

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

125388Orig1s000

Trade Name: Adcetris

Generic Name: brentuximab vedotin

Sponsor: Seattle Genetics, Inc.

Approval Date: August 19, 2011

Indications: The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates.

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APPLICATION NUMBER:

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APPROVAL LETTER



Our STN: BL 125388/0
BL 125399/0

BLA ACCELERATED APPROVAL

August 19, 2011

Seattle Genetics, Inc.
Attention: Elaine Waller
Senior Vice President, Regulatory Affairs
21823 30th Drive Southeast
Bothell, WA 98021

Dear Ms. Waller:

Please refer to your biologics license applications (BLAs) dated February 25, 2011, received February 28, 2011, submitted under section 351 of the Public Health Service Act for ADCETRIS (brentuximab vedotin).

We acknowledge receipt of your submissions dated March 14, 2011; March 17, 2011; March 22, 2011 and March 25, 2011, April 6, 2011, April 11, 2011, April 25, 2011, May 3, 2011, May 10, 2011, May 12, 2011, May 18, 2011, May 20, 2011, May 24, 2011, May 26, 2011, May 31, 2011, June 8, 2011, June 10, 2011, June 14, 2011, June 21, 2011, June 22, 2011, June 24, 2011, June 27, 2011, June 28, 2011, June 29, 2011, June 30, 2011, July 1, 2011, July 7, 2011, July 8, 2011, July 13, 2011, July 15, 2011, July 19, 2011, July 20, 2011, July 22, 2011, July 25, 2011, July 28, 2011, July 28, 2011, July 29, 2011, August 4, 2011, August 9, 2011, August 16, 2011, August 17, 2011 and August 17, 2011.

We are issuing Department of Health and Human Services U.S. License No. 1853 to Seattle Genetics, Inc., Bothell, WA under the provisions of section 351(a) of the Public Health Service Act controlling the manufacture and sale of biological products. The license authorizes you to introduce or deliver for introduction into interstate commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license, you are authorized to manufacture the product brentuximab vedotin. Brentuximab vedotin is indicated for:

- The treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant (ASCT) or after failure of at least two prior multi-agent chemotherapy regimens in patients who are not ASCT candidates, and
- The treatment of patients with systemic anaplastic large cell lymphoma (sALCL) after failure of at least one prior multi-agent chemotherapy regimen.

Under this license, you are approved to manufacture cAC10 monoclonal antibody intermediate at [REDACTED] (b) (4); SGD-1006 intermediate at [REDACTED] (b) (4); and brentuximab vedotin drug substance at [REDACTED] (b) (4). The drug product will be manufactured at [REDACTED] (b) (4). You may label your product with the proprietary name ADCETRIS and will market it in a 50mg vial.

The dating period for brentuximab vedotin shall be 30 months from the date of manufacture when stored at 2-8°C (36-46°F) in the original carton. The date of manufacture shall be defined as the date of [REDACTED] (b) (4) of the formulated drug product. The dating period for your cAC10 antibody intermediate shall be [REDACTED] (b) (4) when stored at [REDACTED] (b) (4). We have approved the stability protocols in your license application for the purpose of extending the expiration dating period of your drug substance, drug product, and antibody intermediate under 21 CFR 601.12.

You currently are not required to submit samples of future lots of brentuximab vedotin 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.

You must submit information to your biologics license application for our review and written approval under 21 CFR 601.12 for any changes in the manufacturing, testing, packaging or labeling of brentuximab vedotin, or in the manufacturing facilities.

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 in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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

ACCELERATED APPROVAL REQUIREMENTS

As requested in your letter of February 25, 2011, marketing approval of this product is granted under the accelerated approval of biological products regulations, 21 CFR 601.40-46. These regulations permit the use of certain surrogate endpoints or an effect on a clinical endpoint other than survival or irreversible morbidity as bases for approvals of products intended for serious or life-threatening illnesses or conditions.

Approval under these regulations requires, among other things, that you conduct adequate and well-controlled studies/clinical trials to verify and describe clinical benefit attributable to this

product. You are required to conduct such trials with due diligence. If postmarketing trials fail to verify that clinical benefit is conferred by brentuximab vedotin, or are not conducted with due diligence, we may, following a hearing in accordance with 21 CFR 601.43(b), withdraw or modify approval.

Granting of these approvals are contingent upon completion of clinical trials to verify the clinical benefit of brentuximab vedotin, as outlined in your letter of July 22, 2011. These postmarketing trials are subject to the reporting requirements of 21 CFR 601.70:

1. **CONFIRMATORY TRIAL-** A randomized phase 3, double-blind, placebo-controlled trial of SGN-35 (brentuximab vedotin) in combination with CH-P versus CHOP as frontline therapy in patients with CD30-positive mature T- and NK-cell lymphomas including systemic ALCL (sALCL). Enrollment of approximately 300 patients is expected with a primary endpoint of progression free survival as determined by an independent blinded review facility. Overall survival is a key secondary endpoint.

Final Protocol Submission Date: 3/2013
Trial Completion Date: 3/2019
Final Report Submission Date: 9/2019

2. **CONFIRMATORY TRIAL -** A randomized phase 3 trial of SGN-35 (brentuximab vedotin) in combination with AVD versus ABVD as frontline therapy in patients with advanced Hodgkin Lymphoma. Enrollment of at least 880 patients is expected with a primary endpoint of progression free survival determined by an independent blinded review facility. Overall survival is a key secondary endpoint.

Final Protocol Submission Date: 09/2012
Trial Completion Date: 12/2018
Final Report Submission Date: 06/2019

Successful completion of either PMR 1 or PMR 2 could be considered to convert the accelerated approval to regular approval for both the Hodgkin lymphoma and sALCL indications.

We expect you to complete design, initiation, accrual, completion, and reporting of these trials within the framework described in your letter of August 10, 2011.

For administrative purposes, all submissions related to this/these postmarketing trials should be clearly designated "Subpart E Postmarketing Trial Requirements".

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to assess a known serious risk of neuropathy with ADCETRIS therapy.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA will not be sufficient to assess this serious risk.

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to assess a known serious risk of neuropathy with ADCETRIS therapy.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following:

3. **FOR BLAs 125388 & 125399- Reversibility/Resolution of drug-induced peripheral neuropathy.** Characterize the severity, duration and reversibility of treatment emergent neuropathy in a prospective trial.

The ongoing placebo-controlled AETHERA trial safety results may be utilized to address this PMR.

Phase 3 Trial Completion Date: 12/2013

Phase 3 Trial Final Report Submission Date: 6/2014

Submit the protocol to your IND (b) (4), with a cross-reference letter to this BLA. Submit all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **“Required Postmarketing Protocol Under 505(o)”**, **“Required Postmarketing Final Report Under 505(o)”**, **“Required Postmarketing Correspondence Under 505(o)”**.

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B and 21 CFR 601.70 to satisfy the periodic reporting requirement under section 505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies

or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF 21 CFR 601.70

In addition, we acknowledge your written commitments as described in your letter of August 10, 2011, as outlined below.

4. Perform additional experimental work to understand the impact of soluble CD30 in serum samples on the determination of anti-drug antibodies.

Final Report Submission Date: 09/2012

5. Provide summary data for validating all in-process product intermediate maximum hold times for the cAC10 manufacturing process at scale in a CBE0.

Final Report Submission Date: 12/2012

6. Perform the bacteriostasis/fungistasis testing for the bioburden test of the bulk drug substance using three batches of BDS samples stored under routine sample storage conditions at 2-8°C. Summary data should be submitted in the next Annual Report.

Final Report Submission Date: 12/2012

7. Commit to reassess brentuximab vedotin drug substance and drug product specifications based on the combination of Intermediate lots used to manufacture SGN-35 BDS and DP when the total number of BDS and DP lots include ≥ 25 lots cAC10 and ≥ 10 lots of SGD-1006 as input intermediates and, as part of your annual Product Quality Review for brentuximab vedotin.

Final Report Submission Date: 03/2016

8. Harmonize all CMC information contained in your application with that contained in DMF (b) (4)

Final Report Submission Date: 11/2011

9. Reevaluate the Limit of Detection (LOD) of methylene blue using standard curve with different concentrations of dye that include concentrations below the LOD. Results of the LOD determination will be appended to the method validation report.

Final Report Submission Date: 12/2011

10. The CDRH guidance referenced for biological indicator (BI) incubation time has been superseded by the CDRH Guidance on BI Premarket Notification 510(k) Submissions.

The guidance refers to BIs used to monitor sterilization processes in health care facilities. BIs intended for use in a manufacturing setting are excluded. The (b) (4) Test BIs used for (b) (4) validation studies should be (b) (4) to confirm that all BIs are negative. This change should be made to the (b) (4) validation protocols at (b) (4) and reported in the next annual report.

Final Report Submission Date: 12/2012

Submit clinical protocols to your IND, with a cross-reference letter to these biologics license applications (BLAs), STN BL [125388/0] and [125399/0]. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your BLAs, STN BL [125388/0] and STN BL [125399/0]. Use the following designators to label prominently all submissions, including supplements, relating to these postmarketing study commitments as appropriate:

- **POSTMARKETING COMMITMENT PROTOCOL**
- **POSTMARKETING COMMITMENT - FINAL STUDY REPORT**
- **POSTMARKETING COMMITMENT CORRESPONDENCE**
- **ANNUAL STATUS REPORT OF POSTMARKETING COMMITMENTS**

For each postmarketing commitment subject to the reporting requirements of 21 CFR 601.70, you must describe the status in an annual report on postmarketing studies/clinical trials for this product. The status report for each study should include:

- information to identify and describe the postmarketing commitment,
- the original schedule for the commitment,
- the status of the commitment (i.e. pending, ongoing, delayed, terminated, or submitted),
- an explanation of the status including, for clinical studies, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the study schedule has changed and an explanation of the basis for the revision.

ADVERSE EVENT REPORTING

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
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

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

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>.

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

CONTENT OF LABELING

Within 14 days of the date of this letter, submit 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> that is identical in content to the enclosed labeling text. The content of labeling should be submitted by updating your application by referencing the SPL file submitted to the drug establishment registration and drug listing system. To do this, place a link in your application submission that directs FDA to your SPL file. For administrative purposes, please designate this submission “**Product Correspondence – Final SPL for approved STN BLAs 125388/0 and 125399/0.**”

In addition, within 14 days of the date of this letter, amend any pending supplement for this BLA with content of labeling in SPL format to include the changes approved in this supplement. For additional information on submitting labeling to drug establishment registration and drug listing and to applications, see the FDA guidances at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072339.pdf> and
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CARTON AND CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed draft labels 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 (October 2005)*. 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 STN BL 125388/0 and 125399/0.**” Approval of this submission by FDA is not required before the labeling is used.

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

PROMOTIONAL MATERIALS

Immediately submit all promotional materials (both promotional labeling and advertisements) to be used within the first 120 days after approval. Send one copy to this division, the Division of HEMATOLOGY PRODUCTS, and two copies of the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

In addition, as required by 21 CFR 601.45, submit all subsequent promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement. Send two copies of the promotional materials and the package insert to the address above.

POST-ACTION FEEDBACK MEETING

New molecular entities and important new biologics qualify for a post-action feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during the drug development and marketing application review process. 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, contact the Division of Hematology Products.

If you have any questions, contact the Regulatory Project Manager, Lara Akinsanya, at (301) 796-9634.

Sincerely,

/Richard Pazdur, M.D./

Richard Pazdur, M.D.

Office Director

Office of Oncology Drug Products

Center for Drug Evaluation and Research

Enclosure

Content of Labeling

Carton and Container Labeling