DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 125326/0

BLA ACCELERATED APPROVAL

October 26, 2009

Glaxo Group Limited d/b/a GlaxoSmithKline
ATTENTION: Philip Witman, M.P.H., M.Phil.
Associate Director, Global Regulatory Affairs
1250 South Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

Dear Mr. Witman:

We are issuing Department of Health and Human Services U.S. License No. 1809 to Glaxo Group Limited d/b/a GlaxoSmithKline, Greenford, Middlesex, UB6 0NN, United Kingdom, 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 ofatumumab. Ofatumumab is indicated for treatment of chronic lymphocytic leukemia (CLL) refractory to alemtuzumab and fludarabine.

Under this license, you are approved to manufacture ofatumumab drug substance at (b) (4) (b) (4). The final formulated product will be manufactured, filled, labeled, and packaged at Glaxo Operations UK Limited at Barnard Castle, Durham, United Kingdom. You may label your product with the proprietary name Arzerra and will market it in a 100 mg/5 mL single-use vial packaged in a carton of 3 vials with 2 filters or a carton of 10 vials with 2 filters.

The dating period for ofatumumab drug product shall be 18 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) (b) (4) of the formulated drug product. The dating period for your drug substance shall be 24 months when stored at 2-8 °C. The expiration date for the packaged product, ofatumumab single-use vials plus filters, 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.

You currently are not required to submit samples of future lots of ofatumumab 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 ofatumumab, or in the manufacturing facilities.

ACCELERATED APROVAL UNDER SUBPART E, 21 CFR 601.40-46:

As requested in your letter of January 30, 2009, 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 trials to verify and describe clinical benefit attributable to this product. Clinical benefit is evidenced by effects such as increased survival or improvement in disease-related symptoms. You are required to conduct such trials with due diligence. If postmarketing trials fail to verify that clinical benefit is conferred by Arzerra (ofatumumab) 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 this approval is contingent upon completion of clinical trials to verify the clinical benefit of ofatumumab, as outlined in your letter of October 6, 2009. This postmarketing trial is subject to the reporting requirements of 21 CFR 601.70

1. To submit a final report for ongoing clinical trial OMB110911, entitled, "A Phase III Open-label, Randomized, Multicenter Trial of Ofatumumab Added to Chlorambucil versus Chlorambucil Monotherapy in Previously Untreated Patients with Chronic Lymphocytic Leukemia" which is intended to verify the clinical benefit of ofatumumab through demonstration of a clinically meaningful effect on progression-free survival. The protocol for clinical trial OMB110911 was submitted to FDA on October 24, 2008 and began patient accrual on December 22, 2008. We also acknowledge receipt of the amended protocol submitted August 21, 2009.

   The timetable you submitted on October 6, 2009 states that you will conduct this trial according to the following milestones:

   - **Patient Accrual 50% Completed (222 patients) by August 30, 2010**
   - **Patient Accrual 75% Completed (333 patients) by March 30, 2011**
   - **Patient Accrual Completed by November 30, 2011**
   - **Trial Completion Date: by October 14, 2013**
   - **Final Report Submission: by June 30, 2014**

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

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

POSTMARKETING REQUIREMENTS UNDER 505(o)

Section 505(o) 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 (section 505(o)(3)(A)).

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 identify an unexpected, serious risk of an anti-drug antibody response or an unexpected, serious risk of cardiac toxicity.

Furthermore, the new pharmacovigilance system that FDA is required to establish under section 505(k)(3) of the FDCA has not yet been established and is not sufficient to assess these serious risks.

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

2. To develop a validated, sensitive, and accurate assay for the detection of an immune response (binding antibodies) to ofatumumab, including procedures for accurate detection of antibodies to ofatumumab in the presence of ofatumumab levels that are expected to be present in the serum or plasma at the time of patient sampling.

   The timetable you submitted on October 6, 2009 states that you will develop this assay according to the following milestone:

   - **Final Report Submission (Assay and Methodology): by March 31, 2010**

Finally, we have determined that only a clinical trial (rather than a nonclinical or observational study) will be sufficient to identify an unexpected, serious risk of an anti-drug antibody response or an unexpected, serious risk of cardiac toxicity.

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

3. To conduct an assessment of anti-drug antibody (ADA) response to ofatumumab with a validated assay (required in PMR 2) capable of sensitively detecting ADA responses in the presence of ofatumumab levels that are expected to be present at the time of patient sampling. ADA response will be evaluated in at least 300 patients**,** including ofatumumab-treated patients enrolled in clinical trial OMB110911. The final report will include information on the level of ofatumumab in each patient's test sample at each sampling time point.

   The timetable you submitted on October 6, 2009 states that you will conduct this assessment from clinical trial data according to the following milestones:

   Patient Accrual Completed: **by November 30, 2011**
   Final Report Submission: **by December 31, 2013**

4. To conduct clinical trial OMB112855, a trial of QTc intervals in patients who have been administered ofatumumab: QTc assessments will be performed in patients who have failed at least one fludarabine-containing regimen (at least two cycles) and failed at least one alemtuzumab-containing regimen (a minimum of at least 12 administrations) or who are considered inappropriate for treatment with alemtuzumab due to lymphadenopathy with at least one lymph node > 5 cm and requiring therapy and who receive the dose and schedule of ofatumumab per the approved prescribing information. The number of patients evaluated for QTc interval changes will be at least 12. For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state ofatumumab concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a comprehensive combined report of the results (including primary data) of clinical trial OMB112855 and of the sub-trial assessing QTc intervals in OMB110911 (see below).

   The timetable you submitted on August 20, 2009, states that you will conduct trial OMB112855 according to the following milestones:

   - **Final Protocol Submission:** **by January 31, 2010**
   - **Patient Accrual Completed:** **by June 30, 2011**
   - **Trial Completion Date:** **by June 30, 2012**
   - **Final Report Submission:** **by December 31, 2012**

5. To conduct an assessment of QTc intervals as a sub-trial in clinical trial OMB110911. The total number of patients in OMB110911 with evaluable ECG measurements will be at least 50 (25 per treatment arm). For the QTc assessments, ECGs will be collected in triplicate at baseline, at steady-state ofatumumab concentrations, periodically on-therapy (e.g., every 3 months), and at the end of treatment. The final report will be a

comprehensive combined report of the results (including primary data) of the sub-trial assessing QTc intervals in OMB110911 and of clinical trial OMB112855.

The timetable you submitted on August 20, 2009, states that you will conduct the QTc sub-trial in OMB110911 according to the following milestones:

- **Final Protocol Submission: by January 31, 2010**
- **Patient Accrual Completed: by June 30, 2011**
- **Trial Completion Date: by June 30, 2012**
- **Final Report Submission: by December 31, 2012**

Submit the protocols to your IND, with a cross-reference letter to this BLA, STN BL 125326. Submit all final reports to your BLA, STN BL 125326. 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 SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B:

In addition, we acknowledge your written commitment as described in your letter of August 20, 2009, as outlined below:

6. To submit the final report for clinical trial Hx-CD20-406 entitled “A single-arm international, multi-center trial of HuMax-CD20, a fully human monoclonal anti-CD20 antibody, in patients with B-cell Chronic Lymphocytic Leukemia who have failed fludarabine and alemtuzumab” which shall include results of objective response rates

according to the IRC and according to the clinical investigators. The final report will provide summary analyses and primary data. Accrual to this trial has been completed.

The timetable you submitted on August 20, 2009, states that you will conduct this trial according to the following milestones.

- **Trial Completion Date: by June 30, 2011**
- **Final Report Submission: by December 31, 2011**

Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **Postmarketing Commitment Protocol**
- **Postmarketing Commitment - Final Report**
- **Postmarketing Correspondence**
- **Annual Status Report of Postmarketing Requirements and 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 commitments for this product. The status report for each commitment 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 trials, the patient accrual rate (i.e. number enrolled to date and the total planned enrollment), and
- a revised schedule if the milestone schedule has changed and an explanation of the basis for the revision.

As described in 21 CFR 601.70(e), we may publicly disclose information regarding these postmarketing commitments on our Web site (http://www.accessdata.fda.gov/scripts/cder/pmc/index.cfm). Please refer to the February 2006 Guidance for Industry: Reports on the Status of Postmarketing Study Commitments - Implementation of Section 130 of the Food and Drug Administration Modernization Act of 1997 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080569.pdf**)** for further information.

POSTMARKETING COMMITMENTS NOT SUBJECT TO REPORTING REQUIREMENTS OF SECTION 506B:

In addition, we acknowledge your written commitments as described in your letter of August 20, 2009, as outlined below:

7. To reassess release and stability specifications for ofatumumab drug substance and drug product through August 31, 2011. The assessment will be submitted in the annual report.

   - **Submission of Assessment : by October 26, 2011**

8. To develop and implement a quantitative specification for the icIEF assay used in the drug substance and drug product stability programs. The assessment will be submitted as a Changes Being Effected-30 (CBE-30) supplement.

   - **Supplement Submission: by October 31, 2011**

9. To develop and validate a semi-quantitative assay for measurement of visible particulates. The test method and specification will be incorporated into drug substance and drug product lot release and stability programs and submitted as a CBE-30 supplement.

   - **Supplement Submission: by October 31, 2011**

10. To submit a Prior Approval Supplement (PAS) for (b) (4)

    - **Supplement Submission: by December 31, 2010**

11. To revise the system suitability criteria for the robotic format of the complement-mediated antibody cytotoxicity potency assay so that the coefficient of variation (CV) (%) for duplicates is consistent with validation limits and is less than or equal to 25%. A final report including details of the system suitability criteria revisions will be submitted and a revised potency assay SOP will be submitted in the annual report. Alternatively, the robot format of the potency assay will be removed from the BLA.

    - **Final Report Submission: by March 31, 2010**

    - **Submission of SOP: by October 26, 2010**

12. To perform leachables studies to characterize the potential presence of volatile leachables from the elastomeric stopper and the presence of (b) (4) under accelerated conditions (25°C) for 6 months and at the recommended storage temperature for 24 months as outlined in the June 5, 2009 submission. The results of these studies will be submitted in the annual report.

    - **Final Report Submission: by October 26, 2012**

13. To establish permanent control action limits for purification step yields and analyze 30 in-control points. The permanent control action limits and the results of the analysis of 30 in-control points will be submitted in the annual report.

- **Final Report Submission :** **by October 26, 2010**

14. To conduct a study or studies to identify the composition of visible particles observed in drug substance lots when particles are observed during ongoing stability studies of the drug substance conformance lots. The results of these studies will be submitted in the annual report.

- **Final Report Submission:** **by October 26, 2010**

15. To confirm the lack of a deleterious effect on the stability of drug substance of reprocessing at the (b) (4) step by monitoring the real-time stability of drug substance lot 09P01105 and performing accelerated stability studies on this lot at 25°C for 6 months and at 40°C for 3 months. The real time and accelerated studies will include the licensed drug substance stability program's tests and acceptance criteria. Real time stability data and results of the accelerated stability studies will be submitted in the annual report.

- **Final Report Submission :** **by October 26, 2010**

16. To update the bioburden test for cell culture, primary recovery, and purification samples from (b) (4) to filtration method. A study will be performed to establish the appropriate volume of each sample in the test. A final study report including the validation information and data for the updated bioburden test will be submitted.

- **Final Report Submission:** **by March 31, 2010**

17. To validate drug substance intermediate hold times for microbial control at commercial scale. A final report containing the validation data will be submitted.

- **Final Report Submission:** **by December 31, 2010**

Submit nonclinical and chemistry, manufacturing, and controls protocols and all final reports to your BLA, STN BL 125326. Please use the following designators to label prominently all submissions, including supplements, relating to these postmarketing commitments as appropriate:

- **Postmarketing Commitment Protocol**
- **Postmarketing Commitment - Final Report**
- **Postmarketing Correspondence**

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

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 4203
Silver Spring, MD 20992-0002

Within 21 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/oc/datacouncil/spl.html, that is identical in content to the enclosed labeling text. For administrative purposes, please designate this submission "Product Correspondence – Final SPL for approved STN BL125326/0." In addition, within 21 days of the date of this letter, amend any pending supplement(s) for this BLA with content of labeling in SPL format to include the changes approved in this supplement.

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 125326**." 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.

As required by 21 CFR 601.45, submit all promotional materials at least 30 days before the intended time of initial distribution of labeling or initial publication of the advertisement with a cover letter requesting advisory comment. Send two copies of the promotional materials to:

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

Please submit final promotional materials with FDA Form 2253 to the above address at the time of initial dissemination of the labeling or at the time of initial publication of the advertisement.

All promotional claims must be consistent with and not contrary to approved labeling. You should not make a comparative promotional claim or claim of superiority over other products unless you have substantial evidence to support that claim.

Please refer to http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

Sincerely,

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

Enclosure: Package Insert, Carton and Container Labels