any other relevant sections of the Common Technical Document for the NDA/BLA application.

**Pharmacovigilance plans**

2.5.5 Overview of Safety, with any protocols for specific studies provided in 5.3.5.4  
Other Clinical Study Reports or other sections as appropriate  
(e.g., module 4 if the study is a nonclinical study).

If the application is not being submitted as a Common Technical Document, include proposed RiskMAPs in the NDA Clinical Data Section (21 CFR 314.50 (d)(5)) or BLA Clinical Data Section (21 CFR 601.25(b)(3)) and clearly label and index them.

- For the most recent publicly available information on CDER's views on RiskMAPs, please refer to the Draft Guidance for Industry Development and Use of Risk Minimization Action Plans and the Draft Guidance for Industry Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at <http://www.fda.gov/cder/guidance/5766dft.pdf> and <http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0189-gdl0001-5767dft.doc>.
- If there is any information on product medication errors from the premarketing clinical experience, ODS requests that this information be submitted with the NDA/BLA application.
- The sponsor is encouraged to submit the proprietary name and all associated labels and labeling for review as soon as available.

GSK state that further consideration of the need for a risk management program will be made upon availability of safety data. Discussions with Division and ODS staff may be requested to discuss the potential need for a Risk Minimization Action Plan (RiskMAP) if necessary.

**OTHER FDA COMMENTS: REGULATORY**

**Demographics**

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

CATE GORY		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG
Gen- der	Males		All Females		Females >50	
Age:	0- $\leq$ 1 Mo.		>1 Mo.- $\leq$ 2Year		>2- $\leq$ 12	
	12-16		17-64		>65	
Race:	White		Black		Asian	
	Other					

**Nomenclature:**

We note that the USP dictionary has 2 possible chemical names listed. Is Nelarabine proposed as the Tradename? Has the Nomenclature Committee reviewed your proposed name?

GSK clarified that Nelarabine is the USAN-designated generic name. Internal trade name review is ongoing and will be submitted to the Agency for preclearance when available.

**ACTION ITEMS:**

1. GSK will submit the proposed tradename for review.
2. GSK will continue to evaluate the need for a risk management program and will follow up with the Division and ODS as necessary.

**UNRESOLVED ISSUES:**

1. If further discussion is needed, GSK will request a teleconference to address Financial Disclosure requirements for the two pivotal studies.

The meeting concluded at 1:40 PM.

\_\_\_\_\_/\_\_\_\_\_  
Maureen A. Pelosi  
Project Manager  
Minutes Preparer

Concurrence Chair: \_\_\_\_\_/  
John R. Johnson, M.D.  
Team Leader

-----  
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/s/

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John Johnson

10/20/04 12:47:02 PM

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

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Pages, including cover sheet: 12

Date: 16 JULY 04

Re: Finalized Meeting Minutes

Urgent

For Review

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● Dear Bob,

Attached are the finalized meeting minutes from our June 30, 2004 teleconference for 506U78. The minutes have an electronic signature on the last page.

Please phone me if I may be of further assistance,

Maureen A. Pelosi  
Senior Regulatory Project Manager

## Teleconference Meeting Minutes

**MEETING DATE:** June 30, 2004    **TIME:** 11 AM    **LOCATION:** Conference Room B

**IND:** 42,778

Meeting Request Submission Date: 4/2/04, Serial #158 (MR)  
Briefing Document Submission Date: 5/25/05, Serial #164 (MP)  
Meeting Granted Fax: 4/08/04

**DRUG:** 506U78

**SPONSOR/APPLICANT:** GlaxoSmithKline

### **TYPE of MEETING:**

1. **EOP 2 Follow-up/ Other - Teleconference**
2. **Proposed Indication:** "NELARABINE FOR INJECTION is indicated for the treatment of \_\_\_\_\_ patients with T-cell \_\_\_\_\_ (acute lymphoblastic and lymphoblastic lymphoma) who have not responded to or whose disease has \_\_\_\_\_ treatment with at least two \_\_\_\_\_ regimens."

### **FDA PARTICIPANTS:**

Richard Pazdur, MD, Division Director  
Grant Williams, MD, Deputy Division Director  
John Johnson, MD, Clinical Team Leader  
Martin Cohen, MD, Reviewer  
Maureen Pelosi, RPh, Project Manager

### **INDUSTRY PARTICIPANTS:** GlaxoSmithKline (for Sponsor telecom on 6/30)

**Christopher Abissi, M.D.** Director, Global Clin Safety & Pharmacovigilance  
**Ohad Amit, Ph.D.** Associate Director, Biometrics and Data Sciences  
**Michelle Casey, Ph.D.** Senior Statistician, Biometrics and Data Sciences  
**Tom Lampkin, Pharm.D.** Director, Oncology, Clin Dev & Medical Affairs  
**Jeremy Levin, M.D., Ph.D.** Senior Director, Oncology, Clin Dev & Medical Affairs  
**Mark Russo, M.D., Ph.D.** Group Director, Oncology, Clin Dev & Medical Affairs  
**J. Mel Sorensen, M.D.** Vice President, Oncology, Clin Dev & Medical Affairs  
**Robert Watson, B.Sc.** Vice President, Regulatory Affairs - Oncology  
**Matt Whitman, B.Sc.** Associate Director, Regulatory Affairs - Oncology

### **GSK Invitees:**

**Anthony Murgo, M.D., M.S.** Associate Branch Chief, Investigational Drug Branch DCTD, National Cancer Institute  
**Malcolm Smith, M.D., Ph.D.** Associate Branch Chief, Clinical Investigations Branch, CTEP, DCTD, National Cancer Institute

**MEETING OBJECTIVES:**

1. To have a follow-up discussion of GSK plans to evaluate neurological events in the Common Technical Document. The NDA submission (December 2004 or early 2005) will be for the use of 506U78 (Nelarabine) in patients with relapsed T-cell malignancies (acute lymphoblastic leukemia and lymphoblastic lymphoma) 506U78 is a pro-drug, ara G, a nucleoside analog class of drug.
2. To answer specific questions contained in the meeting package.

**BACKGROUND:**

An EOP-2 meeting was held in November 2003. The FDA was not enthusiastic regarding submission of an NDA due to the minimal amount of data on safety and efficacy. Nelarabine has unusually severe and troublesome neurotoxicity. The small patient population where Nelarabine use is proposed is best served by randomized clinical trials. Patients who can not participate in such trials could be served by expanded access mechanisms. The FDA suggested further development in randomized trials in less refractory populations and asked what is the status of COG AALL00P2.

**Pivotal Trial**

NCI-sponsored Study PGAA2001 (COG 9673) in patients with relapsed T-cell acute lymphoblastic leukemia (ALL) who are 21 years or younger is the pivotal study supporting registration of nelarabine. The primary endpoint of this study is complete remission (CR) traditionally defined for patients with ALL as no evidence of leukemic blasts in bone marrow, peripheral blood or extramedullary sites and recovery of the peripheral neutrophil count.

A traditional definition of complete response does not distinguish between front-line and relapsed settings and does not allow for the treatment paradigm found in modern relapsed protocols. Current clinical practice for patients with relapsed acute leukemias allow for retreatment of patients prior to full recovery of peripheral counts and for continued retreatment in an effort to induce a clinical remission. Because the focus of treatment in the relapsed setting is directed toward remission induction, interruption of therapy to allow for peripheral hematopoietic recovery is generally not performed. As such, the full recovery of peripheral blood counts cannot be fully assessed and therefore complete remission defined by these traditional response criteria cannot be applied appropriately to relapsed patients.

**Supportive Studies:**

- Protocol PGAA2001 (COG 9673) enrolled children (defined as 21 years or younger) who received nelarabine 650 mg/m<sup>2</sup> on Days 1 to 5 of each 21-day treatment cycle. Efficacy data will be available from approximately **46 evaluable patients** (10 patients received a 900 mg/m<sup>2</sup> dose and 36 received 650 mg/m<sup>2</sup>) who had received two or more prior regimens for refractory T-ALL or T-NHL.
- Protocol PGAA2002 (CALGB19801) enrolled adult patients (defined as 18 years and older) who received nelarabine 1.5 g/m<sup>2</sup> on Days 1, 3, and 5 of each 21-day treatment cycle. Efficacy data will be available from approximately **28 evaluable patients** who had received two or more prior regimens for refractory T-ALL/T-lymphoblastic lymphoma (LBL).

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

**QUESTION 1: Does the Agency agree with the categorization of these terms? Does the Agency have any further recommendation on additional categorizations of terms for analysis?**

The neurologic events that have occurred in patients who have received nelarabine vary in presentation. In an effort to discern if a meaningful pattern exists and assist in the evaluation of possible characteristics that may be associated with higher risk for neurologic events, the following mutually exclusive (except all events) categories will be used to group neurologic events:

1. Peripheral Nervous System Adverse Events
2. Central Nervous System Adverse Events
3. Mental Status Changes Events
4. Ambiguous Category of Neurologic Adverse Events
5. All Neurologic Adverse Events (all of the above)

Assignment of specific MedDRA terms to each of these categories is outlined in Appendix A. The terms listed were selected based on their potential clinical relevance and may or may not have been experienced by a patient who received nelarabine.

**FDA Response:**

Yes, for characterization. Within each category, however, the listing is too complex. Consider limiting terms to those listed in the NCI CTC.

During the teleconference Dr. Cohen asked if GSK was able to assign a grade for each event, if a standard oncology list was used or if it was a GSK list since he had not heard of many of the term in Appendix A. He asked exactly what is included in the 4 categories, how are they listed and graded, will only events assigned a grade be reported, and if GSK could provide a sample.

GSK stated that they will be requesting a preNDA meeting shortly and would include this issue in the briefing document with further explanation.

**Question 2:**

For purposes of conducting the most robust assessment of neurotoxicity possible based on available information, GSK plans to utilize all available neurologic adverse event data from the following completed Phase I and Phase II trials in a combined analysis.

Study ID	Study Title
PGAA1001	A Phase I Study of 2-Amino-9- $\beta$ -D-Arabinofuranosyl-6-Methoxy-9H-Purine (Compound 506) in Children and Adults with Refractory Hematologic Malignancies
PGAA1002	A Phase I Study of 506U78 Administered as a Two Hour Infusion Daily for 3 Consecutive Days in Adult Patients and as a Two Hour Infusion Daily Over 5 Consecutive Days in Pediatric Patients with Refractory Hematologic Malignancies
PGAA1003	A Phase I Study of 506U78 Administered as a Two Hour Infusion on a Day 1, 3, and 5 Schedule in Patients with Refractory Hematologic Malignancies
PGAA1005	Pilot Study of the Pharmacodynamic Investigation of Treatment with GW506U78 Combined with Fludarabine in Refractory Leukemics
PGAA2001 (COG 9673)	A Phase II Study of Compound 506U78 in Patients with Refractory T-Cell Malignancies
PGAA2002 (CALGB 19801)	A Phase II Study of 506U78 in Patients with Refractory Acute Lymphoblastic Leukemia or Lymphoblastic Lymphoma
PGAA2003	A Multicenter Study to Assess the Efficacy of 506U78 in Patients with Chronic Lymphocytic Leukemia Who Have Previously Failed Fludarabine Therapy

While a variety of doses, schedules and patient populations are represented in these studies, GSK believes this combined population of patients (n=461;199 pediatric, 262 adults) is sufficiently homogenous for purposes of assessing neurotoxicity of nelarabine and will allow for a larger sample size than individual studies alone.

In addition, GSK will have access to the complete list of SAEs reported under the NCI IND. These lists are available through GSK's Global Clinical Safety and Pharmacovigilance tracking system. Although not available for inclusion in the analysis of neurologic adverse event, a discussion (e.g. descriptions of the number of subject experiencing events, severity, types of events, etc) will be provided in the NDA Common Technical Document.

**QUESTION 2: Does the Division agree with GSK's proposed population for the analysis of neurotoxicity?**

**FDA Response: Yes**

### QUESTION 3

GSK intends to undertake analyses to identify potential risk factors for neurologic adverse events in patients who receive nelarabine. Using the categories of neurological events defined in Question 1, the following definitions of 'event' will be considered in separate analyses:

1. Peripheral Nervous System Adverse Events ( $\geq$  grade 3)
2. Peripheral Nervous System Adverse Events (any grade)
3. Central Nervous System Adverse Event ( $\geq$  grade 3)
4. Central Nervous System Adverse Event (any grade)
5. Mental Status Change Event ( $\geq$  grade 3)
6. Mental Status Change Event (any grade)
7. Any Neurological Adverse Event ( $\geq$  grade 3)
8. Any Neurological Adverse Event (any grade)

Patient characteristics, dosing parameters, prior and concomitant medications, pharmacokinetic parameter estimates, where available, and disease characteristics will be evaluated for potential association with neurologic adverse events as grouped in Question 1. A complete list of these characteristics is provided in the Integrated Summary Analysis Plan for Safety (Section 8.4). A step-wise process will be utilized.

The first step will test the correlation between neurologic adverse events and each of the multiple characteristics utilizing Spearman rank order correlation coefficient. Step 2 will model the occurrence of neurologic adverse events using logistic regression and will include dose-related and available pharmacokinetic parameters for evaluation. In step 3 those characteristics identified in step 1 as potentially correlated to neurologic events following administration of nelarabine will be further evaluated in a logistic regression model along with significant dose-related and pharmacokinetic parameters identified in step 2. For those characteristics that comprise the final model, odds ratios along with 95% confidence intervals and associated p-values will be provided.

**QUESTION 3: Does the Agency agree with the proposed approach to identify potential risk factors for neurologic adverse events following administration of nelarabine?**

**FDA Response:** Yes. These analyses would be considered exploratory.

**QUESTION 4:**

For each of the eight definitions of neurologic event identified in Question 3, GSK intends to model the cumulative dose to the first occurrence of an event. Subjects who do not experience a neurologic adverse event will be censored at the total cumulative dose received on study. The purpose of the analysis will be to assess the hazard of a neurotoxic event as a function of cumulative dose. Quartiles of dose-to-event and their confidence intervals will be provided.

**Does the Agency agree with this approach?**

**FDA Response:** Yes. These analyses would be considered exploratory.

**APPEARS THIS WAY  
ON ORIGINAL**

## QUESTION 5

Patient narratives will be included in the submission based on patients enrolled in the two pivotal trials (COG9673 and CALGB19801) who have achieved a complete remission. These narratives will be in addition to the customary narratives for expedited safety reports, withdrawals due to adverse events, and patient deaths.

Sample efficacy narratives are included in this briefing document. While the content of each narrative will be limited to available information, the intent is to characterize the patient's overall condition, experience on study, and outcome.

**Are there other groups of patients the Agency would like to have patient narratives available for review? Upon review of the sample narratives, is the structure and content acceptable for review?**

### **FDA Response:**

Please include CRp's and PR's

Please provide all available information. For example, if patients have had a BMT there should be information as to whether engraftment occurred, the percent of marrow blasts and the return of erythroid precursors and megakaryocytes.

For each patient please provide the treatment regimen. Providing only the cooperative group protocol number is not sufficient.

**During the teleconference GSK said they would provide all available information, but stated that hematologic transplant data is missing on most patients. Post transplant CBC results are not available.**

**Dr. Cohen asked GSK to provide whatever is available for evaluation.**

**Dr. Johnson stated that while the primary endpoint was response rate, the secondary endpoint was duration of response and overall survival. If one assumes that the responders have a successful transplant then the post transplant information is needed to determine benefit and to determine whether after 506U78 it is possible to have a successful engraftment or not.**

Question 5 discussion continued:

**GSK said that overall survival is a surrogate for hematological recovery and this would be discussed further in the preNDA briefing document.**

**APPEARS THIS WAY  
ON ORIGINAL**

**QUESTION 6: Provided in Appendix 2 of Attachment 3 is a complete description of the Clinical Safety Summary that GSK plans to provide to support the submission. Does the Agency agree that this analysis plan is acceptable?**

**FDA Response: Yes**

**APPEARS THIS WAY  
ON ORIGINAL**

**QUESTION 7: Note: Fast Track was granted 19 OCT 03 for relapsed T-cell malignancies (acute lymphoblastic leukemia and lymphoblastic lymphoma)**

According to FDA's Guidance for Fast Track Drug Development Programs, products in fast track development programs may be considered for submission of portions of an application before the complete NDA is submitted. Reference is also made to FDA's Draft Guidance document, "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA".

We are planning to submit the NDA for nelarabine in a Common Technical Document (CTD) format. We expect to be able to submit the preclinical and the chemistry, manufacturing and controls (CMC) sections approximately 3 months ahead of the clinical data section. In accordance with the Fast Track Guidance document, we will provide a submission schedule for the different sections of the CTD at a pre-NDA meeting.

**Can the Nelarabine NDA be submitted under the Pilot 1 program? If not, is the Division willing to accept portions of the CTD prior to receipt of the complete application (rolling submission)?**

**FDA Response:**

This question will be deferred until further clinical data is submitted to the agency.

**APPEARS THIS WAY  
ON ORIGINAL**

**ACTION ITEMS:**

**GSK will submit a request for a preNDA meeting and address FDA's concerns regarding Questions 1 & 5 in the meeting briefing document.**

**APPEARS THIS WAY  
ON ORIGINAL**

**UNRESOLVED ISSUES:**

1. Missing hematologic post transplant data.

**APPEARS THIS WAY  
ON ORIGINAL**

The meeting concluded at 12 PM.

\_\_\_\_\_  
Maureen A. Pelosi  
Project Manager  
Minutes Preparer

Concurrence Chair: \_\_\_\_\_ / \_\_\_\_\_  
John Johnson, M.D.  
Medical Team Leader

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/s/

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John Johnson  
7/18/04 12:58:54 PM

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

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Maureen Pelosi

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Pages, including cover sheet: 11

Date: 09 JUL 04

Re: Signed Teleconference Minutes for IND 42,778

Urgent

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● Dear Mary Faye,

Attached are our June 23, 2004 finalized minutes from the 506U78 CMC teleconference with electronic signature.

Please phone me if I may be of further assistance,

Maureen A. Pelosi, RPh  
Senior Regulatory Project Manager

## TELECONFERENCE MINUTES

**MEETING DATE:** June 23, 2004    **TIME:** 10:30 AM    **LOCATION:** Conference Room B

**IND: 42,778**

Meeting Request Submission Date: 4-8-04 MR-159  
Briefing Document Submission Date: 5-21-04 MP-162  
Meeting Granted Date: 4-13-04

**DRUG: 506U78 / Nelarabine**

**SPONSOR/APPLICANT: GlaxoSmithKline**

**TYPE of MEETING: pre-NDA CMC**

### FDA PARTICIPANTS:

Nallaperumal Chidambaram, PhD, Team Leader  
Xiao Hong Chen, PhD, Reviewer  
Maureen Pelosi, RPh, Sr. Project Manager, Reg. Affairs

### INDUSTRY PARTICIPANTS: GlaxoSmithKline

Mary Faye S. Whisler, Ph. D., Assistant Dir., New Submissions N. America, Global CMC Reg. Affairs  
Bruce Boyett, Ph. D., Director, Product Development  
Martin Ramsden, Ph. D., Technical Manager and Site Data Manager (UK)  
Jan Thirkettle, Ph.D., Team Leader (UK)  
Chris MD Beels, Ph. D. Director, Chemical Strategies, Chem. Development (UK)  
Martyn Voyle, Director, Synthetic Chemistry (UK)  
Norma Collinsworth, Regional Director, Global New Substances, N. Amer. (RTP)

### MEETING OBJECTIVES:

Reference is made to the initial pre-NDA meeting held on July 22, 2003, and corresponding FDA meeting minutes dated August 8, 2003. The objective is to receive Agency feedback on some additional CMC questions related to drug substance and to provide CMC information to address the following action items from the July 2003 meeting including:

1. provide more information on the
2. provide comparative data between the
3. to answer specific questions submitted in the meeting package.

**APPEARS THIS WAY  
ON ORIGINAL**

### QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Does the Agency agree that \_\_\_\_\_ for the synthesis of 506U78? (Section 1.2);

**FDA Response:**

\_\_\_\_\_ may be designated as \_\_\_\_\_ you should provide  
the following additional information to justify your position:

- How \_\_\_\_\_ is manufactured by the supplier and also literature references/articles for the preparation of this material.
- A list of possible vendors that will be manufacturing this material.
- Demonstrate that it is truly commercially available and show any modifications you provided to the vendor for the manufacturing process and controls of \_\_\_\_\_

GSK stated that there are around \_\_\_\_\_ suppliers and more than 100 literature references. Their focus is an \_\_\_\_\_ company.

Specifications are very tight. GSK said that they would submit the information as an IND amendment.

Dr. Chidambaram stated that FDA would provide feedback on the amendment if it is not adequate.

**APPEARS THIS WAY  
ON ORIGINAL**

2. Does the Agency agree that the proposed tests will control the quality of the \_\_\_\_\_ (Section 1.2); \_\_\_\_\_

**FDA Response:**

Yes, the proposed tests appear to be appropriate for controlling the quality of the \_\_\_\_\_ you should also propose a \_\_\_\_\_ test. We recommend that you also include a specification for \_\_\_\_\_, in the specifications for \_\_\_\_\_

**GSK agrees. They have specifications for the \_\_\_\_\_ impurities mentioned. They are still evaluating the \_\_\_\_\_ test.**

**APPEARS THIS WAY  
ON ORIGINAL**

3. Does the Agency agree that the testing proposed will suitably control the quality of the  
(Section 1.3);

**FDA Response:**

First of all, we need to clarify that the manufacturing process for 506U78 is

The testing proposed to control the  
drug substance appears to be acceptable.

**GSK agrees.**

**APPEARS THIS WAY  
ON ORIGINAL**

4. Because the Agency agree with the GSK proposal that a specification for drug substance? (Section 1.4) does the test is not required in the

**FDA Response:**

No. you should propose a specification for of the drug substance.

GSK accepts the fact that the test to identify the drug substance. GSK agrees to include the and is a unique test in the specifications.

APPEARS THIS WAY  
ON ORIGINAL

5. Does the Agency agree that the proposed specification tests are suitable to control the quality of 506U78 used in the commercial product? (Section 1.4)

**FDA Response:**

The proposed specifications for 506U78 appear to be suitable to control the quality of 506U78 provided that you also include testing for \_\_\_\_\_

**GSK agreed to look at development and initial commercial batches. They asked if the test could be eliminated if they provide the data to demonstrate that there is no**

**Dr. Chen stated that she is concerned about the** \_\_\_\_\_

\_\_\_\_\_, FDA may consider the request.

**Appears This Way  
On Original**

6. Does the Agency agree that the proposed NDA stability data package for 506U78 is sufficient? (Section 1.6);

**FDA Response:**

No. The proposed three batches of stability data can not be considered as primary stability data. They can be treated as supportive stability data. You should provide primary stability data for three batches of drug substance manufactured by using the commercial process.

**After discussion, GSK agreed to provide the following:**

- Supportive data for 3 drug substance (DS) batches from [redacted] manufactured at [redacted] that has [redacted] data under long term conditions and [redacted] data under accelerated conditions
- Two [redacted] pilot batches [redacted], with 3 months data at NDA filing and additional 3 months update during NDA review
- From [redacted] commercial batches [redacted] release data with [redacted] months data during review including long term and accelerated stability studies

APPEARS THIS WAY  
ON ORIGINAL

7. Does the Agency agree that we have now adequately addressed your concerns regarding the \_\_\_\_\_ produced by the previous process and \_\_\_\_\_ produced by the proposed commercial process? (reference Section 2).

**FDA Response:**

Yes. We agree.

**APPEARS THIS WAY  
ON ORIGINAL**

**ACTION ITEM:**

1. GSK will submit a CMC information amendment addressing literature references/articles, vendors for \_\_\_\_\_ to demonstrate that it is truly commercially available in response to FDA queries for Question #1.
2. GSK will submit a Drug Product stability packet as an information amendment.

**APPEARS THIS WAY  
ON ORIGINAL**

There were no unresolved issues.

**APPEARS THIS WAY  
ON ORIGINAL**

The meeting concluded at 11:30 AM.

\_\_\_\_\_  
Maureen A. Pelosi  
Project Manager  
Minutes Preparer

ConcurrenceChair: \_\_\_\_\_ / \_\_\_\_\_  
Nallaperumal Chidambaram, Ph.D.  
CMC Team Leader

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/s/

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Nallaperumal Chidambaram  
7/9/04 01:56:38 PM

# Fax



## DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Richard Swenson

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Pages, including cover sheet: 14

Date: 05 Dec 03

Re: EOP2 Meeting Nelarabine / T-cell

**Urgent**

For Review

Please Comment

Please Reply

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Dear Richard,

Attached are the meeting minutes from our 11-24-03 Nelarabine meeting.

Regards,

Maureen Pelosi

## MEETING AGENDA

**MEETING DATE:** 11/24/03 **TIME:** 2:30 PM **LOCATION:** Conference Room G

**IND:** 42,778

Meeting Request Submission Date: 8/29/03, Serial #138

Briefing Document Submission Date: 10/24/03 #141

Meeting Granted Fax: 9/12/03

**DRUG:** 506U78

**SPONSOR/APPLICANT:** GlaxoSmithKline

### TYPE of MEETING:

1. **EOP 2**
2. **Proposed Indication:** "NELARABINE FOR INJECTION is indicated for the treatment of patients with acute lymphoblastic leukemia and lymphoblastic lymphoma) who have not responded to or treatment with at least two regimens"

### FDA PARTICIPANTS:

Grant Williams, MD, Deputy Director  
John Johnson, MD, Team Leader  
Martin Cohen, MD, Reviewer (Meeting Chair)  
David McGuinn, PhD, P/Tox Reviewer  
Ning Li, PhD, Biometrics Team Leader  
YongChen Wang, Phd, Biometrics Reviewer  
Atiqur Rahman, PhD, OCPB Team Leader  
Sophia Abraham, PhD, OCPB Reviewer  
Maureen Pelosi, RPh, Project Manager

**ODAC:** Janice Dutcher, MD (Written Response)

**NCI:** Anthony Murgu, M.D., M.S., Associate Branch Chief, Investigational Drug Branch  
DCTD, National Cancer Institute  
Malcolm Smith, M.D., Ph.D. Associate Branch Chief, Clinical Investigations  
Branch, CTEP, DCTD, National Cancer Institute

**INVITEES:** Steven Hirschfeld, Md, PhD, Medical Officer  
David Gan, MD, DSI, Compliance  
Kate Phelan, Safety Evaluator, DDRE  
Robert Kang, Project Manager, DDRE

**INDUSTRY PARTICIPANTS: (for Sponsor meeting on 11/24)**

**GlaxoSmithKline**

**Mel J Sorensen, M.D.** Vice President, Oncology, Clin Dev and Medical Affairs

**Mark Russo, M.D., Ph.D.** Director, Oncology, Clin Dev and Medical Affairs

**Peter Ho, M.D.** Vice President, Discovery Medicine

**Tom Lampkin, Pharm.D.** Director, Oncology, Clin Dev and Medical Affairs

**Ohad Amit, Ph.D.** Manager, Biometrics and Data Sciences

**Andrei Breazna, Ph.D.** Senior Statistician, Biometrics and Data Sciences

**Roxanne Jewell, Ph.D.** Director, Clinical Pharmacokinetics

**Craig Metz, Ph.D.** Vice President, Regulatory Affairs

**Richard Swenson, Ph.D.** Director, Regulatory Affairs - Oncology

**GSK Consultants**

**MEETING OBJECTIVES:**

1. To provide an overview of the results of the pivotal trials and to discuss the planned NDA submission (December 2004 or early 2005).
2. To answer specific questions submitted in the meeting package.

**APPEARS THIS WAY  
ON ORIGINAL**

## BACKGROUND:

### Pivotal Trial

NCI-sponsored Study PGAA2001 (COG 9673) in patients with relapsed T-cell acute lymphoblastic leukemia (ALL) who are 21 years or younger is the pivotal study supporting registration of nelarabine. The primary endpoint of this study is complete remission (CR) traditionally defined for patients with ALL as no evidence of leukemic blasts in bone marrow, peripheral blood or extramedullary sites and recovery of the peripheral neutrophil count.

A traditional definition of complete response does not distinguish between front-line and relapsed settings and does not allow for the treatment paradigm found in modern relapsed protocols. Current clinical practice for patients with relapsed acute leukemias allow for retreatment of patients prior to full recovery of peripheral counts and for continued retreatment in an effort to induce a clinical remission. Because the focus of treatment in the relapsed setting is directed toward remission induction, interruption of therapy to allow for peripheral hematopoietic recovery is generally not performed. As such, the full recovery of peripheral blood counts cannot be fully assessed and therefore complete remission defined by these traditional response criteria cannot be applied appropriately to relapsed patients.

### Supportive Studies

- Protocol PGAA2001 (COG 9673) enrolled children (defined as 21 years or younger) who received nelarabine 650 mg/m<sup>2</sup> on Days 1 to 5 of each 21-day treatment cycle. Efficacy data will be available from approximately **46 evaluable patients** (10 patients received a 900 mg/m<sup>2</sup> dose and 36 received 650 mg/m<sup>2</sup>) who had received two or more prior regimens for refractory T-ALL or T-NHL.
- Protocol PGAA2002 (CALGB19801) enrolled adult patients (defined as 18 years and older) who received nelarabine 1.5 g/m<sup>2</sup> on Days 1, 3, and 5 of each 21-day treatment cycle. Efficacy data will be available from approximately **28 evaluable patients** who had received two or more prior regimens for refractory T-ALL/T-lymphoblastic lymphoma (LBL).

### Indication

"NELARABINE FOR INJECTION is indicated for the treatment of \_\_\_\_\_ patients with \_\_\_\_\_ (acute lymphoblastic leukemia and lymphoblastic lymphoma) who have not responded to or \_\_\_\_\_ **following** treatment with at least two \_\_\_\_\_ regimens."

### FDA Comments Prior to Answering Specific Questions

Based on the review of the briefing document, the FDA is not enthusiastic regarding submission of an NDA at this time. This NDA as proposed has considerable risk of non-approval. There is a minimal amount of data on safety and efficacy. Nelarabine has unusually severe and troublesome neurotoxicity. The small patient population where Nelarabine use is proposed is best served by randomized clinical trials. Patients who can not participate in such trials could be served by expanded access mechanisms.

The FDA suggests further development in randomized trials in less refractory populations. What is the status of COG AALL00P2?

#### **Discussion at the meeting:**

- The sponsor explained that this is a toxicity study.

#### **After discussion, it was agreed that:**

- Randomized trials are difficult to conduct due to the small number of patients and to the time involved ( 5-10 years) .
- The incidence of toxicity may be more manageable at this proposed dosage.
- The incidence of serious neurotoxicity may be lower than FDA's initial impression.
- The FDA will take the issues under consideration with delineation of patient benefit and neurotoxicity documentation.

**APPEARS THIS WAY  
ON ORIGINAL**

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

**Question #1a: For our planned efficacy presentation in the NDA, is the definition of complete remission\* (CR\*) acceptable to FDA as the primary endpoint?**

**FDA Response:**

No. CR\* is a provisional endpoint. If a significant number of patients entered alternative therapies before recovery of at least the white blood cell count the Agency may not be able to evaluate the significance of a CR\*. Despite the fact that strata 2 of the COG study speaks to the proposed indication all 4 strata should be reviewed to get a better estimation of CR rate and duration.

See also question 7a.

After discussion at the meeting:

- It was agreed that the relevance of CR\* depends upon the review of data and percent of patients who had successful transplants.
- Please present the data for review ( some patients went on to transplant and others to different treatments).
- The Applicant needs to show that an adequate proportion of patients had a CR of good duration and prolonged survival after Nelarabine followed by transplant or in a few cases maintenance with Nelarabine.

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ON ORIGINAL**

**Question #1b: Complete remission rates (CR and CR\*) will be presented with percentages and 95% confidence intervals computed using the exact binomial method. Standard time-to-event methods (i.e., Product Limit Method) will be used for secondary time-to-event endpoints (e.g., Overall Survival and Duration of Response). [A description of the analyses supporting efficacy and safety is provided in the statistical appendix to the briefing document.] Does the agency have any comments on the proposed methods of analysis for the efficacy or safety data?**

**FDA Response:**

The 95% confidence interval for the remission rate and product limit method for the secondary time-to-event endpoints are acceptable.

See introductory comment and answers to questions 1a and 7a.

**Question #2: If the Division finds the submitted efficacy/safety data compelling, could these studies form the basis for approval for the proposed indication?**

**FDA Response:**

This is a review issue. See FDA introductory comment and answers to questions 1a and 7a.

Please provide a detailed bibliography and summary (efficacy and safety) of published studies of patients with T-cell malignancies (acute lymphoblastic leukemia and lymphoblastic lymphoma) who have not responded to or whose disease has progressed during treatment with two standard regimens.

**APPEARS THIS WAY  
ON ORIGINAL**

**Question #3: Is the pooling of data from these different sources acceptable to provide an overall summary of the safety profile of nelarabine? Is the size of the proposed safety database acceptable?**

**FDA Response:**

Safety analysis should initially be by dose for both the day 1-5 q28 day schedule and for the day 1, 3, 5 q 21-28 day schedule . If the results obtained with the various Nelarabine doses and schedules are comparable a final summation of all of the safety information for the five dose regimens from Phase II studies is acceptable

**Question #4: GSK intends to perform a detailed analysis of the cases of neurotoxicity including evaluating any association with clinical characteristics. Aside from possible dose reductions, discontinuation advice, or special cautions to prescribers for patient populations who may be identified to be at increased risk, what recommendations would the Division have regarding neurotoxicity with nelarabine?**

**FDA Response:**

None at this time because insufficient data were provided to make an assessment Perhaps advice may be offered after the data is reviewed.

**ODS: (Kate Phelan)Comments on GSK Question #4 regarding analysis of neurotoxicity cases:**

The table mock-ups that show how neurotoxicity cases will be analyzed by GSK (pages 64-67 of briefing document) do not include analysis by age. ODA would like to see age examined as a factor in the development of neurotoxicity, at least pediatric (0 – 16 years) versus adult (17+ years).

ODS requests a separate analysis of cases of irreversible neurotoxicity. Are there any characteristics that might identify susceptible patients or situations that contribute to irreversibility? Are there any clinical signs that herald the onset of irreversibility? Does drug discontinuation limit the severity of irreversible effects?

**APPEARS THIS WAY  
ON ORIGINAL**

**Question #5: The FDA Guidance Document addresses limitations in reporting efficacy data. Can the Division provide GSK with guidance on the most acceptable method of approach in dealing with safety data from Cooperative Group sources?**

**FDA Response:**

Collection of safety data varies widely amongst the NCI Cancer Cooperative Groups. Duration and outcome of serious adverse events must be adequately documented. The focus of this application review will probably be on neurological events.

**Question #6: Both clinical studies intended to provide pivotal data in our planned NDA are not comparative studies. GSK plans to provide a review of the limited available literature covering treatment of patients at second or greater relapse. Is this approach acceptable to the Division?**

**FDA Response:**

Yes

**APPEARS THIS WAY  
ON ORIGINAL**

**Question 7a:** Does the Agency agree that even a short duration of response is clinically meaningful if it is sufficient to potentially advance a patient with relapsed or refractory disease to subsequent therapy?

**FDA Response:**

No. The patient may relapse shortly after receiving the subsequent therapy. If there is continued follow up after therapy is changed and the patient remains in remission, that will likely represent benefit of Nelarabine therapy.

FDA will not assume that a CR with Nelarabine will lead to a successful BMT. It is necessary to demonstrate that this is the case.

**Question 7b:** Is it acceptable to the Agency to evaluate duration of response for patients who have received additional therapy if the additional therapy was started while the patient was in remission induced by nelarabine (506U78)?

**FDA Response:** See answer to question 7a

**APPEARS THIS WAY  
ON ORIGINAL**

**Question #8: Pharmacokinetic information for nelarabine and ara-G with both the 5-day continuous and 3-day alternate dosage regimens were consistent. Pharmacokinetic data are available from patients given doses below and above the proposed range of doses. Does the Division agree that the pharmacokinetics of nelarabine are adequately described?**

**FDA Response:**

Yes, you have adequately described the pharmacokinetics of both nelarabine and ara-G in adult and pediatric patients. However, you should address the following issues in the NDA for labeling purposes:

- The pharmacokinetics or pharmacokinetics/pharmacodynamics of nelarabine and ara-G in patients with renal impairment.
- The pharmacokinetics or pharmacokinetics/pharmacodynamics of nelarabine and ara-G in patients with hepatic impairment.
- Inhibition and induction potential of nelarabine and ara-G in *in vitro* system with human liver microsomes. Depending on the results from the *in vitro* microsomal studies, formal drug-drug interaction studies should be conducted.
- Provide analysis exploring drug exposure and neurologic toxicities.

After discussion at the meeting:

- The sponsor stated that the above will be difficult to address but that they would try.

**Question # 9 PRECLINICAL ADME: Does the agency agree that this preclinical ADME package is sufficient to support the registration of Nelarabine?**

**FDA Response:**

Yes

**APPEARS THIS WAY  
ON ORIGINAL**

**Comments and Requests from Office of Drug Safety:**

- If the Sponsor and/or FDA believe that there are product risks that merit more than conventional professional product labeling (i.e. package insert or PI) and postmarketing surveillance to manage risks, then the Sponsor is encouraged to engage in further discussions with FDA about the nature of the risks and the potential need for a risk management program.
- If risk management programs or pharmacovigilance plans are felt to be necessary, they should be included in Module I of the Common Technical Document for the NDA application. If the NDA application is not being submitted as the Common Technical Document, any proposed plans for risk management should be included in the Clinical Section and be clearly labeled and indexed.
- The Sponsor is referred to the draft Concept Papers on Risk Management Programs and Risk Assessment of Observational Data: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment which can be located electronically at <http://www.fda.gov/cder/meeting/riskManageII.htm> and <http://www.fda.gov/cder/meeting/riskManageIII.htm>.
- If there is any information on product medication errors from the clinical IND, ODS requests that this information be submitted with the NDA application.
- The Sponsor needs to submit the proprietary name and all associated labels and labeling for review as soon as possible.

**APPEARS THIS WAY  
ON ORIGINAL**

**ACTION ITEMS:**

1. Sponsor: Please request another pre-NDA meeting when appropriate.
2. Sponsor: Please explore the mechanism of neurotoxicity

There were no unresolved issues.

The meeting concluded at 3:45 PM.....

\_\_\_\_\_  
Maureen A. Pelosi  
Project Manager  
Minutes Preparer

Concurrence Chair: \_\_\_\_\_ /

Martin Cohen, M.D.  
Medical Officer

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ON ORIGINAL**

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/s/

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Martin Cohen

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