CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125166

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

LICENSING ACTION RECOMMENDATION

Applicant: Alexion Pharmaceuticals **STN:** STN 125166/0

Product:

Eculizumab

Indication / manufacturer's change:

Treatment of paroxysmal nocturnal hemoglobinuria (PNH)

☐ Approval:
- ☐ Summary Basis For Approval (SBA) included
- ☐ Memo of SBA equivalent reviews included

☐ Refusal to File: Memo included
☐ Denial of application / supplement: Memo included

RECOMMENDATION BASIS

☐ Review of Documents listed on Licensed Action Recommendation Report

☐ Inspection of establishment ☐ Inspection report included

☐ BiMo inspections completed ☐ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ☐ Categorical Exclusion

☐ Review of labeling Date completed _____ ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

☐ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: _____ Date: _____

Product Office's Responsible Division Director(s)*:

_____ Date: 3/15/07

_____ Date: _____

DMPQ Division Director*: _____ Date: 3/8/07

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

☐ Compliance status checked ☐ Acceptable ☐ Hold Date: _____

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) _____ Date: _____

Responsible Division Director _____ Date: 3/8/07
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

LICENSING ACTION RECOMMENDATION

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■ Review of labeling Date completed _____ ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch _____

CLEARANCE – REVIEW

Review Committee Chairperson: _____ Date: 03-01-07

Product Office's Responsible Division Director(s)*:

Kathleen A. Hoover Date: 03-01-2007

Robert Davis Reiss Date: 03-12-2007

DMPQ Division Director* : _____ Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: _____

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) _____ Date: 03/02/07

Responsible Division Director _____ Date: 03-12-2007
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

BLA STN: 125166/0
Letter Date: 9/15/06
Stamped Date: 9/15/06

1.3.5.3. Exclusivity Request

Patent Exclusivity is not being requested at this time. We understand that exclusivity is not available for applications being submitted pursuant to 21CFR, Part 601 and the Public Health Service Act (42 U.S.C. 262) as a biological license application (BLA)

BL STN: 125166/0
Letter date: 9/15/06
Stamped date: 9/15/06

1.3.3 Debarment Certification

Alexion Pharmaceuticals, Inc. does hereby certify that it did not and will not use in any capacity the services of any person debarred under section 306(a) or 306(b) of the Federal Food, Drug and Cosmetic Act in connection with this Biological License Application (BLA) being submitted in the electronic Common Technical Document (e-CTD) format.

Signature: _____ for Date: 16 Feb 2017

Thomas Dubin, Esq.
Vice President & General Counsel

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

BLA # : 125166/0 **Supplement Type (e.g. SE5):** N/A **Supplement Number:** N/A

Stamp Date: 9/15/06 **PDUFA Goal Date:** 3/16/07

HFD 160 **Trade and generic names/dosage form:** Soliris™ (eculizumab)

Applicant: Alexion Pharmaceuticals **Therapeutic Class:** _____

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

☑ **Yes. Please proceed to the next section.**

☐ **No. PREA does not apply. Skip to signature block.**

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):** N/A

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s): 1

Indication #1: Treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH) to reduce the need for blood cell transfusion and to stabilize hemoglobin concentrations

Is this an orphan indication?

✓ **Yes. PREA does not apply. Skip to signature block.**

☐ **No. Please proceed to the next question.**

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:** _____

tudies are fully waived, then pediatric information is complete for this indication. Enter into RMS-BLA Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Waived.

ction B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

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 RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Partially Waived

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

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 RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Deferred

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

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 RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Data Submitted and Complete.

This page was completed by:

Florence O. Moore FOM 2/9/07
Regulatory Project Manager

cc: **BLA 125166/0**
Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT ROSEMARY ADDY OR GRACE CARMOUZE

(revised for TBP licensing products 9-15-2006)

RECORD OF TELEPHONE CONVERSATION

BLA: 125166/Alexion/Eculizumab

Today's date: March 14, 2007

Telephone: 203-272-2596

Speakers: Glen Jones

For Alexion: Arthur Awards, Cornelius Dunn, Richard Khazzaka

For FDA: Glen Jones, Florence Moore, Sheila Rawls

Alexion requested this t-con to briefly go over Alexion's final version of the vial and container labels submitted March 14, 2007. FDA recommended that for consistency eculizumab should be in lower case and to unbold some of the text e.g. Rx, temperature etc. to free up space on the vial and carton labels.

Alexion stated that they would like the vial and carton labels finalized by March 15, 2007 so they can start printing. FDA advised Alexion that they will be printing the labels at risk if they did so before an action is actually taken. Alexion acknowledged FDA's advised and stated that they had discussed the risk internally and are willing to take the risk.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 13, 2007

From: Florence Moore, M.S., DMIHP/OODP/CDER

Subject: Soliris (Eculizumab) Carton and Vial Labeling Review

---

Alexion originally submitted draft carton and vial labeling to BLA STN 1215166/0 on September 15, 2006, in their original BLA application for Soliris. The carton and vial labeling and package insert were sent to OSE/DMETS, DDMAC, and the OPS/DMA review staff for comments, in addition to review comments from DMIHP/OODP. On February 7, 2007 we forwarded via email comments regarding the vial and carton labeling from OSE/DMETS

A. Container Label

1. Ensure that the established name is at least as prominent as the size o the proprietary name in accordance to 21 CFR 610.61(b).

2. DMETS recommends that the total drug content and product strength be presented directly under the established name in the same font size, with theme color background, utilizing two different lines, and within a box border. Additionally, the total drug content should be the primary expression of strength followed immediately by the mg per mL concentration. Revise all labels and labeling to read:

   Soliris
   (Eculizumab Injection
   300 mg/ 30mL
   10 mg/mL

   Expressing the total drug content and product strength in this manner will help prevent practitioners from misinterpreting the total drug content of the product. Medication errors can occur when a user or practitioner reads the product strength (e.g. 10 mg/mL) but fails to read or calculate the drug content.

3. Statements contained in the blue banner on the top and on the bottom highlighted and given more prominence than other important information such as the proprietary name, established name, and total drug content. DMETS recommends deletion of the blue boxing.

4. Increase the prominence of the store under refrigerator statement. AS currently presented, this information is buried in the text on the side panel.

4 Page(s) Withheld

_____ Trade Secret / Confidential

✔ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 9

Moore, Florence O

From: Moore, Florence O
ent: Tuesday, March 13, 2007 3:48 PM
To: Nancy Motola
Cc: 'Arthur Edwards'
Subject: PMC Request

Importance: High

Dear Nancy,

Per your discussions with Dr. Rieves, please provide a communication (email/other) that commits to the following PMC:

"To conduct a randomized, controlled clinical study to assess the effects of anticoagulant withdrawal among PNH patients receiving eculizumab. This study will randomize at least 100 anticoagulated patients to either continue or discontinue anticoagulation therapy. The major outcomes will assess the safety of discontinuation of anticoagulant therapy while continuing eculizumab, especially with respect to providing important evidence that this discontinuation does not increase the risk for recurrence of thrombotic events in these patients. A full study report and data from this study will be submitted to the BLA and may be included in a label revision, contingent upon the importance of the study results. The study protocol will be submitted to the investigational new drug application (IND) by [redacted] and patient accrual completed no later than [redacted]
A final study report will be submitted no later than [redacted]

Alexion may propose alternative dates.

Please respond to this request by COB 5 PM today. Please let me know if you accept our text. If not please modify and send it back to me ASAP.

Thanks,

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903

Tel: 301-796-1423
Fax: 301-796-9849

Moore, Florence O

From: Moore, Florence O
Sent: Monday, March 12, 2007 11:49 AM
To: Nancy Motola
Cc: 'Arthur Edwards'
Subject: PMC Information Request

Importance: High

Dear Nancy:

As discuss during this morning's t-con with you, myself and Dr Rieves: Please see the FDA wording for the PMC:

Alexion, please revise your PMC commitment letter to contain the following additional modification (item e):

1. To evaluate long-term safety of eculizumab by analyzing outcomes in the Soliris Safety Registry for a time period of no less than five years. At the end of the five year period, a study report will be submitted to the Biological License Application (BLA) that describes the major safety findings from the registry program, including the specific items listed below and proposing labeling changes as appropriate. Additionally, annual interim reports will be submitted to the BLA, along with expedited reports as specified below. The protocol for addressing this PMC will be submitted to the IND by May 31, 2007, and the five year study report will be submitted by June 30, 2012. All patients within the registry will be followed for the occurrence of:

    a. Serious infections, defined as infections necessitating or prolonging hospitalization or resulting in death. Alexion commits to collecting follow-up information from these patients to assess the nature of the serious infection, the duration of hospitalization, the major features of the clinical course and the survival status. Expedited reporting (15 day telephone or facsimile Medwatch communication) will be provided for the occurrence of these serious infections.

    b. Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy;

    c. Use of Eculizumab among pediatric patients under 16 years of age, to include collection of Eculizumab dosage information, as well as the same information being required for adult patients in the registry;

    d. Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to the women exposed to Eculizumab during the pregnancy.

    e. Thrombotic events, including the nature of the event, the clinical outcome as well as the anticoagulant management prior to and after the event.

Regards,

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381

Silver Spring MD 20903

Tel: 301-796-1423
Fax: 301-796-9849

Moore, Florence O

From: Hastings, Kenneth L
Sent: Friday, March 09, 2007 8:43 AM
To: Moore, Florence O
Cc: Laniyonu, Adebayo A
Subject: RE: BLA 125166 Eculizumab PT review

Hi Florence: I have the package and have read over it, and I concur that it may be approved based on the review of nonclinical data. If you would like a memo in DFS, let me know and I'll enter one, but otherwise its good to go - Ken

---

From: Moore, Florence O
Sent: Thursday, March 08, 2007 2:43 PM
To: Hastings, Kenneth L
Cc: Laniyonu, Adebayo A
Subject: RE: BLA 125166 Eculizumab PT review
Importance: High

Good afternoon Ken,

The action package is due to the office tomorrow. Have you had a chance to look at the non-clinical reviews. Are you going to concur by email or are you going to sign the document? Please advice, I can come up to get the signed copy to add to the package.

Thanks,
Florence

From: Moore, Florence O
Sent: Monday, February 26, 2007 2:04 PM
To: Hastings, Kenneth L; Laniyonu, Adebayo A
Cc: Biade, Siham
Subject: RE: BLA 125166 Eculizumab PT review

Good afternoon Ken,

I stopped by your office today to give you the pharm/tox review but it seems you were out of the office (your lights were out). I slid the red envelop with the review under your door.

Please send your concurrence and any tertiary reviews that you may have my way. If none the signed concurrence will be fine.

Thanks,
Florence

From: Hastings, Kenneth L
Sent: Monday, February 26, 2007 9:14 AM
To: Laniyonu, Adebayo A
Cc: Biade, Siham; Moore, Florence O
Subject: RE: BLA 125166 Eculizumab PT review

Hi Bayo: Thanks for the heads-up. I assume there's no p/t issues? - Ken

---

From: Laniyonu, Adebayo A
Sent: Monday, February 26, 2007 7:23 AM
To: Hastings, Kenneth L
Cc: Biade, Siham; Moore, Florence O
Subject: BLA 125166 Eculizumab PT review

Hi Ken,

You are about to receive the hard copy of P/T review of Eculizumab BLA within the next few days through

Florence Moore, the PM for the submission. BLAs apparently need paper signatures, hence the need for a hard copy.

The Review is about 50 pages, and I did not write a secondary review; basically concurring with Siham's review and recommendation.

Thanks

Bayo

RECORD OF TELEPHONE CONVERSATION

BLA: 125166/Alexion/Eculizumab

Today's date: March 9, 2007

Telephone: 203-272-2596

Speakers: Rick Pazdur (FDA) and Leonard Bell (Alexion)

For Alexion: Nancy Motola, Art Edwards, Leonard Bell

For FDA: Rick Pazdur, Karen Weiss, Kathy Robie Suh, Dwaine Rieves, Andrew Dmytrijuk, Jyoti Zalkikar, Florence Moore

FDA called Alexion to briefly discuss their options regarding the final first cycle review of their application. FDA reminded Alexion that the PDUFA date is close and that we needed closure to determine whether to issue a Complete Review Letter or an Approval Letter. FDA indicated that by this time of the review, the final action letter is drafted and circulating for comments and we needed to know which route to take.

FDA reiterated that as previously discussed, the Study E05-001 (a single arm, open label, extension study) cannot be regarded as adequate and well controlled study due to the limitations of the historical design and the historical database construct/rigor. Alexion continued questioning FDA and ultimately FDA noted that this issue had been settled from the reviewer perspective and the review findings are not negotiable. However, FDA and Alexion came into an agreement that that the following statement should go in the label regarding the thrombotic events:

> "There were fewer thrombotic events with Soliris treatment than during the same period of time prior to treatment. However, the effect of Soliris upon the prevention or treatment of thrombotic events has not been established. [*see Warnings and Precautions (5)].*"

[redacted]

FDA briefly went over minor changes that were needed to finalize the label. FDA advised Alexion to submit the final agreed upon label no later than 9 AM Monday, March 12, 2207.

ALEXION
pharmaceuticals

March 7, 2007

Rafel Dwaine Rieves, M.D.
Acting Director
Division of Medical Imaging and Hematology Products (HFD 160)
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: SOLIRIS™ (eculizumab)
BLA #125166
General Correspondence: Response to a Pending Application

Dear Dr. Rieves:

Reference is made to Alexion Pharmaceuticals, Inc.'s Biologic License Application #125166 for SOLIRIS™ (eculizumab) for the treatment of patients with paroxysmal nocturnal hemoglobinuria (PNH), and to the Division's e-mail of March 6, 2007, to Alexion outlining the Division's request for a Post Marketing Commitment. That comment is as follows:

Alexion commits to submitting a comprehensive description of the Soliris Guardian Program [Risk Minimization Action Plan (RiskMAP)], including all items listed below. Fulfillment of this post-marketing commitment will be contingent upon FDA concurrence with the Soliris Guardian Program. Submission of all items listed below will occur no later than May 18, 2007. Alexion has revised the RiskMAP since the 22 Feb 2007 version based upon Agency feedback.

1. A final version of the Soliris Guardian Program (RiskMAP) document that, in addition to any other items, provides information fully consistent with the approved prescribing information.

352 Knotter Drive ▾ Cheshire, CT 06410 ▾ Tel: 203-272-2596 ▾ Fax: 203-271-8198 ▾ www.alxn.com

c. Extent of compliance with RiskMAP requirements such as the percentage of patients that were vaccinated prior to receiving Soliris and the percentage of patients that were re-vaccinated at 3-year or 10-year intervals (as applicable)
d. Analysis of all data collected in the Soliris Safety Registry, [redacted]
e. Results from all health care provider and patient surveys, including:
    - any known data about patients or physicians who refused to participate in the surveys
    - any known data about survey participants who are considered "lost" (drop-outs)."

If there are any questions regarding this submission, please contact me at (203) 271-8241.

Sincerely,

Arthur D. Edwards
for

Nancy C. Motola, PhD, RAC
Senior Vice President, Regulatory and Quality

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0430
Expiration Date: April 30, 2009
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Alexion Pharmaceuticals Inc.	3/7/07
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
203-272-2596	203-271-8191
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 352 Knotter Drive Cheshire, CT 06410	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE** Rafel Dwaine Rieves, MD Acting Director Division of Medical Imaging and Hematology Products (HFD 160), Food and Drug Administration Center for Drug Evaluation and Research, 5901-B Ammendale Road, Beltsville, MD 20705-1266

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 125166

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
eculizumab	SOLIRIS™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
h5G1.1-mAb	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Sterile Parenteral Solution for Intravenous Infusion	300 mg (10mg/mL)	Intravenous Infusion

(PROPOSED) INDICATION(S) FOR USE:
Paroxymal Nocturnal Hemoglobinuria (PNH)

APPLICATION DESCRIPTION

APPLICATION TYPE *(check one)* ☐ NEW DRUG APPLICATION (CDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☒ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☒ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

1) Lonza Biologics Inc (drug substance manufacturing and packaging, drug substance in-process and release testing), 101 International Drive, Portsmouth, NH 03801, FEI: 3001451441, BB-MF 2500, contact: Ian Elvins, Vice President of Global Quality, phone: 603-610-5358.

2) Lonza Biologics plc (cell bank creation and storage, drug substance release testing), 228 Bath Road, Slough, Berkshire SL1 4DX, UK, FEI: 1000583959, contact: Eleanor Taaffe, Head of Quality Assurance, UK, phone: +44 1753 777067.

[redacted]

5) Alexion Pharmaceuticals Inc. (drug substance release and stability testing, drug product release and stability testing), 352 Knotter Drive, Cheshire, CT 06410, FEI: n/a, contact: Nancy Motola, PhD, RAC, Senior VP Regulatory and Quality Assurance, phone: 203-271-8241. (Alexion Pharmaceuticals Inc. site is ready for inspection)

[redacted]

[redacted]

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* General Correspondence; Response to Pending Application: Post Marketing Commitment

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
Arthur D Edwards for	Nancy C. Motola, PhD, RAC Senior Vice President, Regulatory and Quality	3/7/07

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
352 Knotter Drive, Cheshire, CT 06410	(203) 271-8241

Public reporting burden for this collection of information is estimated to average 24 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:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

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.

MEMORANDUM

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

DATE: February 28, 2007

TO: Rafel Rieves, M.D., Acting Director
Division of Medical Imaging and Oncology Products

VIA: Florence Moore, M.S., Regulatory Health Project Manager
Division of Medical Imaging and Oncology Products

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

THROUGH: Toni Piazza-Hepp, Pharm.D., Deputy Director
Division of Surveillance, Research, and Communication Support

SUBJECT: OSE/DSRCS Review of Patient Labeling (Medication Guide and Patient Safety Card) for Soliris (eculizumab) injection, solution for intravenous use, BLA 125166

Background and Summary

The sponsor submitted patient labeling for Soliris (eculizumab) injection, solution for intravenous use, BLA 125166, on February 26, 2007, in the form of a Patient Package Insert (PPI) and a Patient Safety Card. OSE is recommending a Medication Guide for the product for the serious and significant public health concern regarding an increased incidence of serious infections with the product, especially meningococcal infections and the need for meningococcal vaccination prior to starting treatment with this product. Medication Guides are required to be distributed with the drug product; PPIs have voluntary distribution.

Comments and Recommendations

1. See the attached documents (marked and clean copies) for our suggested revisions for the Medication Guide and Patient Safety Card. We have reformatted the Medication Guide and simplified the wording to enhance readability. We have removed unnecessary information and ensured consistency with the Full Prescribing Information (FPI). Medication Guides must be based on the approved professional labeling for the drug product [208.20(a)(2)]. Pertinent revisions to the FPI should be reflected in the Medication Guide. We also simplified the wording in the Patient Safety Card where possible.

2. We recommend (although not required) that the Medication Guide and Patient Safety Card be the sole patient education materials so as not to overwhelm patients with information. We also recommend (although not required) that the Medication Guide be sent to prescribers offices so that patients can receive the important safety messages prior to starting treatment.

3. Refer to 201.57(18) *Patient Counseling Information*. The full text of the Medication Guide should be reprinted immediately following this section or must accompany the label. For prescriber convenience, we recommend (although not required) that the text of the Medication Guide be reprinted in the FPI. A separate copy of the Medication Guide meeting the specified font-size requirements should be available for patient distribution.

Comments to the review division in the attached documents are ***bolded, underlined and italicized***. Please call us if you have any questions.

9 Page(s) Withheld

_____ Trade Secret / Confidential

✓ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 10

Record of Telephone Call

BLA: 125166/Alexion/Eculizumab

Today's date: February 26, 2007

Speakers:

For FDA: Andrew Dmytrijuk, Kathy Robie Suh, Dwaine Rieves
For Alexion: Lonnie Bell and Nancy Mortola

FDA called to emphasize the importance of submitting all patient labeling information and revised package insert asap. The sponsor stated they plan 2 forms of patient labeling: a patient information leaflet (which is tantamount to med guide) and patient card. FDA stated it would consider these and review the documents asap.

Alexion Responses to 2/20/07 FDA Postmarketing Commitments (PMC) for Soliris BLA #125166

This document is Alexion's response to FDA's letter (sent via fax) of 20 Feb 07, outlining their requests for PMCs. FDA's requested PMCs are in *italic*. Alexion Responses are in regular font.

Postmarketing Studies subject to reporting requirements of 21 CFR 601.70.

FDA PMC #1

1. *Alexion commits to evaluating long-term safety of Eculizumab by analyzing outcomes in the* [redacted] *for a time period of no less than five years. At the end of the five year period, a study report will be submitted to the Biological License Application (BLA) that describes the major safety findings from the registry program, including the specific items listed below and proposing labeling changes as appropriate. Additionally, annual interim reports will be submitted to the BLA, along with expedited reports as specified below. The protocol for addressing this PMC will be submitted to the IND by XX, XXXX and the five year study report will be submitted by XX, XXXX. All patients within the registry will be followed for the occurrence of:*

   a. *Serious infections, defined as infections necessitating or prolonging hospitalization or resulting in death. Alexion commits to collecting follow-up information from these patients to assess the nature of the serious infection, the duration of hospitalization, the major features of the clinical course and the survival status. Expedited reporting (15 day telephone or facsimile Medwatch communication) will be provided for the occurrence of these serious infections.*

   b. *Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy;*

   c. *Use of Eculizumab among pediatric patients under 16 years of age, to include collection of Eculizumab dosage information, as well as the same information being required for adult patients in the registry;*

   d. *Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to the women exposed to Eculizumab during the pregnancy.*

Alexion Responses to 2/20/07 FDA Postmarketing Commitments (PMC) for Soliris BLA #125166

Alexion Response to PMC #1:

Following discussion (20 Feb 07) with officials from DMIHP and OODP, Alexion has decided [redacted]. Instead, Alexion will implement the Soliris Safety Registry. In view of this change, Alexion proposes to change the wording of this PMC as follows:

1. **Alexion commits to evaluating long-term safety of eculizumab by analyzing outcomes in the Soliris Safety Registry for a time period of no less than five years. At the end of the five year period, a study report will be submitted to the Biological License Application (BLA) that describes the major safety findings from the registry program, including the specific items listed below and proposing labeling changes as appropriate. Additionally, annual interim reports will be submitted to the BLA, along with expedited reports as specified below. The protocol for addressing this PMC will be submitted to the IND by May 31, 2007, and the five year study report will be submitted by June 30, 2012. All patients within the registry will be followed for the occurrence of:**

    a. **Serious infections, defined as infections necessitating or prolonging hospitalization or resulting in death. Alexion commits to collecting follow-up information from these patients to assess the nature of the serious infection, the duration of hospitalization, the major features of the clinical course and the survival status. Expedited reporting (15 day telephone or facsimile Medwatch communication) will be provided for the occurrence of these serious infections.**

    b. **Malignancy, including the nature of the malignancy and the survival status of patients who develop a malignancy;**

    c. **Use of Eculizumab among pediatric patients under 16 years of age, to include collection of Eculizumab dosage information, as well as the same information being required for adult patients in the registry;**

    d. **Pregnancy, including the clinical course of each pregnancy and the detection of congenital abnormalities among babies born to the women exposed to Eculizumab during the pregnancy.**

Alexion Responses to 2/20/07 FDA Postmarketing Commitments (PMC) for Soliris BLA #125166

FDA PMC #2

2. *Alexion commits to developing a validated and quantitative assay for the measurement of human anti-human antibodies (HAHA) for the detection of antibody formation to Eculizumab. This assay will assess potential immune responses to the whole Eculizumab molecule. Description of the validated assay will be submitted to the BLA as a CBE 30 by July 9, 2008.*

Alexion Response to PMC#2

Alexion agrees and commits to this PMC.

FDA PMC #3

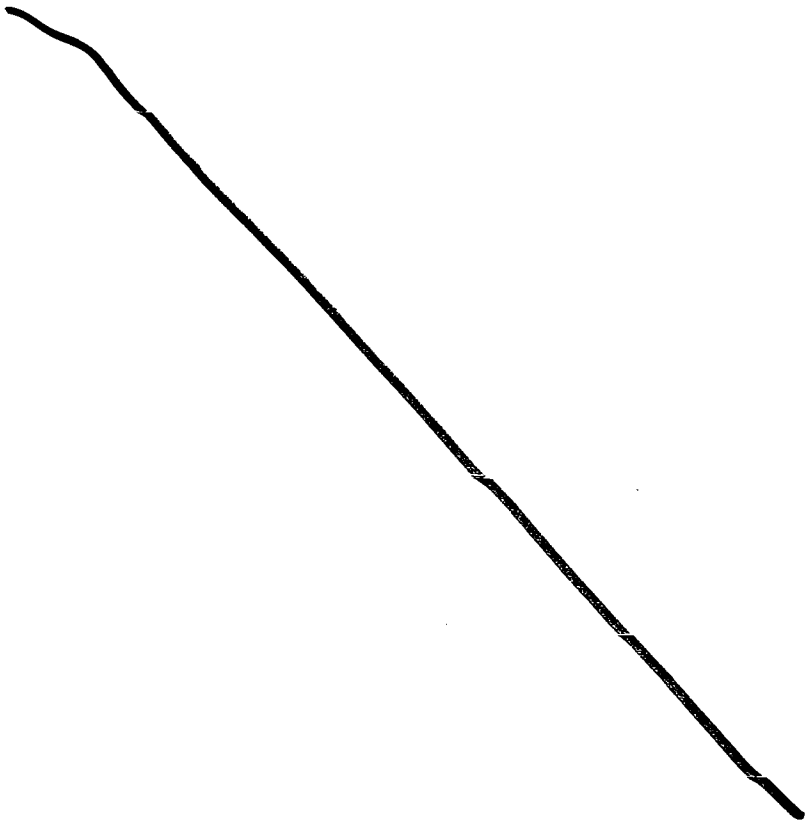
3. *Alexion commits to developing a validated and sensitive assay for the measurement of neutralizing HAHA to Eculizumab. Alternatively, Alexion commits to submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed and that the assessment of serum lactate dehydrogenase (LDH) is a sufficiently sensitive indicator of the presence of neutralizing antibodies. This information will be submitted to the BLA by XX, XXXX.*

Alexion Response to PMC#3

Alexion commits to a date for submitting to the BLA, and proposes to change the wording of this PMC as follows:

3. **Alexion commits to developing a validated and sensitive assay for the measurement of neutralizing HAHA to Eculizumab. Alternatively, Alexion commits to submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed and that the assessment of serum lactate dehydrogenase (LDH) is a sufficiently sensitive indicator of the presence of neutralizing antibodies. This information will be submitted to the BLA by July 9, 2008.**

FDA PMC #4



4. **Alexion will utilize samples from the ongoing E05-001 Phase III extension study (approximately 170 patients for at least 2 years) as test samples for the new validated HAHA assays. Alexion will continue to obtain serum samples from those patients who transition from E05-001 to the Soliris Safety Registry, at intervals of no less than one year, and continue this collection process for an additional three years. Sample collection will cease during this additional three year period for patients who terminate eculizumab administration. Additionally, serum samples will be obtained based upon physician reports of suspected loss of eculizumab bioactivity, based upon unanticipated alterations in serum lactic dehydrogenase (LDH) concentrations. All serum samples will be assayed at least annually and the results provided within an annual report to the BLA. Clinical data, to include the results of serum lactic dehydrogenase (LDH) concentrations, will also be obtained from any patients who evidence antibody formation. The protocol describing Alexion's plan for responding to this commitment will be submitted by May 1, 2007 and the final study report submitted by January 31, 2011.**

Alexion Responses to 2/20/07 FDA Postmarketing Commitments (PMC) for Soliris BLA #125166

Postmarketing Studies not subject to reporting requirements of 21 CFR 601.70.

FDA PMC #5

5. *Alexion commits to revalidating the linearity and accuracy of the Osmolality method across the full specification range using a combination of product samples diluted to lower osmolality and product samples spiked with osmolality standards. The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.*

Alexion Response to PMC #5

Alexion agrees and commits to this PMC.

FDA PMC #6

6. *Alexion commits to revalidating the linearity of the IEF method across a load range of* [redacted] *The revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.*

Alexion Response to PMC #6

Alexion agrees and commits to this PMC.

FDA PMC #7

7. *Alexion commits to revising the IEF method SOP to specify that the method is validated only for a* [redacted] *. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.*

Alexion Response to PMC #7

Alexion agrees and commits to this PMC.

Alexion Responses to 2/20/07 FDA Postmarketing Commitments (PMC) for Soliris BLA #125166

FDA PMC #8

8. Alexion commits to improving and revalidating the existing hemolytic assay. Improvements include increasing the number of sample replicates and qualifying the chicken erythrocytes reagent. The revised method SOP and revalidation plan will be submitted in advance to FDA for review and endorsement. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

Alexion Response to PMC #8

Alexion agrees and commits to this PMC.

FDA PMC #9

9. Alexion commits to developing a new quantitative biological activity assay to replace the existing hemolytic assay, or submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed. This information will be submitted to the BLA by February 29, 2008. Validation of the quantitative biological activity assay will be submitted by XX, XXXX.

Alexion Response to PMC #9

Alexion defines the supplement type and also commits to a date for submitting to the BLA, and proposes to change the wording of this PMC as follows:

9. Alexion commits to developing a new quantitative biological activity assay to replace the existing hemolytic assay, or submit documentation to FDA demonstrating with due diligence that a suitable assay could not be feasibly developed. This information will be submitted to the BLA as a CBE 30 by February 29, 2008. Validation of the quantitative biological activity assay will be submitted by July 9, 2008.

FDA PMC #10

10. Alexion commits to providing FDA with a completed drug substance and drug product container closure system leachables evaluation using end-of-shelf-life, long-term 2 – 8°C stability samples. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

Alexion Response to PMC #10

Alexion agrees and commits to this PMC.

Alexion Responses to 2/20/07 FDA Postmarketing Commitments (PMC) for Soliris BLA #125166

FDA PMC #11

11. Alexion commits to develop a suitable [redacted] assay and subsequently confirm [redacted] on three drug substance batches. This information will be submitted to the BLA as a CBE 30 by August 31, 2007.

Alexion Response to PMC #11

Alexion agrees and commits to this PMC.

RECORD OF TELEPHONE CONVERSATION

BLA: 125166/Alexion/Eculizumab

Today's date: February 20, 2007

Telephone: 203-272-2596

Speakers:

For Alexion: Nancy Motola, Art Edwards, Christopher Mojcik, Leonard Bell, Jason Meyenburg, Robert Geller, Raul Herrera

For FDA: Kathy Robie Suh, Dwaine Rieves, Andre Dmytrijuk, Florence Moore, Joyce Weaver, Claudia Karwoski, Betsy Scroggs

FDA called the sponsor to briefly discuss certain regulatory concerns related to their propose RiskMAP submitted 2/9/07 (see OSE attached comments sent to the sponsor 2.20/07). FDA requested clarity on the component of their RiskMAP and advised the proposed RiskMAP needs modification.

FDA asked Alexion to clarify their intended distribution method for eculizumab. Alexion stated that there is a verification form that will verify and document that patients have been vaccinated etc which will be forwarded to Alexion prior to the release of the product through a third contract party (a specialty pharmacy).

FDA requested Alexion send their distribution method in writing and also to address patients receiving the drug through infusion centers. FDA also asked Alexion to describe the functions in the RiskMAP and who will be providing the functions.

FDA requested that a medication guide that is patient friendly should be submitted for

[redacted]

Alexion acknowledged FDA's advice and recommendations and indicated they will look over the FDA RiskMAP comments and get back to the agency as quickly as possible.

RECORD OF TELEPHONE CONVERSATION

BLA: 125166/Alexion/Eculizumab

Today's date: February 20, 2007

Telephone: 203-272-2596

Speakers:

For Alexion: Nancy Motola, Lonnie Bell

For FDA: Kathy Robie Suh, Dwaine Rieves, Karen Weiss

FDA called the sponsor to briefly discuss certain regulatory concerns related to a restricted distribution. Alexion stated that it was never their intent to restrict distribution of Soliris--instead, they intended that the label state vaccination was necessary but they did not intend for distribution to be based upon receipt of verification of vaccination. They noted that they understood the confusion regarding the currently worded RiskMapp text.

FDA suggested that they may wish to provide a brief summary of a proposal to revise the RiskMapp to accurately reflect their intentions/thoughts regarding actions necessary for safe use of the product. Alexion is to supply a page or two summary of this proposal by the end of the day. FDA noted the proposal would be circulated to the review team and FDA would attempt to respond as soon as possible.

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 02/15/07

TO: Florence Moore, Regulatory Health Project Manager
Andrew Dmytrijuk, M.D., Clinical Reviewer
Division of Medical Imaging and Hematology Products, HFD-160

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Tejashri Purohit-Sheth, M.D.
Clinical Reviewer, GCP 2, HFD-47
Division of Scientific Investigations

SUBJECT: Preliminary Evaluation of Clinical Inspections, Pending Receipt of EIRs

BLA: 125166/0

NME: Yes

APPLICANT: Alexion Pharmaceuticals

DRUG: Soliris™ (eculizumab)

THERAPEUTIC CLASSIFICATION: Priority 6-Month Review

INDICATION: Paroxysmal Nocturnal Hemoglobinuria

CONSULTATION REQUEST DATE: 11/30/06

DIVISION ACTION GOAL DATE: 2/19/07

PDUFA DATE: 3/17/07

I. BACKGROUND:

Alexion Pharmaceuticals submitted this BLA for the use of Eculizumab for the treatment of transfusion dependent paroxysmal nocturnal hemoglobinuria (PNH). PNH is an acquired chronic hemolytic anemia that results from a somatic mutation of the phosphatidylinositol glycan complementation class A (PIG-A) gene in pluripotent hematopoietic stem cells. Eculizumab is a humanized monoclonal antibody that inhibits terminal complement, like CD59. Since CD59 inhibits terminal complement in normal individuals, the lack of this results in several clinical features of the disease. It is hypothesized that eculizumab's inhibitory action on terminal complement will effectively stop the intravascular hemolysis, obviate and lessen the need for blood transfusions, and possibly decrease the incidence of life threatening thrombosis.

Primary support for the indication came from the pivotal study # C04-001, TRIUMPH: A Hemoglobin Stabilization and Transfusion Reduction Efficacy and Safety Clinical Investigation, Randomized, Multicenter, Double-Blind, Placebo-Controlled, Using Eculizumab in Paroxysmal Nocturnal Hemoglobinuria. A DSI audit was requested because eculizumab is a new molecular entity and is the first product for this sponsor.

Two clinical sites, 027 (Dr. Young) and 070 (Dr. Hillmen) and the sponsor (Alexion Pharmaceuticals) were selected for inspection. The two clinical sites were selected for inspection due to high enrollment; the sponsor was selected for inspection because eculizumab is a new molecular entity and it is the first product for this sponsor.

II. RESULTS (by protocol/site):

Name of CI and site #	City, State*	Country	Protocol #	Insp. Date	EIR Received Date	Final Classification
Dr. Neal Young NHLBI – National Institutes of Health Site #: 027	Bethesda, MD	USA	C04-001	1/8/07-1/22/07	Pending	Pending
Dr. Peter Hillmen Leeds General Infirmary Site #070	Leeds	UK	C04-001	1/12/07-2/10/07	Pending	Pending
Alexion Pharmaceuticals	Cheshire, CT	USA	C04-001	1/24/-1/29/07	Pending	Pending

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

1. **Dr. Neil Young: Site 027**
NHLBI – National Institutes of Health

9000 Rockville Pike
Bethesda, MD 20892

a. What was inspected?
A total of 5 subjects were randomized to this site and data audit on all subjects was conducted in accordance with the clinical investigator compliance program, CP 7348.811. Informed Consent was verified in 100% of subjects. The audit included comparison of source documentation to CRFs.

b. Limitations of inspection
The EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator, and the FAXed 483s.

c. General observations/commentary
Generally, it appears that the investigator was found to have executed the study adequately, although a few deviations from FDA regulations were noted, and an FDA Form 483 was issued for these observations (described below).

The observations listed in the FDA Form 483 that was issued are summarized below:

Observation 1
Three out of three female subjects did not have monthly urine pregnancy tests during the screening, observation, and treatment phase as required by Section 6.0 of Study Protocol #05-H-0048, which was approved by the IRB along with Protocol #C04-001.

Observation 2
One out of three subjects was administered one incorrect dose of investigational drug: Subject was administered 180 mL of investigational drug as the fourth infusion of May 18, 2005, rather than 120 mL as required by Protocol #C04-001.

Observation 3
One out of three subjects was not given the rescue medication on the date of the first investigational drug infusion as required by Protocol #C04-001. Subject received the first investigational drug infusion on May 17, 2005; however, the rescue medication was not administered until May 24, 2005.

Observations noted above are based on the Form FDA 483 and communications from field investigator; an inspection summary addendum will be generated if conclusions change upon receipt and review of the official EIR.

d. Assessment of data integrity:
The data from Dr. Young's site appear acceptable as collected and generated according to the original protocol. However, the clinical impact of administering the wrong dose for a given scheduled visit for one subject will need to be evaluated by the Review Division.

Observation 1 states that pregnancy tests were not conducted monthly as required by a parallel protocol (nearly identical to C04-001). In a letter dated February 5, 2007 to the FDA, the inspector states that Protocols 05H-008 was identical to C04-001 with the exception that the former required the NIH Human Subjects Protection language and monthly pregnancy screenings. Since both were approved concomitantly, the inspector cited the failure to conduct monthly pregnancy screenings. It appears that this violation was not related to C04-001, and therefore unlikely to affect the data integrity of C04-001 study results.

Observation 2 cited the investigator for administration of an incorrect dose of drug for the scheduled study visit. The clinical impact of administering a higher dose (180 mL rather than 120 mL) for a given scheduled visit will need to be evaluated by the Review Division. In Dr. Young's response letter dated February 5, 2007, he states that this error resulted from the practice of tracking visits by both Visit Number and Study Week. However, this error in dosing did not result in any adverse effects for the subject.

Observation 3 cited the investigator for not providing rescue medication as required by the protocol during the first infusion of study drug. The investigator states that this error resulted because the NIH Clinical Center Information System, a complex network of information systems designed to support the good conduct of clinical research, was not fully operational at the time of the study, so this order in particular was not followed. The clinical impact of this protocol violation will need to be evaluated by the Review Division, although, it appears that this violation would be unlikely to significantly affect data integrity.

Therefore, it appears that the data as collected and generated is acceptable; however, DSI recommends that the Review Division evaluate the clinical impact of the protocol violations as identified above.

2. **Dr. Peter Hillmen, Site #070**
Leeds General Infirmary
[redacted]
St. George St.
Leeds LS1 3EX, UK

a. What was inspected?
A total of 12 subjects were randomized to this site and data audit was conducted on all subjects in accordance with the clinical investigator compliance program, CP 7348.811.

b. Limitations of inspection
The EIR was not available at the time this CIS was written. The findings summarized below were based on a brief fax from the inspector.

c. General observations/commentary
The investigator appeared to have conducted the study according to the protocol and there do not appear to be any significant deviations from regulations. Review of all records for the 12 randomized subjects found no major deficiencies or discrepancies. There were no unreported AEs.

An inspection summary addendum will be generated if conclusions change upon receipt and review of the official EIR.

d. Assessment of data integrity:
The data from Dr. Hillmen's site appear acceptable as collected and generated according to the original protocol.

3. **Sponsor Inspection: Alexion Pharmaceuticals**
Corporate Headquarters
Regulatory Affairs
352 Knotter Drive
Cheshire, CT 06410

a. What was inspected?
This inspection covered the sponsor/monitor practices related to Protocol #C04-001, conducted at the corporate headquarters for Alexion's Regulatory Affairs in Cheshire, CT. The inspection evaluated the sponsor's documentation of selection of qualified investigators for the study, financial disclosures, and training of clinical investigators. Additionally, the inspection verified that the sponsor followed up on problems encountered with the clinical investigators. Monitoring of the sites was conducted by a CRO with oversight from the sponsor. Monitoring reports, transfer of obligations agreements, and IRB approved informed consents for the required elements were also reviewed. The sponsor's method of tracking adverse events and serious adverse events, in addition to a data audit comparing the data listings for the two clinical sites inspected were also reviewed.

b. Limitations of inspection
The EIR was not available at the time this CIS was written. Summary of inspection results is based on preliminary communication with the Field Inspector.

c. General observations/commentary
The sponsor appears to be compliant with regulations with respect to sponsor responsibilities. The inspector did not identify any significant deviations.

d. Assessment of data integrity:
The sponsor appears to be compliant with regulations and no issues affecting data integrity were identified during the sponsor inspection.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, the study data collected by Drs. Young and Hillmen appear acceptable. Although an FDA Form 483 was issued to Dr. Young, it does not appear that the noted protocol violations would significantly impact data integrity; however, DSI recommends that the Review Division evaluate the clinical impact of the two protocol violations noted at Dr. Young's site.

Follow-Up Actions:
Observations noted above are based on the Form FDA 483 and communications from the field inspectors. DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending EIRs and the supporting inspection evidence and exhibits.

2/15/07

Tejashri Purohit-Sheth, M.D.
Medical Officer
Good Clinical Branch II
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments

2/15/07

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

Moore, Florence O

From: Moore, Florence O
Sent: Wednesday, February 14, 2007 11:21 AM
To: 'Nancy Motola'
Subject: RE: 125166/0 Information Request

Thanks Nancy.

From: Nancy Motola [mailto:MotolaN@alxn.com]
Sent: Wednesday, February 14, 2007 10:35 AM
To: Moore, Florence O
Cc: Arthur Edwards; Nancy Motola
Subject: RE: 125166/0 Information Request

Dear Florence,

We have given your request to the appropriate people to handle. I am not sure when the answers will be available, as we are in the midst of an ice storm and a lot of people are not in the office. Nevertheless, we will answer as quickly as possible. I'll keep you posted.

Nancy

From: Moore, Florence O [mailto:florence.moore@fda.hhs.gov]
Sent: Wednesday, February 14, 2007 9:33 AM
To: Nancy Motola
Cc: Arthur Edwards
Subject: STN: 125166/0 Information Request
Importance: High

Good morning Nancy:

DMIHP Pharm/Tox is requesting the information below:

Please provide historical control data of spontaneous neoplasms in [redacted]:CD-1 (ICR)BR mice, used in studies of 26 weeks duration performed by the conducting laboratory.

Dead/moribund males were observed in the F1 generation in study 6709-107 (Study for effects on pre- and post natal development, including maternal function in the mice with BB5.1). Do these males come from the same or different litters?

Thanks,

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381

Silver Spring MD 20903

Tel: 301-796-1423
Fax: 301-796-9849

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: February 13, 2007

From: Florence O. Moore, M.S., DMIHP/OODP/CDER

Subject: OSE Preapproval Safety Conference for 125166/0

The OSE (Office of Surveillance and Epidemiology) safety conference meeting was an internal team meeting with the Division of Medical Imaging and Hematology Products (DMIHP) to discuss Alexion's Soliris™ which is indicated for the treatment of paroxysmal nocturnal hemoglobinuria (PNH)

FDA Attendees included:

Florence Moore
Richard Pazdur
Karen Weiss
Rafel Rieves
Kathy Robie Suh
Andrew Dmytrijuk
Jang-Ik Lee
Hong Zhao
Yuan (Richard) Chen
Jyoti Zalkikar
Siham Biade
Adebayo Laniyonu
Mary Dempsey
Rajnikanth Madabushi
Samuel Chan
Betsy Scroggs
Susan Lu
Sean Bradley
Kurt Brorson
Lilliam Rosario
Toni Piazza Hepp
Solomon Iyasu
Mark I Avigan
Rosemary Johann-Liang
Allen Brinker
Michelle Jessen
Joyce Weaver
Alina Mahmud
Claudia B Karwoski
Mary Wiley

The OSE safety conference began with a presentation and overview of the application by DMIHP to OSE.

The team discussed follow-up of patients for infections including meningitidis and other serious viral infections and considered a possibility of having the sponsor do a PMC follow up for meningitidis and other serious viral infections.

OSE asked about the risk of meningitidis and recommendations other than vaccination, [redacted] DMIHP indicated that the sponsor has attempted to address this in their RiskMAP but the RiskMAP team and DMIHP will ask sponsor for clarifications.

Other questions that needed clarifications from the sponsor were the concern about how the drug will get to the clinicians or end users. Will patients go to infusion centers for the drug to be administered? DMIHP and the Risk Management Team will seek clarification from the sponsor on these issues.

The following action Items were identified at the meeting:

- DMIHP to request information on patients who received vaccination prior to undergoing treatment from the sponsor.
- DMIHP and OSE to discuss the RiskMAP and labeling
-
- DMIHP to consult DAVP division on viral infections.

Safety conference adjourned and the review team moved on to discuss the proposed PMCs.

Moore, Florence O

From: Moore, Florence O
Sent: Friday, February 09, 2007 4:51 PM
To: 'Nancy Motola'
Cc: 'Arthur Edwards'
Subject: FW: Response to FDA Request for Preclinical Related Information
Importance: High

Nancy,

another request from the pre-clinical team below.
Please, confirm the sterility of the BB5.1 lot 2640001 used in preclinical studies

Thanks,
Florence

From: Arthur Edwards [mailto:EdwardsA@alxn.com]
Sent: Friday, February 09, 2007 1:05 PM
To: Moore, Florence O
Cc: Nancy Motola
Subject: Response to FDA Request for Preclinical Related Information

Dear Florence:

Please find attached the response to your request of February 8, 2007 regarding the following:

The updated Certificate of Analysis (C of A) with the Results of the Repeat Test for Sterility for all Toxicology studies conducted using Lot 2640001.

Question: Do you want this information plus the information we provided to Dr. Chen yesterday to be also included in the total final response package that we are submitting to the FDA? I'm asking to make sure we provide you with what you're expecting to see in the final response package.

Thank you

Best regards,

Art

Arthur D. Edwards
Sr. Director, Regulatory Affairs

prohibited. If there is any reason to believe you are not the intended recipient, please notify the sender immediately by return email and delete this communication and destroy all copies. Thank you.

Moore, Florence O

From: Moore, Florence O
Sent: Thursday, February 08, 2007 9:53 AM
To: 'Nancy Motola'
Cc: EdwardsA@alxn.com
Subject: RE: BLA #125166: Datasets for LDH Levels

Good morning Nancy,

According to our reviewer, tables which give LDH levels in PNH patients are not good enough. He needs data to perform analysis and to confirm the numbers of "LDH Levels at End of Study" in Table 4 Study 1 Efficacy Result of Soliris label (line 293). If you can tell us the name of dataset or email a data file that includes subject id, treatment group, visit number and LDH level, he will be able to calculate the 2. If you have any questions on this please feel free to call Dr Chen at 301-796-1657.

Also, Dr. Rieves our Acting Division Director (if I haven't told you already Dr. Mills have left the Agency) would like us to schedule a t-con with you to discuss the edits for 1-1:30 PM today.

Thanks,
Florence

From: Nancy Motola [mailto:MotolaN@alxn.com]
Sent: Wednesday, February 07, 2007 3:22 PM
To: Moore, Florence O
Cc: EdwardsA@alxn.com; Nancy Motola
Subject: Re: BLA #125166: Datasets for LDH Levels

Dear Florence,

Below are the locations (in the BLA e-CTD) of tables which give LDH levels in PNH patients. I hope this is what you are looking for. If not, please clarify and I will get it for you.

The following Tables show the change from baseline LDH for the eculizumab studies:

Table 2.7.3.6-17 shows the change from baseline LDH for the C04-001 study. The Table shows LDH values for eculizumab treated patients vs. placebo for every visit through 26 weeks as well as the P value for drug vs. placebo.

Table 2.7.3.6-27 shows the change from baseline for the C04-001, C04-002 and the combined C04-001, C04-002 populations. As described above, this table shows the change from baseline LDH for eculizumab treated patients at each visit as well as the P value compared to baseline LDH levels for each study.

We understand that it will probably not be until noon tomorrow that we get the PI.

Thanks, Nancy

RECORD OF TELEPHONE CONVERSATION

BLA: 125166

Speakers: Kathy Robie Suh, Andrew Dmytrijuk, Dwaine Rieves all for FDA
Nancy Mortola and others for Sponsor

Today's date: 1/31/07

FDA called the sponsor and asked the questions listed below. Discussion topics included FDA's current inability to verify any claims of improved patient reported outcomes, independent of hemolysis effects or lessening/avoiding the need for transfusion. FDA requested the sponsor provide any analyses that may verify the independence of patient reported outcomes from hemolysis/transfusion need. Other information will be forwarded as listed below.

1. Q1...The facit scores suggest that transfusion importantly impacts the response to the questionnaire since the scores increase about 7 to 10 points from screening visit to baseline. Hence, any reduction in transfusion incidence should also be reflected in an improvement in facit scores--what data are available to verify that eculizumab improves symptoms of fatigue in the absence of decreasing the need for transfusion? Available information appears to indicate that it is impossible to dissect free this effect due to the inherent interaction of transfusion with fatigue. Discussion: sponsor to attempt to address.

2. Q2...To confirm regarding response to question 2...did any of these 8 patients with accelerated clearances have positive HAHA? Discussion: No.

3. Q3...Did subject 011-001 have positive HAHA? Do you interpret these results/other results as suggesting that physicians should consider decreasing the dosing interval to 12 days if LDH/signs of hemolysis do not resolve? Discussion: the subject did not have HAHA. Yes, LDH may be useful as a guide for dose interval adjustment.

4. Q4...clear. Not discussed.

5. Q5...Overall, of the 195 patients exposed to eculizumab that Alexion is aware of--we understand 4 died (including a patient in a physician sponsored IND). Do you have a description/narrative of the death of the physician sponsored patient death? Discussion: this will be forwarded. The sponsor clarified that total exposure consists of 196 patients.

6. Q6...Overall, we understand 3 PNH patients (out of 195...2%) had evidence of antibody formation...what are the LDH results during the time period before and after the + response (2 months before/2 months after)? Discussion: this will be forwarded.

RECORD OF TELEPHONE CONVERSATION

BLA: 125166

Today's date: January 29, 2007

Speakers: Dwaine Rieves for FDA and Nancy Mortola for Alexion

Phone: 203-271-8241

I called Alexion and made the requests listed below/as relayed by Ms. Moore using secure email. They stated they would respond soon.

1) What was the difference in the FACIT-fatigue score between the screening visit and the first day of the study agent administration by group (active vs placebo)?

2) How do you explain the increased clearance of eculizumab and hemolysis in 8 SHEPHERD patients?

3) Please summarize the clinical course of Subject 011-001 in TRIUMPH; this subject had increases in LDH in the later course of the study? How do you explain these increases in LDH?

4) In SHEPHERD, how many patients avoided transfusion over the entire one year study period?

5) Overall, we understand 195 PNH patients have received eculizumab. Please supply a tabular summary of all deaths among these 195 patients (5 deaths?) as well as a summary of all patients who discontinued SOLIRIS and identify whether accelerated hemolysis was detected or other adverse reactions were reported after the discontinuation.

6) Regarding the description of HAHA:

a. The December 16, 2006 integrated summary of safety states, on page 138, that 2 PNH patients developed HAHA. However, the table listing printed out on January 8, 2007 ("HAHA table listing") identifies elevated titers in five or more patients. Please reconcile this difference and clearly describe your definition of a positive HAHA response.

b. Please describe why the following subjects terminated the studies prematurely--patient ID numbers are c01-004-026010 (1:2500 developed HAHA in E01--004); c01-004-034011 (1:100 developed HAHA in E01-004) and c01-004-040006 (1:2500 developed in C04-001).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: **Florence O. Moore, M.S.**

To: **File: STN 125166/0**

Subject: **Mid-Cycle Meeting Summary**

Sponsor: **Alexion Pharmaceuticals**

Product: **Eculizumab (Soliris™)**

Date, Location, & Time of Meeting: **January 4, 2007**
WO Rm 1313
2:00 p.m. – 3:30 p.m.

Purpose:

Midcycle meeting to discuss Alexion's BLA to support the use of eculizumab for treatment of [redacted] paroxysmal nocturnal hemoglobinuria (PNH).

Midcycle Meeting Agenda:
Administrative

- Timeline/Relevant Milestones
  - Pre-approval mtg- Feb 5, 2007
  - Goal Date- Mar. 9, 2007
  - **PDUFA Due Date- Mar 16, 07**

- Proprietary Name: Soliris™

Review Status

- CMC
  - DMA
  - DMPQ/TFRB
- Clinical Pharmacology
- Clinical/Biostatistics

Relevant Milestones:

- BLA Filed: October 27, 2006
- Deficiencies identified: by November 28, 2006
- First Action Due Date: March 16, 2007
- Goal Date: March 9, 2007
- Labeling Meeting 1: January 25, 2007
- Team Meeting 4 (Preapproval Safety Conference)

Review Committee:

Clinical –Andy Dymitrijuk
PK – Jang-Ik Lee
DMPQ- Gilbert Salud
DMPQ- Brenda Uratani
Stats – Richard Chen
CMC – Joe Kutza
CMC- Michelle Jessen,
CMC- Kurt Brorson
CMC- Gurpreet Gill-Sangha
P/T – Siham Biade
RPM – Florence Moore

ODS/DDRE- (Samuel Chan RPM)
DSI- Tejashri Purohit-Sheth
DDMAC- Sean Bradley
ODS/DMETS- Linda Wisniewski/Todd Bridges
ODS/DSRCS- Jennifer Rouine/Betty Scroggs
Pharmacometric - Raj Madabushi
OSE/RISK Management- Mary Dempsey/ Claudia Karwoski
SEALD Endpoint: Melissa Furness
SEALD Labeling: Robin Anderson/Iris Masucci

Team Leaders

Clinical – Kathy Robie Suh
CMC – Joseph Kutza/Michelle Jessen
DMPQ- Brenda Uratani
P/T – Adebayo Laniyonu
PK – Hong Zhao
Stats – Jyoti Zalkikar
RPM Team Leader –Alice Kacuba

Division Heads

DMIHP- George Mills/Dwaine Rieves
DMA – Kathleen Clouse/Patrick Swann

Other FDA Representatives:

Richard Pazdur
Karen Weiss
Samuel Chen
Mary Dempsey
Laurie Burke
Melissa Furness

[redacted]

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 11075

Alexion Pharmaceuticals
Attention: Nancy Motola, Ph.D., RAC
Senior Vice President, Regulatory and Quality
352 Knotter Drive
Cheshire, CT 06410

Dear Dr. Motola:

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

We also refer to your amendment dated November 7, 2007, containing a protocol for an expanded access study in support of BLA 125166/0 for Eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH).

We have the following comments and recommendations:

1. As described in the November 22, 2006 telephone conversation, you may proceed with the study.

2. During the conduct of the study , please optimize collection of the following data:

    a. The specific reason and criteria by which each patient is enrolled in this study. As described in the study protocol, eligible subjects must have "one or more" of five possible manifestations of PNH. Please ensure that the study documents document which PNH manifestations prompt study enrollment (of the five possible PNH manifestations).

    b. For patients who are receiving systemic corticosteroids at enrollment, please document the doses and any subsequent changes in steroid use.

    c. For patients who experience a thromboembolic event, document the manifestation of the event, including the mode of diagnosis for any venous thromboembolic event.

This should allow for a better understanding of the types of patients being enrolled and the results of their disease management and adverse events related to venous thromboembolism.

3. Please submit a final statistical analysis plan for review. In general, we anticipate that this plan will consist of a summary of the major study outcomes, especially the safety outcomes during and following any cessation of Eculizumab administration.

Linked Applications	Sponsor Name	Drug Name
IND 11075	ALEXION PHARMACEUTIC	Eculizumab [Humanized Monoclonal Antibody (h5G1.1) to C5]

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

/s/

RAFEL D RIEVES
01/08/2007

Moore, Florence O

From: Moore, Florence O
Sent: Wednesday, December 20, 2006 1:11 PM
To: 'Nancy Motola'
Cc: Arthur Edwards; [redacted]
Subject: RE: Information Request

Thanks Nancy.

Florence

From: Nancy Motola [mailto:MotolaN@alxn.com]
Sent: Wednesday, December 20, 2006 11:06 AM
To: Moore, Florence O
Cc: Arthur Edwards; [redacted]
Subject: RE: Information Request

Dear Florence,

I received your e-mail and the appropriate people are checking this out. I will get back to you by tomorrow at the latest regarding the status of these data.

Nancy

Nancy C. Motola, PhD, RAC
Senior Vice President, Regulatory and Quality
Alexion Pharmaceuticals Inc.
352 Knotter Dr.
Cheshire, CT 06410
Ph: (203) 272-2596
Fax: (203) 271-8198
motolan@alxn.com

From: Moore, Florence O [mailto:florence.moore@fda.hhs.gov]
Sent: Wednesday, December 20, 2006 10:29 AM
To: Nancy Motola
Cc: Arthur Edwards; [redacted]
Subject: Information Request

Good morning Nancy,

Please see the information being requested by our PK/PD reviewers:

Please submit the data for single dose and multiple dose Pharmacokinetic and Pharmacodynamic data for eculizumab as .xpt files. Also submit the datasets for the population PK and PK/PD analysis, especially the data files provided in appendices 5 and 9 of the "Summary Report - Eculizumab Pharmacokinetics and Pharmacodynamics Compartmental Analysis and PK/PD Modeling" as .xpt files.

Please follow the following format:

Please submit datasets to support the population analysis:

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

model development decision tree and/or table which gives an overview of modeling steps.

If you have already submitted the data please point us to the the location of the data in your submission package.

Thank you,

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2381
Silver Spring MD 20903

Tel: 301-796-2050
Fax: 301-796-9849

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

11/2/06

Memorandum

From: Florence O. Moore, DMIHP, HFD-160

Subject: STN 125166/0 Internal Meeting Summary

Sponsor: Alexion Pharmaceuticals.

Product: Eculizumab

Indication: For Treatment of paroxysmal nocturnal hemoglobinuria (PNH)

Date, Location, & Time of Meeting: November 2, 2006, CDER White Oak Room 2327 10:00 – 11:00 AM

Alexion's Representatives: Nancy Motola, Leonard Bell, M.D. Chief Executive Officer, Christopher Mojcik, M.D., Ph.D. Sr. VP, Clinical Development, Nancy Motola, Ph.D. Sr. VP, Regulatory Affairs and Quality, Raoul Herrera, M.D. Sr. Director, Post Marketing Pharmacovigilance, Henk-Andre Kroon, M.D. Sr. Medical Director, Clinical Development

FDA Representatives: Dwaine Rieves, Kathy Robie Suh, Andrew Dmytrijuk, Florence Moore,

Summary:

Alexion walked DMIHP through their Eculizumab PNH and Non-PNH Studies Patient Narratives slides and discussed briefly, their concept on the expanded access program. Alexion stated they are willing to work with the agency on any additional studies needed for eculizumab. DMIHP also indicated they will work with Alexion to get the drug to patients who need it.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: **Florence O. Moore, M.S.**

To: **File: STN 125166/0**

Subject: **Application Orientation Meeting Summary**

Sponsor: **Alexion Pharmaceuticals**

Product: **Eculizumab (Soliris™)**

Date, Location, & Time of Meeting: **October 31, 2006**
WO Rm 1421 and 1419
11:30 a.m. – 1:00 p.m.

Purpose:

Application Orientation Meeting to support the use of eculizumab for treatment of [redacted] paroxysmal nocturnal hemoglobinuria (PNH).

Meeting Summary:

The Application Orientation Meeting was held for Alexion to give an overview of their BLA Application to support the use of eculizumab which has been the subject of IND 11075 for treatment of [redacted] paroxysmal nocturnal hemoglobinuria (PNH). See attached Alexion's presentation.

FDA Attendees:

Richard Pazdur
Karen Weiss
Dwaine Rieves
Kathy Robie Suh
Andre Dmytrijuk
Florence Moore
Patrick Swann
Joe Kutza

43 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- II

1 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 12

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: **Florence O. Moore, M.S.**

To: **File: STN 125166/0**

Subject: **Filing Meeting Summary**

Sponsor: **Alexion Pharmaceuticals.**

Product: **Eculizumab**

Date, Location, & Time of Meeting: **October 27, 2006**
WO, Conference Room 1313
1:00 p.m. – 2:00 p.m.

Purpose:

To discuss the filablity of STN: 125160/0 for Eculizumab and discuss CMC, Clinical Pharmacology, Clinical Studies, deficiencies identified.

Relevant Milestones:

- BLA Filed: October 27, 2006
- Deficiencies identified: by November 28, 2006
- First Action Due Date: March 16, 2007

Summary of Review Status:

Administrative/Regulatory

- Addition to the BLA review team was discussed. DMA has added two additional reviewers (Michelle Jessen and Gurpreet Gill-Sangha). Janet Barletta has been replaced by Brenda Uratani as the second DMPQ reviewer

- The labeling was submitted in PLR and SPL format in the submission, the document room has to load it right into the Gsreview tool and the CBER EDR.

- A team meeting will be scheduled by November 30 to discuss updates and issues related to the application.

- Timeline update was discussed.

CMC

- DMA had no filing issues, but there are a lot of deficiencies that has been identified and will be discussed with the sponsor.

- TFRB had no filing issues.

Pre-Clinical/Toxicology

- There were no Preclinical filing issues.

Clinical Pharmacology

- There were no Clinical Pharmacology filing issues identified

Clinical

- There were no Clinical filing issues identified

Biostatistics

- There were no Biostatistics filing issues identified

Conclusion: The review team was in agreement that BLA 125166/0 is filable.

Review Committee:

Andrew Dmytrijuk /DMIHP
Tushar Kokate/DMIHP
Florence Moore/DMIHP
Yuan Who (Richard) Chen/DBV
Jang-Ik Lee/DCP
Joseph Kutza/DMA
Michelle Jessen
Gilbert Salud/TFRB
Tejashri Purohit-Sheth/ DSI

Other FDA Representatives:

Kathy Robie Suh/ DMIHP
Hong Zhao/DCP
Brenda Utarani/ DMPQ

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: [redacted] Product: Eculizumab Applicant: Alexion

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): Traditional (CTD)

Filing Meeting: Date 10/27/06 Committee Recommendation (circle one): (File) RTF

RPM: [signature] 10/27/06
(signature/date)

Attachments:

- ☐ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ____ Part A – RPM
  - ✓ Part B – Product/CMC/Facility Reviewer(s): Guidance Author Brenda Uratani
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____ _____ _____ _____
- ☐ Memo of Filing Meeting

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Quality overall summary [2.3]	(Y)	N	
❑ Drug Substance	(Y)	N	
❑ Drug Product	Y	N	
❑ Facilities and Equipment	(Y)	N	
❑ Adventitious Agents Safety Evaluation	(Y)	N	
❑ Novel Excipients	Y	N	
❑ Executed Batch Records	Y	N	
❑ Method Validation Package	(Y)	N	
❑ Comparability Protocols	(Y)	N	

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	
Drug Substance [3.2.S]			
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	(Y)	N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	(Y)	N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	(Y)	N	
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	(Y)	N	
❑ process validation (prospective plan, results, analysis, and	(Y)	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	(Y) N	
❑ characterization of drug substance	(Y) N	
❑ control of drug substance	(Y) N	
o specification		
o justification of specs.		
o analytical procedures		
o analytical method validation		
o batch analyses		
o consistency (3 consecutive lots)		
o justification of specs.		
❑ reference standards	(Y) N	
❑ container closure system	(Y) N	
❑ stability	(Y) N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P]		
❑ description and composition	(Y) N	
❑ pharmaceutical development	(Y) N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
❑ batch formula	(Y) N	N/A
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
❑ controls of critical steps and intermediates	(Y) N	
❑ process validation including aseptic processing & sterility assurance:	(Y) N	
o 3 consecutive lots		
o other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin)		
☑ control of drug product (justification of specifications; analytical method validation)	(Y) N	
☑ container closure system [3.2.P.7]	(Y) N	
o specifications (vial, elastomer, drawings)		
☑ availability of DMF		N/A
o closure integrity		
o administration device(s)		
☑ stability	(Y) N	
☑ summary		
☑ post-approval protocol and commitment		
☑ pre-approval		
o protocol		
o results		
o method validation		
Diluent (vials or filled syringes) [3.2P']		
☑ description and composition of diluent	(Y) N	
☑ pharmaceutical development	(Y) N	
☑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
☑ batch formula	(Y) N	
☑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	N/A
☑ controls of critical steps and intermediates	(Y) N	
☑ process validation including aseptic processing & sterility assurance:	(Y) N	
o 3 consecutive lots		
o other needed validation data		
☑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	(Y) N	
☑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	(Y) N	
☑ reference standards	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity	(Y) N	N/A
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	(Y) N	
Other components to be marketed (full description and supporting data, as listed above):		
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part of kit)	Y N	
Appendices for Biotech Products [3.2.A]		
❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination	(Y) N	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production	(Y) N	
❑ novel excipients	Y N	
USA Regional Information [3.2.R]		
❑ executed batch records	(Y) N	
❑ method validation package	(Y) N	
❑ comparability protocols	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	(Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	Y N	
includes data demonstrating consistency of manufacture	Y N	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
certification that all facilities are ready for inspection	(Y) N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ LAL instead of rabbit pyrogen ❑ mycoplasma ❑ sterility ❑ ❑	Y N Y N (Y) N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	(Y) N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	(Y) N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is it possible to ask the firm to send legible copies of floor plans (containing air cleanliness classification, flow of material, product and personnel)?

The electronic copy of floor plans are too faint to be legible.

Recommendation (circle one): (File) RTF

Reviewer: _____ Type (circle one): Product (Chair) (Facility (DMPQ))
(signature/ date) Brenda Uhl

Concurrence:
Branch/Lab Chief: Brenda Uhl Division. Director: _____
(signature/ date) (signature/ date)

Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (http://www.fda.gov/cber/regsopp/8404.htm). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see http://www.fda.gov/cber/ich/ichguid.htm).

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CBER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 125166/0 Product: Eculizumab Applicant: Alexion

Final Review Designation (circle one): Standard (Priority)

Submission Format (circle all that apply): Paper (Electronic) Combination

Submission organization (circle one): (Traditional) CTD

Filing Meeting: Date 10/27/06 Committee Recommendation (circle one): (File) RTF

RPM: [signature] 10/27/06
(signature/date)

Attachments:

- ☑ Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - ☑ Part A – RPM
  - ____ Part B – Product/CMC/Facility Reviewer(s): _____ _____ _____
  - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____ _____
  - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____ _____ _____ _____
- ☑ Memo of Filing Meeting

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed ❑ including list of all establishment sites and their registration numbers ❑ If foreign applicant, US Agent signature.	Y N Y N Y N	
Comprehensive Table of Contents	Y N	
Debarment Certification with correct wording (see * below)	Y N	
User Fee Cover Sheet	Y N	
User Fee payment received	Y N	N/A Orphan drug status
Financial certification &/or disclosure information	Y N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Pediatric rule: study, waiver, or deferral	Y N	
Labeling: ❑ PI –non-annotated ❑ PI –annotated ❑ PI (electronic) ❑ Medication Guide ❑ Patient Insert ❑ package and container ❑ diluent ❑ other components ❑ established name (e.g. USAN) ❑ proprietary name (for review)	Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. 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 the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ protocols for clinical trials present ❑ all electronic submission components usable (e.g. conforms to published guidance)	(Y) N (Y) N	
companion application received if a shared or divided manufacturing arrangement	Y N	N/A
if CMC supplement: ❑ description and results of studies performed to evaluate the change ❑ relevant validation protocols ❑ list of relevant SOPs	Y N Y N Y N	NA
if clinical supplement: ❑ changes in labeling clearly highlighted ❑ data to support all label changes ❑ all required electronic components, including electronic datasets (e.g. SAS)	Y N Y N Y N	NA
if electronic submission: ❑ required paper documents (e.g. forms and certifications) submitted	Y (N)	NA

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? NA

Does this submission relate to an outstanding PMC? NA

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name:
- Dates:

Recommendation (circle one): File RTF

RPM Signature: Branch Chief concurrence: Alice Kamba 10/27/06

125166/0

STN ~~125166/0~~ Product Eculizumab

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y (N)	not absolutely necessary but inconvenient
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
☑ Biopharmaceutics and associated analytical methods	Y (N)	1 page. not sufficient but reviewable, information located some where
☑ Clinical pharmacology [includes immunogenicity]	(Y) N	
☐ Clinical Efficacy [for each indication]	Y N	
☐ Clinical Safety	Y N	
☑ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y (N)	still reviewable without it but inconvenient
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5,3]	(Y) N	
☑ Biopharmaceutic	(Y) N	assays only
☑ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y) N	
☑ Pharmacokinetics (PK)	(Y) N	
☑ Pharmacodynamic (PD)	(Y) N	
☐ Efficacy and Safety	Y N	
☐ Postmarketing experience	Y (N)	N/A
☑ Case report forms	(Y) N	
☑ Individual patient listings (indexed by study)	(Y) N	
○ electronic datasets (e.g. SAS)	Y N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
☑ legible	(Y) N	
☑ English (or certified translation into English)	(Y) N	
☑ compatible file formats	(Y) N	
☑ navigable hyper-links	(Y) N	
☑ interpretable data tabulations (line listings) & graphical displays	(Y) N	

STN 125/66/0 Product Eculizumab

Examples of Filing Issues	Yes?	If not, action & status
☑ summary reports reference the location of individual data and records	(Y) N	
☑ protocols for clinical trials present	(Y) N	
☑ all electronic submission components usable	Y N	
statement for each clinical investigation: ☑ conducted in compliance with IRB requirements	(Y) N	
☑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	Y N	NA to Clin Pharm
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y N	NA
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	(Y) N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(X) N	NA to Clin Pharm

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	Y N	NA to Clin Pharm
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	Y (N)	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	NA to Clin Pharm
all information reasonably known to the applicant and relevant to the safety and efficacy described?	Y N	NA to Clin Pharm

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
C02-001	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
E02-001	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
X03-001	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
C04-001	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
C04-002	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
E05-001	(Y)	N	Y	N	NR	(Y)	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

listed studies conducted in PNH only.

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

No, from a Clin Pharm standpoint

Is an Advisory Committee needed?

No, from a Clin Pharm standpoint

Recommendation (circle one): File RTF

Reviewer: Jaigh Lee 10/17/06 Type (circle one): Clinical (Clin/Pharm) Statistical
(signature/ date)

Concurrence:

~~Branch Chief:~~ Team Leader Hong Zhao 10/18/06 Division. Director: Atiqur Rahman 10/24/06
(signature/ date) (signature/ date)

STN 125166/0 Product Eculizumab

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
❑ Biopharmaceutics and associated analytical methods	Y N	
❑ Clinical pharmacology [includes immunogenicity]	Y N	
❑ Clinical Efficacy [for each indication]	(Y) N	
❑ Clinical Safety	(Y) N	
❑ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
❑ Biopharmaceutic	Y N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
❑ Pharmacokinetics (PK)	Y N	
❑ Pharmacodynamic (PD)	Y N	
❑ Efficacy and Safety	(Y) N	
❑ Postmarketing experience	Y N	
❑ Case report forms	(Y) N	
❑ Individual patient listings (indexed by study)	(Y) N	
○ electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or certified translation into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	

STN 125166/0 Product Eculizumab

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	(Y) N	
❑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	(Y) N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	N/A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	Y N	
comprehensive analysis of safety data from all current world-wide knowledge of product	Y N	

STN 125166/0 Product Eculizumab

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y) N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?	Financial disclosure or certification submitted?	SAS & other electonic datasets complete & usable?	BiMo sites identified?
C04-001	(Y) N	Y N NR	(Y) N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR
	Y N	Y N NR	Y N	Y N NR

Y= yes; N=no; NR=not required

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): (File) RTF 10-22-06

Reviewer: [signature] Type (circle one): Clinical Clin/Pharm (Statistical)
(signature/ date)

Concurrence:

Branch Chief: Jyoti Zalkikar Division. Director: Alaka Chakravarty
(signature/ date) 10-22-06 (signature/ date) 10/25/06

Part B – Product/CMC/Facility Reviewer(s)

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Quality overall summary [2.3]	(Y)	N	
❑ Drug Substance	(Y)	N	
❑ Drug Product	(Y)	N	
❑ Facilities and Equipment	(Y)	N	
❑ Adventitious Agents Safety Evaluation	(Y)	N	
❑ Novel Excipients	Y	(N)	No novel excipients
❑ Executed Batch Records	(Y)	N	
❑ Method Validation Package	(Y)	N	
❑ Comparability Protocols	(Y)	N	

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	(Y)	N	
Drug Substance [3.2.S]			
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	(Y)	N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	(Y)	N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	(Y)	N	
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	(Y)	N	
❑ process validation (prospective plan, results, analysis, and	(Y)	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	(Y) N	
❑ characterization of drug substance	(Y) N	
❑ control of drug substance	(Y) N	
o specification		
o justification of specs.		
o analytical procedures		
o analytical method validation		
o batch analyses		
o consistency (3 consecutive lots)		
o justification of specs.		
❑ reference standards	(Y) N	
❑ container closure system	(Y) N	
❑ stability	(Y) N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P]		
❑ description and composition	(Y) N	
❑ pharmaceutical development	(Y) N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
❑ batch formula	(Y) N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
❑ controls of critical steps and intermediates	(Y) N	
❑ process validation including aseptic processing & sterility assurance:	(Y) N	
o 3 consecutive lots		
o other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin) ❑ control of drug product (justification of specifications; analytical method validation)	(Y) N	
❑ container closure system [3.2.P.7] ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity ○ administration device(s)	(Y) N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval ○ protocol ○ results ○ method validation	(Y) N	
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent	Y (N)	Not applicable; no diluent is provided with the product.
❑ pharmaceutical development	Y (N)	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y (N)	
❑ batch formula	Y (N)	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y (N)	
❑ controls of critical steps and intermediates	Y (N)	
❑ process validation including aseptic processing & sterility assurance: ○ 3 consecutive lots ○ other needed validation data	Y (N)	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y (N)	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y (N)	
❑ reference standards	Y (N)	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity	Y (N)	Not applicable.
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y (N)	
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	Y (N) Y (N)	Not applicable.
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination	Y N	→ TFRB memo will address
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production	(Y) N	
❑ novel excipients	Y (N)	No novel excipients.
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	(Y) N (Y) N (Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or translated into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
❑ summary reports reference the location of individual data and records	(Y) N	Much individual data not provided.
❑ all electronic submission components usable	(Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	(Y) N	
includes data demonstrating consistency of manufacture	(Y) N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
certification that all facilities are ready for inspection	(Y) N	
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y) N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	(Y) N (Y) N (Y) N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y (N)	Not applicable.
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	— TFRB memo will address
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	— ✓
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y (N)	Not applicable

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

Recommendation (circle one): File RTF

Reviewer: _____ Type (circle one): (Product (Chair)) Facility (DMPQ)
(signature/ date) Gurpreet Gillsanfra

Concurrence:
Branch/Lab Chief: _____ 10/26/06 Division. Director: Kathleen Clouse 10/26/06
(signature/ date) (signature/ date)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

DATE: October 5, 2006

FROM: Rafel Dwaine Rieves
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Office of New Drug
Center for Drug Evaluation and Research

SUBJECT: Designation of BLA application review status
Sponsor: Alexion Pharmaceuticals
Product: Eculizumab
Indication: Treatment of paroxysmal nocturnal hemoglobinuria (PNH)

TO: BLA file STN 125166/0

The review status of this file submitted as a BLA application is designated to be:

☐ Standard (10 months) ☒ Priority (6 months)

Rafel Dwaine Rieves, M.D.: Date 10-5-06

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

OCT 05 2006

Our STN: BL 125166/0

Alexion Pharmaceuticals
Attention: Nancy Motola, Ph.D., RAC
Senior Vice President, Regulatory and Quality
352 Knotter Drive
Cheshire, CT 06410

Dear Dr. Motola:

We have received your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

Our Submission Tracking Number (STN): BL 125166/0

Name of Biological Product: Soliris™/Eculizumab

Indication: Treatment of Paroxymal Nocturnal Hemoglobinuria (PNH)

Date of Application: September 15, 2006

Date of Receipt: September 15, 2006

User Fee Goal Date: March 17, 2007

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website: http://www.fda.gov/oc/datacouncil/spl.html.

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

From: Florence O. Moore, M.S.

Subject: First Committee for STN 125166/0

Sponsor: Alexion Pharmaceuticals

Product: Eculizumab

Date, Location, & Time of Meeting: **October 5, 2006**
WO Bldg 22 Conference Room 2376
12:30– 12:00 p.m.

Purpose:

To introduce review team and discuss the timelines for the review process of the BLA submission.

Summary:

The review team met to discuss Alexion's submission of a BLA for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). This supplement has been assigned 125166/0. The review schedule is a priority BLA submission with a 6-month review clock (Action Due Date: **March 17, 2007**).

The review team also discussed the following topics:

- Consults
- Timeline of the application review process.
- Filing Meeting
- Post Submission Meeting
- Advisory Committee
- Midcycle Meeting

A filing decision needs to be made by **November 14, 2006**. The review team was advised to forward the signed-off filing review memo to the RPM by interoffice mail (HFD-160) no later than November 7, 2006

First Action Due: March 17, 2007

Review Committee:

Clinical –Andy Dymitrijuk
PK – Jang-Ik Lee
CMC – Joe Kutza
CMC- Michelle Jessen,
CMC- Gurpreet Gill-Sangha
P/T – TBD
DMPQ- Gilbert Salud
DMPQ- Janet Barletta
Stats – Richard Chen
RPM – Florence Moore
DDMAC- Sean Bradley

Other FDA Representatives:

Dwaine Rieves, Deputy Director, DMIHP
Kathy Robie Suh, Clinical Team Leader
Patrick Swann, Acting Deputy Director DMA
Hong Zhao, PK Team Leader
Jyoti Zalkikar, Team Leader, OPSS

STN BL 125166/0: Eculizumab
Sponsor: Alexion Pharmaceuticals

BLA REVIEW TIMELINE

As of September 19, 2006

Indication: treatment of paroxysmal nocturnal hemoglobinuria (PNH)

Sequence Number	DCC Number	STN Number	Type
0000	60003642	125166/0//0	Original Application

Here is a link to the .enx file:
\\Cbsap58\M\eCTD_Submissions\STN125166\125166.enx

X		Item	Due/Hold Date	Target/Close Date
	1	**Submission Letter Date**		9/15/06
	2	**Stamp Rec'd Date**		9/15/06
	3	**Distribute to team (via EDR)**		9/26/06
	4	**Committee Assignment Date**	9/29/06	9/26/06
	5	**First Committee MTG**	10/6/06	10/5/06
	6	**Filing Meeting Date**	10/30/06	10/27/06
	7	**Post Submission Mtg**		10/26/06
	8	**Filing Action Date**	11/14/06	11/7/06
	9	**Deficiencies ID Date**	11/28/06	11/21/06
	10	**Team Meeting (Mid Cycle)**		1/4/07
	11	**CMC Inspection**		
	12	**DSI Inspection**		
	13	**Advisory Committee Mtg**		
	14	**Labeling Meeting**		1/18/07
	15	**PRIMARY Review Due**		2/1/07
	16	**SECONDARY Rev Due**		2/6/07
	17	**PM Rev**		2/9/07
	18	**CPMS Rev**		2/14/07
	19	**Action Pak TO DD**		2/19/07
	20	**DD Review**		2/16/07
	21	**Action Pak TO Office**		2/23/07
	22	**Office Review**		3/2/07
	23	**Goal Date**		**3/9/07**
*	24	**6-Month PDUFA Due Date**	**3/17/07**	**3/16/07**

*** PDUFA Due Date is Friday, Mar-16-07 because Mar-17-07 falls on a Saturday.**

Reviewer Assignment

Clinical –Andy Dymitrijuk
PK – Jang-Ik Lee
DMPQ- Gilbert Salud
DMPQ- Janet Barletta
Stats – Richard Chen
CMC – Joe Kutza
CMC- Michelle Jessen,
CMC- Gurpreet Gill-Sangha
P/T – TBD
RPM – Florence Moore

Consults

ODS/DDRE- TBD
DSI- TBD
DDMAC- Sean Bradley
ODS/DMETS-
ODS/DSRCS- ??

Team Leaders

Clinical – Kathy Robie Suh
CMC – Joe Kutza
DMPQ- Brenda Uratani
P/T – Adebayo Laniyonu
PK – Hong Zhao
Stats – Jyoti Zalkikar
CPMS – Kaye Kang/Alice Kacuba

Division Heads

DMIHP- George Mills/Dwaine Rieves
DTP – Kathy Clouse/Patrick Swann

Advisory Committee –
Date: TBD
Members: TBD

Signatory Authority – Office Director

Moore, Florence O

From: Moore, Florence O
Sent: Friday, September 29, 2006 3:18 PM
To: 'Nancy Motola'
Subject: Eculizumab

Importance: High

Follow Up Flag: Follow up
Due By: Monday, September 25, 2006 9:30 AM
Flag Status: Flagged

Hi Nancy,

Can you please provide us with a table that lists all processes and batch numbers of eculizumab that were used in each clinical and clinical pharmacology study as soon as possible? If you already included the table in the BLA, please let me know the location of the table in the eCTD.

Thanks.
Florence

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
(WO: 22, Mailstop 4447)

DATE RECEIVED: August 2, 2006 **DATE OF DOCUMENT:** June 28, 2006	**DESIRED COMPLETION DATE:** September 2, 2006	**OSE REVIEW #:** 05-0262-1

TO: George Mills, M.D.
Director, Division of Medical Imaging and Hematology Products
HFD-160

THROUGH: Nora Roselle, PharmD., Team Leader 12/22/06
Denise Toyer, PharmD., Deputy Director 12/22/06
Carol Holquist, RPh, Director 12/22/06.
Division of Medication Errors and Technical Support, HFD-420

FROM: Linda M. Wisniewski, RN, Safety Evaluator 12/22/06
Division of Medication Errors and Technical Support, HFD-420

PRODUCT NAME: **Soliris**
(Eculizumab Injection)
300 mg/30 mL (10 mg/mL)

BLA#: 125166/0 (BB-IND 11075)

BLA HOLDER: Alexion Pharmaceuticals, Inc.

RECOMMENDATIONS:

DMETS reverses its initial decision and does not believe Soliris will be confused with Solurex. However, DMETS has identified two additional proposed proprietary names, which are currently under review by the Agency, that have the potential for confusion with Soliris,
These names have potential for strong orthographic and phonetic similarities. Thus, DMETS believes that these three product names should not co-exist in the marketplace and recommends that only the first product to be approved should receive the name.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sam Chan, project manager, at 301-796-2283.

Division of Medication Errors and Technical Support (DMETS)
Office of Surveillance and Epidemiology
WO: 22; Mailstop: 4447
Center for Drug Evaluation and Research

PROPRIETARY NAME REBUTTAL

DATE OF REVIEW: August 8, 2006

BLA#: 125166/0 (BB-IND 11075)

NAME OF DRUG: Soliris
(Eculizumab Injection)
300 mg/30 mL (10 mg/mL)

BLA HOLDER: Alexion Pharmaceuticals, Inc.

***NOTE: **This review contains proprietary and confidential information that should not be released to the public.**

I. INTRODUCTION:

This consult was written in response to a request from the Division of Medical Imaging and Hematology Products (HFD-160), for a re-assessment of the proprietary name, 'Soliris', regarding potential name confusion with the name Solurex. The name Soliris was previously reviewed by DMETS in OSE Consult 05-0262, dated May 15, 2006, and was found unacceptable due to its similarity in orthographic appearance, phonetic similarity, and overlapping product characteristics with Solurex. On June 28, 2006 the sponsor submitted a rebuttal requesting reconsideration of DMETS conclusion on Soliris. Additionally, the sponsor also included an independent name analysis conducted by [redacted] for review and comment.

PRODUCT INFORMATION

Soliris is a monoclonal antibody indicated in the treatment of paroxysmal nocturnal hemoglobinuria. It is intravenously administered and dosed during the induction period at 600 mg every week for four weeks and during the maintenance phase at 900 mg every other week. It is supplied in vials containing 10 mg/mL with a total of 300 mg/vial.

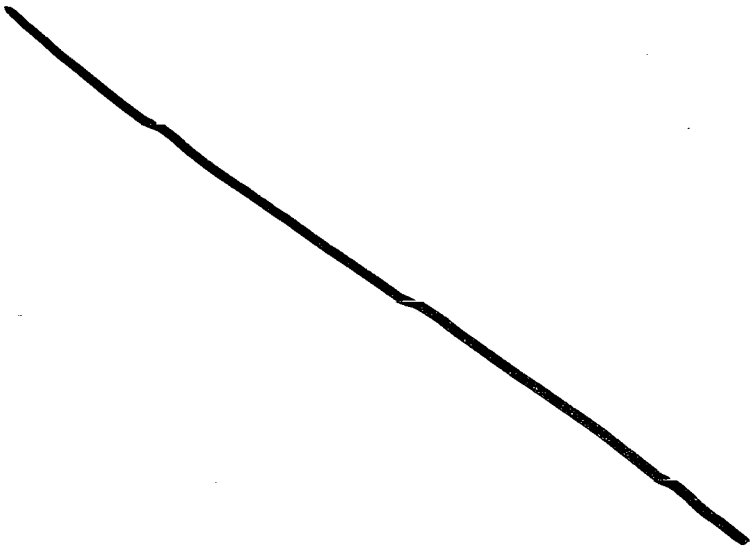
II. RISK ASSESSMENT:

A. Reconsideration of the Proprietary Name Soliris

In the previous DMETS review we noted potential for orthographic similarity between Soliris and Solurex. Solurex is a generic brand name for Dexamethasone Sodium Phosphate. DMETS' primary concerns about the potential for confusion between Soliris and Solurex, is the potential for a written order for Soliris to be misinterpreted as Solurex. If an order for Soliris were misinterpreted as Solurex, an internet search using the Google search engine would reference the active ingredient dexamethasone. Commonly used references such as the 2006 Red Book and Micromedex, also link Solurex to dexamethasone. Additionally, Drug Facts and Comparisons lists Solurex as dexamethasone in the 'How Supplied Section.' The potential for overlap at a 600 mg dose further enhances our concern.

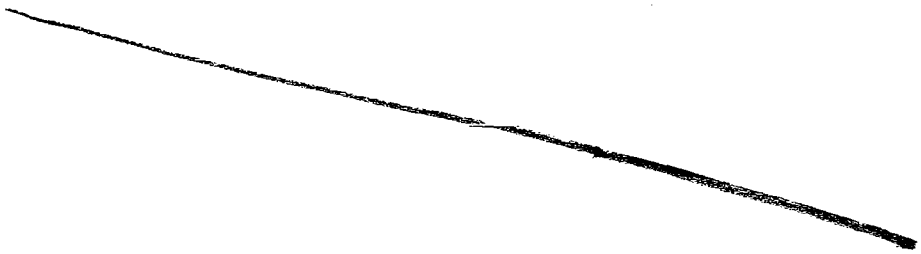
In response to DMETS' concerns, the sponsor has submitted the following information to help diminish DMETS concerns regarding this potential for confusion. The sponsor's comments appear in italics followed by DMETS comments.

1.

2. 

3.

4. The sponsor submitted two independent name analyses in support of the proposed proprietary name, Soliris

a. 

DMETS Comments:

The differences identified by [redacted] were all addressed in sections II-A2 and II-A3 of this review.

b. The sponsor states that [redacted]

[redacted] *has performed an assessment of the proposed proprietary name and its similarity to Solurex and has concluded that: "Although there are similarities between the names Soliris and Solurex and both are injectables, there are many significant differences which would cause one to avoid mixing up the 2 products. These differences, along with the fact that this drug's manufacturer is no longer in business and the drug is no longer available, lead to his recommendation in support of Alexion's request for reconsideration of the proposed proprietary name, Soliris."*

[redacted] *has identified that the two products, Soliris and Solurex, are similar in that both names look alike and sound alike, and that they are both intravenous products.* [redacted] *has also identified that the differences in the products' dispensing characteristics, such as: strength, dose, frequency of administration, indication of use, and storage would help to differentiate these two products.*

DMETS Comments

DMETS does not agree with [redacted] that the above mentioned differences, such as frequency of administration and product storage, will be sufficient differentiating factors. For example, a one time order could be written for both of these products. Additionally, if misinterpretation occurs at the time of receipt of the order, the storage conditions will not prevent the healthcare practitioner from misinterpreting the name. DMETS also has concerns about the potential overlap at the 600 mg dose. However, in light of the past limited marketing of Solurex DMETS believes that protocols where high dose Dexamethasone may have been used likely would not have included the name Solurex, but the established name. Additionally, the conditions of use of high dose of steroids (such as in a trauma unit where response time is of utmost

importance), would likely preclude the staff from conducting an internet search. Therefore, the conditions required for the overlap at 600 mg were less likely to occur and thus diminished DMETS concerns regarding this product.

The sponsor has submitted substantial information to minimize DMETS' concerns with regards to potential confusion between Soliris and Solurex. However, DMETS has identified two new pending proprietary names that may create potential confusion with Soliris. These two names are discussed below in Section B.

B. New Pending Proprietary Names of Concern

DMETS has identified [redacted] *** as additional look-alike and sound-alike names that were submitted to the Agency for review after DMETS original consult dated May 15, 2006. See Table 1 below for product characteristics.

Table 1: Additional names identified by DMETS that have look-alike/sound-alike potential with Soliris.

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
Soliris	Eculizumab Injection 300 mg/30 mL vial (10 mg/mL0	Induction: 600 mg once per week for 4 weeks. Maintenance: 900 mg every other week	NA
[redacted]			

1. [redacted]

*** NOTE: This review contains proprietary and confidential information that should not be released to the public.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

IND 11075

Alexion Pharmaceuticals, Inc.
Attention: Paul J. Alessandro, M.S.
Vice President, Regulatory and Quality
352 Knotter Drive
Chesire, CT 06410

Dear Mr. Alessandro:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Eculizumab [Humanized Monoclonal Antibody (h5G1.1) to C5].

We also refer to the meeting held on March 28, 2006, between representatives of your firm and this agency. A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at (301) 796-2050.

Sincerely yours,

{See appended electronic signature page}

Florence O. Moore, M.S.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Enclosure - Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Date: April 17, 2006

From: Florence O. Moore, M.S., DMIHP, HFD-160

To: Alexion Pharmaceuticals Inc.

Subject: IND 11075 Pre-BLA Meeting Summary

Meeting Date:	**March 28, 2006** **Time: 1:30-3:00 PM**
Location:	**CDER White Oak Bldg 22 Conference Room 1313**
Sponsor:	**Alexion Pharmaceuticals Inc.**
Product:	**Eculizumab** **[Humanized Monoclonal Antibody (h5G1.1) to C5]**
Proposed Use:	**Treatment of paroxysmal nocturnal hemoglobinuria (PNH)**
Type of Meeting:	**Type B/Pre-BLA**
FDA Lead	**Kathy Robie-Suh, M.D., Ph.D.**
Meeting Chair:	**Dwaine Rieves, M.D.**
Meeting Recorders:	**Florence Moore, M.S.**
External Participant Lead:	**Paul Alessandro**
Meeting Purpose:	**To discuss the proposed content and submission of plan for the Biologic License Application in e-CTD format.**
Attendees:	**FDA Attendees:** Office of Oncology Drug Products Division of Medical Imaging and Hematology Products Rafel (Dwaine) Rieves, M.D., Deputy Director Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader John Lee, M.D., Medical Reviewer Kyong (Kaye) Kang, Pharm.D, Chief Project Manager Staff Florence Moore M.S., Regulatory Health Project Manager Office of Biostatistics Division of Biometrics V Richard Chen, Ph.D. Biostatistics Reviewer

Office of Clinical Pharmacology
Division of Clinical Pharmacology V
Hong Zhao, Ph.D., Team Leader
Jang-Ik Lee, Ph.D., Clinical Pharmacology Reviewer

Office of Biotechnology Products
Division of Monoclonal Antibody (DMA)
Patrick Swann, Ph.D. Acting Deputy Director
Joseph Kutza, Ph.D. Product Team Leader/Reviewer

Office of Compliance
Division of Manufacturing and Product Quality (DMPQ)
Patricia Hughes, Ph.D., Microbiologist

Office of New Drug
Study Endpoints and Labeling Development Team
Laurie Burke, M.D.

Office of Science and Health Coordination
Office of Orphan Products Development
Henry Startzman, M.D.

Sponsor Attendees: See attachment 1, slide 2

Note: ***FDA provided draft responses to the questions submitted in the meeting package by Alexion Pharmaceuticals, Inc. by facsimile transmission on March 24, 2006.***

Meeting Summary

At the beginning of the meeting, Alexion acknowledged receiving the FDA's responses to the submitted questions. Alexion gave a slide presentation to clarify some of FDA's questions from the facsimile (see Attachment 1). What follows is a summary of the sponsor's questions, FDA's response by facsimile and specific discussions and clarifications sought by Alexion regarding FDA's responses.

Sponsor Questions, FDA Response and Discussions

Questions regarding Submission Format and Logistics

1. *The proposed Biologic License Application (BLA) will be submitted in eCTD format in accordance with 21 CFR §601.2 and §601.14 and applicable ICH and FDA guidance documents.*

   Does the Agency concur with the proposed format of the BLA?

   FDA Response (by facsimile): Yes

   Discussion at the meeting: There were no further comments made or clarification sought on this section.

2. *The draft labeling for inclusion in the proposed application will be submitted in compliance with applicable FDA guidance documents as follows:*

   a. *Draft container and carton labeling will be provided in PDF file format*

   b. *The draft package insert will be provided in SPL format and as a Microsoft Word file for reviewer convenience*

   c. *The annotated package insert will be submitted in Microsoft Word® file format*

   d. *All labeling samples will be provided in PDF file format*

   Is the proposed format of the draft labeling sufficient to support submission of the BLA?

   FDA Response (by facsimile): The proposed format appears reasonable.

   Discussion at the meeting: There were no further comments made or clarification sought on this section.

3. *The proposed application will include a request for a categorical exclusion from including an Environmental Assessment per 21CFR §25.31.*

   Does the Agency have comments on the proposed request for a categorical exclusion from including an Environmental Assessment described above?

   FDA Response (by facsimile): No comment. We suggest you request categorical exclusion in the BLA submission.

   Discussion at the meeting: There were no further comments made or clarification sought on this section.

4. *The proposed application will contain a request for an exemption from the requirement for pediatric studies per 21CFR§601.27(d).*

   Does the Agency have comments on the proposed request for an exemption from the requirement for pediatric studies described above?

   FDA Response (by facsimile): Your application should include a summary of any available pediatric experience. You should include your request for pediatric exemption in your BLA submission and provide justification for the request.

   Discussion at the meeting: There were no further comments made or clarification sought on this section.

5. *The proposed Proprietary Name for the product is Soliris™ (eculizumab) and a request for preliminary review of the proposed Proprietary Name was submitted to the IND on November 15, 2005 (IN Serial No. 069).*

Does the Agency have comments on the proposed Proprietary Name?

FDA Response (by facsimile): The name evaluation is currently under review in Division of Medication Errors & Tech Support (DMETS).

Discussion at the meeting: There were no further comments made or clarification sought on this section.

6. *A request for review of the proposed Quality of Life Validation Plan was submitted to the IND on November 18, 2005 (IN Serial No. 070) in order to solicit Agency feedback on the following topics:*

   a. *We believe that the justification for the use of the [redacted] (FACIT-F and EORTC) and the approach to selection and validation of these instruments is appropriate and adequate for this rare disease patient population.*

   b. *We also believe that the clinically compelling results obtained from the statistical analysis plan for QOL data (FACIT-F and EORTC) provided for in the TRIUMPH protocol are sufficient to support mention of QOL results in labeling.*

   Does the Agency have comments on the adequacy of the approach to validation of the [redacted] and the support for inclusion of QOL related results in labeling based on the statistical analysis plan from the TRIUMPH protocol?

FDA Response (by facsimile): Please see the draft guidance document available at: www.fda.gov/cder/guidance/5460dft.pdf. It describes the type of documentation we request to support the adequacy of a patient reported outcome instrument to support labeling claims. Please summarize relevant instrument and development and validation documentation and submit with the BLA.

Discussion at the meeting: There were no further comments made or clarification sought on this section.

7. *Alexion plans to request priority review of the proposed application. Since there are no available therapeutic products specifically indicated for the PNH patient population, Soliris™ (eculizumab) would provide a significant therapeutic advance as the first approved therapy specifically indicated for PNH patients and, as such, priority review of the proposed application is warranted.*

   Does the Agency have comments on the proposed request for priority review of the BLA described above?

FDA Response (by facsimile): We acknowledge that currently there are no available products specifically indicated for treating PNH, and that eculizumab may be a significant advance in the treatment of PNH.

However, the current lack of a specific therapy or the potential for significant advance is not sufficient to warrant a priority review. We note that your prior request for Fast Track Designation was not granted. Decision on priority review will be made after your application has been received. You may request priority review and provide further justification in your submission.

Discussion at the meeting: Alexion asked for feedback on their question on priority review in the briefing package and gave a presentation on why they would want to request a priority review (see Attachment 1 slides 14-20).

FDA recommended that Alexion submit a request for priority review in the BLA submission with the appropriate efficacy, safety and benefit/risk justification.

8. *In light of the compelling results obtained in the completed TRIMPH efficacy study (C04-001), and in order to make Soliris™ (eculizumab) available to PNH patients as soon as possible, we intend to submit the original application upon completion of the per protocol 6-month interim analysis of the SHEPHERD (C04-002) safety study, before completion of the full 12 months of treatment duration proscribed under the SHEPHERD protocol.*

Alexion believes that the proposed clinical data package at the time of original submission will provide sufficient evidence to support the review and approval of the proposed Soliris™ (eculizumab) BLA for the orphan PNH indication, as it will contain an adequate and well-controlled clinical study that provides a definitive demonstration of the effectiveness and safety of the product when compared to placebo in the PNH patient population, combined with long-term safety data from chronic administration to 195 PNH patients and supportive safety data from 711 additional clinical trial subjects exposed to eculizumab.

The long-term safety data includes 191, 60, and 10 PNH patients with 6, 12, and 36 months of chronic eculizumab exposure, respectively, totaling approximately 180 patient-years exposure in the PNH population. Supportive long-term safety data from the additional 711 eculizumab clinical trial subjects totaling approximately 650 patient-years of eculizumab exposure, including approximately 460 patients with chronic eculizumab exposure for greater than 15 months, will be provided in the original application. At the time of original submission, the proposed application will contain:

a. *Administrative information, application summaries, and draft labeling*

b. *Final reports for the 14 nonclinical pharmacology, pharmacokinetic, and toxicology studies*

c. *All chemistry, manufacturing and controls information required to support review of the proposed commercial drug substance and drug product*

d. *Final clinical study reports for 11 trials in non-PNH indications*

e. *Final clinical study reports for 4 PNH studies, including the compelling clinical efficacy results observed in TRIPH (C04-001)*

f. *A final report of the per protocol 6-month interim analysis of the ongoing SHEPHERD (C04-002) study and all available safety data from the ongoing Extension (E05-001) study as of March 1, 2006*

g. *An integrated summary of safety from all patients in eculizumab clinical trials, including 191,60, and 10 PNH patients with 6, 12, and 36 months of chronic exposure, respectively*

h. *A commitment to submit the final study report for the SHEPHERD study at a mutually agreed upon time point during the review of the application*

Does the Agency have comments on the proposed BLA submission plan described above?

FDA Response (by facsimile):

Please identify the final time point when all complete study reports will be submitted for FDA review. We are concerned that the interim results from the SHEPHERD study may not be adequate to evaluate the safety of eculizumab, including long term safety specific to patients with PNH.

Within your BLA please address the following topics in detail. However, at the upcoming meeting, please briefly comment on the potential for significant hemolysis, particularly when patients do not comply with the treatment regimen, develop a neutralizing antibody which renders continued therapy ineffective, or are unable to continue to obtain the drug. Please also briefly comment on the unknown relationship among eculizumab therapy, PNH, and the potential emergence of hematologic ([redacted]), immune, or infectious disorders. Additionally, please briefly summarize your plans for managing risks that may be associated with long-term eculizumab use, including your plans for conducting post-marketing studies or establishing patient registries to define long term effects.

Discussion at the meeting: Alexion indicated they anticipate submitting the BLA in June 2006 and clarified that March 2006 will be the cut off date for data collection. The SHEPHERD safety data update will be submitted to the BLA in October 2006 (cleaned-up data from locked database). However, the on-going extension trial will not have a cut off date (Alexion plans on continuing eculizumab therapy for these patients indefinitely, see slides 21- 24).

Alexion commented regarding the exploration of unknown relationship between long-term eculizumab therapy and potential emergence of hematologic disorders in patients with PNH (see slides 28-30). Alexion further noted that setting up a PNH patient registry for eculizumab is in progress and the role of the registry in continued, on-going safety monitoring will be addressed as a post-marketing commitment (PMC).

In response to FDA's comment and concern about potentially life-threatening hemolysis in patients for whom eculizumab therapy cannot be continued, the sponsor noted that severe hemolysis was not observed in a few patients that withdrew from the study. Although the numbers of subjects and extent of follow up are very limited, the sponsor noted that abrupt withdrawal of eculizumab therapy after prolonged therapy appears not to pose a risk of severe, potentially life-threatening hemolysis. In the studies to date, safety procedures intended to deal with this potential risk were not needed.

5 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 13

Regulatory

FDA takes this opportunity to inform Alexion that they can meet with the Office/Division staff in a post-submission meeting shortly following the submission of the BLA.

FDA anticipates that this meeting will consist of an overview of the application, with a focus upon describing those aspects of the submission critical to supporting Alexion's product's safety and efficacy. Presentations are generally one hour, followed by a half-hour question and answer session.

The applicant, not consultants, presents important information on each technical aspect (i.e., clinical statistical, CMC or product information, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the application. These meetings are generally held after the BLA submission and prior to the filing date.

FDA also wishes to inform Alexion that, contingent upon FDA's review findings; FDA may seek a discussion of the BLA findings at an Advisory Committee (AC). Additional information regarding this option will be discussed with Alexion during the BLA review.

Discussion at the meeting: There were no further comments made or clarification sought on this section.

15 Page(s) Withheld

✓ Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Administrative- 14