

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125557Orig1s000

Trade Name: Blincyto

Generic Name: blinatumomab

Sponsor: Amgen, Inc

Approval Date: December 3, 2014

Indications: Blincyto™ (blinatumomab) is indicated for treatment of Philadelphia chromosomenegative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

CENTER FOR DRUG EVALUATION AND RESEARCH

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RESEARCH**

APPLICATION NUMBER:

125557Orig1s000

APPROVAL LETTER



BLA 125557

BLA ACCELERATED APPROVAL

Amgen, Inc.
Attention: Tai H. Yu, MS
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop 17-2-A
Thousand Oaks, CA 91320-1799

Dear Mr. Yu:

Please refer to your Biologics License Application (BLA) dated September 19, 2014, received September 19, 2014, submitted under section 351 of the Public Health Service Act for Blincyto™ (blinatumomab).

We acknowledge receipt of your amendments dated September 25, 26 (2), 30; October 7, 8, 10, 16, 17, 21, 23, 24, 29, 30, 31; November 5, 6, 14, 18, 19, 21, 25; December 1, and 2, 2014.

LICENSING

We have approved your BLA for Blincyto™ (blinatumomab) effective this date. You are hereby authorized to introduce or deliver for introduction into interstate commerce, Blincyto™ (blinatumomab) under your existing Department of Health and Human Services U.S. License No. 1080. Blincyto™ (blinatumomab) is indicated for treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL).

MANUFACTURING LOCATIONS

Under this license, you are approved to manufacture blinatumomab drug substance at (b) (4). The final formulated product and intravenous stabilizer solution will be manufactured and filled at (b) (4) and labeled and packaged at Amgen Manufacturing Limited, Juncos, Puerto Rico. You may label your product with the proprietary name Blincyto and will market it in a 4 mL single-use vial containing 35 mcg blinatumomab lyophilized powder for injection.

DATING PERIOD

The dating period for Blincyto shall be 36 months from the date of manufacture when stored at 2- 8°C. The dating period for intravenous stabilizer solution shall be 60 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of (b) (4). The dating period for

blinatumomab drug substance shall be (b) (4) months from the date of manufacture when stored at (b) (4). The expiration date for the packaged product, Blincyto plus the intravenous stabilizer solution, shall be dependent on the shortest expiration date of any component.

We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance and drug product under 21 CFR 601.12.

FDA LOT RELEASE

You are not currently required to submit samples of future lots of Blincyto to the Center for Drug Evaluation and Research (CDER) for release by the Director, CDER, under 21 CFR 610.2. We will continue to monitor compliance with 21 CFR 610.1, requiring completion of tests for conformity with standards applicable to each product prior to release of each lot.

Any changes in the manufacturing, testing, packaging, or labeling of Blincyto, or in the manufacturing facilities, will require the submission of information to your biologics license application for our review and written approval, consistent with 21 CFR 601.12.

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

We request that the labeling approved today be available on your website within 10 days of receipt of this letter.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and container labels that are identical to the carton and immediate container labels submitted on November 21, 2014, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled "Providing Regulatory Submissions in Electronic Format – Human

Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)". Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission "**Product Correspondence – Final Printed Carton and Container Labels for approved BLA 125557/0.**" Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with final printed labeling (FPL) that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for Blincyto™ (blinatumomab) was not referred to an FDA advisory committee because the clinical trial design is acceptable, the application did not raise significant safety or efficacy issues that were unexpected for a drug/biologic of this class, and there were no controversial issues that would benefit from advisory committee discussion.

ACCELERATED APPROVAL REQUIREMENTS

Products approved under the accelerated approval regulations, 21 CFR 601.41, require further adequate and well-controlled studies/clinical trials to verify and describe clinical benefit. You are required to conduct such studies/clinical trials with due diligence. If postmarketing studies/clinical trials fail to verify clinical benefit or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw this approval. We remind you of your postmarketing requirement specified in your submission dated October 30, 2014. This requirement, along with required completion dates, is listed below.

This postmarketing clinical trial is subject to the reporting requirements of 21 CFR 601.70:

PMR 2836-1 Complete the trial and submit the final report and data to verify and describe the clinical benefit of blinatumomab, including efficacy and safety from Protocol 00103311, a Phase 3 randomized, open-label, active-controlled trial comparing blinatumomab to standard of care for treatment of patients with relapsed or refractory Ph-negative B-cell precursor acute lymphoblastic leukemia (ALL). Enrollment of approximately 400 patients is expected, and the primary endpoint is overall survival.

Final Protocol Submission:	Completed 08/2014
Trial Completion:	08/2016
Final Report Submission:	06/2017

Submit final reports to this BLA as a supplemental application. For administrative purposes, all submissions relating to this postmarketing requirement must be clearly designated "**Subpart E Postmarketing Requirement.**"

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because this drug product for this indication has an orphan drug designation, you are exempt from this requirement.

**POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING
REQUIREMENTS UNDER SECTION 506B**

We remind you of your postmarketing commitments:

PMC 2836-2 To perform real-time drug substance commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of shelf life. The results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug substance will be provided in the final report.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 04/2015

PMC 2836-3 To perform real-time drug product commercial container closure system leachate studies using appropriate test methods to identify and quantify volatile organic compounds (VOC), semi-VOC, non-VOC, and trace metals at the end of shelf life. The results of this study and the toxicology risk evaluation for the levels of leachates detected in the drug product will be provided in the final report.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 08/2016

PMC 2836-4 To re-evaluate blinatumomab drug substance lot release and stability specifications after 12 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 01/2021

PMC 2836-5 To re-evaluate blinatumomab drug product lot release and stability specifications after 12 lots have been manufactured at the commercial scale. The corresponding data, the analysis and statistical plan used to evaluate the specifications, and any proposed changes to the specifications will be provided in the final report.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2018

PMC 2836-6 To conduct maximum hold time validation of [REDACTED] (b) (4) for two additional batches (for a total of three batches).

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2016

PMC 2836-7 To conduct bioburden qualification of [REDACTED] (b) (4) and to conduct endotoxin method qualification of [REDACTED] (b) (4).

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 4/2015

PMC 2836-8 To develop a reliable endotoxin detection method for release of drug substance (DS), drug product (DP), and intravenous stabilizing solution (IVSS) not subject to low endotoxin recovery.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 10/2015

PMC 2836-9 To conduct a risk assessment to ensure microbial control and mitigate risks of endotoxin contamination during drug substance (DS), drug product (DP), and intravenous solution stabilizer (IVSS) manufacturing. Risk mitigating actions should include establishment of endotoxin limits on appropriate input materials as determined by the risk assessment.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2015

PMC 2836-10 To assess the pyrogenic response in rabbits to drug product (DP) and to intravenous stabilizing solution (IVSS) spiked with control standard endotoxin. If the pyrogenic response is positive, the rabbit pyrogen test should be used as an interim test until a reliable endotoxin detection method is developed.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 02/2015

PMC 2836-11 To conduct [REDACTED] (b) (4)
[REDACTED] The results from these studies will be
used to support the proposed [REDACTED] (b) (4)
[REDACTED] as
supported by currently available microbial data.

The timetable you submitted on December 1, 2014, states that you will conduct this study according to the following schedule:

Final Report Submission: 12/2015

Submit clinical protocols to your IND 100135 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this BLA. In addition, under 21 CFR 601.70 you should include a status summary of each commitment in your annual progress report of postmarketing studies to this BLA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol,**” “**Postmarketing Commitment Final Report,**” or “**Postmarketing Commitment Correspondence.**”

RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS

Section 505-1 of the FDCA authorizes FDA to require the submission of a risk evaluation and mitigation strategy (REMS), if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks [section 505-1(a)].

In accordance with section 505-1 of FDCA, we have determined that a REMS is necessary for Blincyto™ (blinatumomab) to ensure the benefits of the drug outweigh the risks of cytokine release syndrome, neurologic toxicity, and preparation/administration errors.

We have also determined that a communication plan is necessary to support implementation of the REMS.

Your proposed REMS, submitted on December 2, 2014 and appended to this letter, is approved. The REMS consists of a communication plan and a timetable for submission of assessments of the REMS.

Your REMS must be fully operational before you introduce Blincyto™ (blinatumomab) into interstate commerce.

The REMS assessment plan should include, but is not limited to, the following:

1. Launch date of Blincyto
2. An evaluation of healthcare providers' awareness and understanding of the following risks associated with Blincyto use. The evaluation should include only prescribers who have prescribed Blincyto, pharmacists who have prepared and dispensed Blincyto, and nurses who have administered Blincyto.
 - Life-threatening or fatal cytokine release syndrome
 - Severe, life-threatening or fatal neurological toxicities
3. An evaluation of pharmacists' and infusion nurses' awareness and understanding of the risks of preparation and administration errors associated with Blincyto. The evaluation should include only pharmacists who have prepared and dispensed Blincyto, and nurses who have administered Blincyto.
4. A description of the implementation of the communication plan, including
 - Number of healthcare providers, pharmacists, and professional societies targeted by the REMS
 - Number of REMS letters sent to healthcare providers, pharmacists, and professional societies via email and standard mail with the dates the letters were sent. Include the number of letters sent via mail because the emailed letter was undeliverable. Also include the number of returned or undeliverable letters. For letters sent via email, include the number of letters successfully delivered, and the number of email letters opened by the recipients.
 - Which professional societies distributed the REMS letters to their membership

- Sources of the distribution lists for healthcare providers and pharmacists
- Number of REMS fact sheets distributed by Amgen representatives during follow-up details/visits with healthcare providers during the 12 months after approval of the REMS.
- Date and name of the scientific meetings where Amgen had a booth and a list of the materials displayed
- Date the REMS website became active, and number of unique site visits to the Blincyto REMS website during the assessment period.

The requirements for assessments of an approved REMS under section 505-1(g)(3) include with respect to each goal included in the strategy, an assessment of the extent to which the approved strategy, including each element of the strategy, is meeting the goal or whether 1 or more such goals or such elements should be modified.

We remind you that in addition to the assessments submitted according to the timetable included in the approved REMS, you must submit a REMS assessment when you submit a supplemental application for a new indication for use as described in section 505-1(g)(2)(A) of the FDCA.

If the assessment instruments and methodology for your REMS assessments are not included in the REMS supporting document, or if you propose changes to the submitted assessment instruments or methodology, you should update the REMS supporting document to include specific assessment instrument and methodology information at least 90 days before the assessments will be conducted. Updates to the REMS supporting document may be included in a new document that references previous REMS supporting document submission(s) for unchanged portions. Alternatively, updates may be made by modifying the complete previous REMS supporting document, with all changes marked and highlighted. Prominently identify the submission containing the assessment instruments and methodology with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125557 REMS CORRESPONDENCE
(insert concise description of content in bold capital letters, e.g.,
UPDATE TO REMS SUPPORTING DOCUMENT - ASSESSMENT
METHODOLOGY)**

Prominently identify the submission containing the REMS assessments or proposed modifications with the following wording in bold capital letters at the top of the first page of the submission:

**BLA 125557 REMS ASSESSMENT

NEW SUPPLEMENT FOR BLA 125557
PROPOSED REMS MODIFICATION**

**NEW SUPPLEMENT (NEW INDICATION FOR USE)
FOR BLA 125557
REMS ASSESSMENT
PROPOSED REMS MODIFICATION (if included)**

If you do not submit electronically, please send 5 copies of REMS-related submissions.

PROMOTIONAL MATERIALS

Under 21 CFR 601.45, you are required to submit, during the application pre-approval review period, all promotional materials, including promotional labeling and advertisements, that you intend to use in the first 120 days following marketing approval (i.e., your launch campaign). If you have not already met this requirement, you must immediately contact the Office of Prescription Drug Promotion (OPDP) at (301) 796-1200. Please ask to speak to a regulatory project manager or the appropriate reviewer to discuss this issue.

As further required by 21 CFR 601.45, submit all promotional materials that you intend to use after the 120 days following marketing approval (i.e., your post-launch materials) at least 30 days before the intended time of initial dissemination of labeling or initial publication of the advertisement. We ask that each submission include a detailed cover letter together with three copies each of the promotional materials, annotated references, and approved package insert (PI)/Medication Guide/patient PI (as applicable).

Send each submission directly to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotions (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

REPORTING REQUIREMENTS

You must submit adverse experience reports under the adverse experience reporting requirements for licensed biological products (21 CFR 600.80). You should submit postmarketing adverse experience reports to:

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

Prominently identify all adverse experience reports as described in 21 CFR 600.80.

You must submit distribution reports under the distribution reporting requirements for licensed biological products (21 CFR 600.81).

You must submit reports of biological product deviations under 21 CFR 600.14. You should promptly identify and investigate all manufacturing deviations, including those associated with processing, testing, packing, labeling, storage, holding and distribution. If the deviation involves a distributed product, may affect the safety, purity, or potency of the product, and meets the other criteria in the regulation, you must submit a report on Form FDA-3486 to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
5901-B Ammendale Road
Beltsville, MD 20705-1266

Biological product deviations, sent by courier or overnight mail, should be addressed to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Compliance Risk Management and Surveillance
10903 New Hampshire Avenue, Bldg. 51, Room 4206
Silver Spring, MD 20903

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment

Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, call Kris Kolibab, Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling
REMS

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

/s/

RICHARD PAZDUR
12/03/2014