CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	October 20, 2009
From	Patricia Keegan, M.D.
Subject	Division Director Summary Review
BLA #	STN BL 125325-0
Applicant Name	Glaxo Group Limited d/b/a GlaxoSmithKline
Date of Submission	January 30, 2009
PDUFA Goal Date	October 31, 2009
Proprietary Name / Established (USAN) Name	ARZERRA™/ ofatumumab
Dosage Forms / Strength	Solution for intravenous infusion;100mg/5mL
Proposed Indication(s)	**"ARZERRA is a human monoclonal antibody against CD20 indicated for the treatment of patients with chronic lymphocytic leukemia who have received prior therapy.**
Recommended Action for NME:	Approval

b(4)

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Regulatory Project Manager Review	Raymond Chiang
Medical Officer Review	Steven Lemery, M.D.
Statistical Review	Jenny Zhang, Ph.D.
Pharmacology Toxicology Review	Andrew McDougal, Ph.D., D.A.B.T.
CMC (OBP) Review	Subramanian Muthukkumar, Ph.D.
Clinical Pharmacology Reviews	Jun Yang Ph.D. & Justin Earp, Ph.D.
DDMAC consult review	Jeffrey Trunzo, RPh, MBA
DSI	Sharon Gershon, Pharm.D.
CDTL Review	Joseph E. Gootenberg, M.D.
OSE/DMEPA reviews	Tselaine Jones Smith, Pharm.D.
OSE/DRISK	Mary Dempsey
OSE/SEALD consult review	Iris Massucci, Pharm.D.
OC/DMPQ/MAPCB/BMT Reviews	Bo Chi, Ph.D & Donald Obenhuber, Ph.D.
OPS/OBP carton review	Kimberly Rains, Pharm.D.
Pediatric & Maternal Health Staff consult	Jeanine Best MSN, RN, PNP

OND=Office of New Drugs
CMC=Chemistry, Manufacturing, and Controls
OBP=Office of Biotechnology Products
OC=Office of Compliance
DDMAC=Division of Drug Marketing, Advertising, and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DRISK= Division of Drug Risk
CDTL=Cross-Discipline Team Leader

Division Director Summary Review

1. Introduction

This applicant requests accelerated approval based on demonstration of durable, objective tumor responses in a single, multicenter trial enrolling a heterogenous population of 154 patients with multiply relapsed or refractory chronic lymphocytic leukemia (CLL). The major issues with this application that will be discussed in this review are the scope of the indication supported under the accelerated approval regulations (21 CFR 601.40), the inadequate justification of the dose studied, trial design deficiencies leading to uncertainty regarding the precise magnitude of the treatment effect, and the recommendation by the statistical team leader that the application not be approved. In general, the clinical development program was suboptimal with regard to determination of the appropriate dose and characterization of safety and efficacy, thus it is particularly important that labeling is restricted to those with an unmet medical need.

The original IND (IND 11719) for ofatumumab was submitted on May 20, 2004. The clinical program for ofatumumab for the treatment of B-cell CLL at the time of the BLA submission consisted of three completed studies, Hx-CD20-402, Hx-CD20-406, and Hx-CD20-407, evaluating the activity of ofatumumab as monotherapy in relapsed (402) or refractory (406) settings, or in combination with standard chemotherapy in the frontline setting (407). The data supporting this application are derived from two of these studies, Hx-CD20-402 and Hx-CD20-406, enrolling a total of 181 patients. Even for an orphan disease, with an estimated 15,490 new cases diagnosed in the US in 2009[1], the number of patients studied is very small, thus limiting the reliability of the observed results, as will be discussed further in Sections 2, 5, 7, and 8, below.

Study Hx-CD20-402 enrolled a total of 33 patients; there was a 39% partial response rate with a median duration of response of 16 weeks across the entire study. This is the only study to evaluate the dose-response relationship of ofatumumab monotherapy dose on activity and safety; in this study there were no responses reported for patients enrolled in the 500mg (n=3) or 1000mg (n=3) cohorts and 13 responses among the 27 patients enrolled at the 2000mg dose cohort.

Study Hx-CD20-406 utilized a fixed dose (2000 mg) of ofatumumab for 11 doses and was designed to evaluate safety and activity of ofatumumab monotherapy in two populations of CLL patients; i.e., patients who are refractory to fludarabine and alemtuzumab, and patients who are refractory to fludarabine and for whom alemtuzumab was deemed inappropriate due to the presence of bulky lymphadenopathy.

Ofatumumab received Fast Track designation for the investigation of ofatumumab in combination with fludarabine for treatment of patients with previously untreated CLL to show an improvement in progression free survival as compared with fludarabine therapy in December 2004. The development program for ofatumumab monotherapy, including the

[1] http://seer.cancer.gov/csr/1975_2006/results_single/sect_01_table.01.pdf

proposed confirmatory study (OMB110911) to verify clinical benefit, is not part of the Fast Track development program.

Key interactions between FDA and Genmab or GlaxoSmithKline regarding the clinical development program are listed below:

- August 26, 2005 – general advice meeting held prior to completion of dose-finding studies. FDA stated that initiation of studies intended to support accelerated approval should await completion of studies characterizing the dose-response relationship and toxicity profile. FDA also noted that accelerated approval based on durable responses should exceed a threshold response rate of more than 20% with a median duration of at least 4-6 months would be required in a single arm study conducted in patients with unmet medical need; alternatively, a controlled study would be required to demonstrate superiority to available therapy

- November 30, 2005 End-of-Phase 1 meeting - FDA confirmed that durable objective response rate could be an acceptable surrogate endpoint reasonable likely to predict clinical benefit in a patient population with an unmet medical need, i.e., no alternative therapy. Genmab proposed to conduct a study in patients who "failed" both fludarabine and alemtuzumab to satisfy the requirement for demonstrating benefit in patients with an unmet medical need and in a study enrolling at least 100 patients.

- Dec. 2005 – submission of protocol Hx-CD20-406 to IND 11719
  - On April 11, 2006 and May 5, 2006, FDA provided written advice stated that overall response rate (ORR) and duration of response should be analyzed separately for patients with disease refractory to both fludarabine and alemtuzumab (DR) and not pooled with results from patients with bulky, fludarabine-refractory, alemumtuzumab-naïve disease(BFR). Genmab also advised that an ORR of 10-20% considered unlikely to predict clinical benefit but that an observed rate in which in which the lower bound of 95% CI around ORR was $\geq$ 25% would be of interest assuming, median duration of response should be $\geq$ 4 months in the DR population.
  - June 2006- first patient enrolled
  - September 2006- amendment 2; revised definition of fludarabine refractory (no longer includes "intolerant patients"
  - April 2007 – amendment 3- agreed to analyzed DR and BFR separately; sample size increased from 100 pts pooled, to 66 patients in DR and BFR subgroups
  - Oct 2007- amendment 4- increased sample size to 100 pts in DR and BFR subgroups; provided for interim analysis of ORR in DR subgroup once 66 pts accrued.
  - May 19, 2009 –interim analysis conducted.

- April 2008- sponsorship of IND 11719 was transferred to GlaxoSmithKline (GSK)

Presubmission/Submission activity

At the Sept. 29, 2008, pre-BLA meeting, GSK reported the interim analysis results for Study Hx-CD20-406: 59% overall response rate in the DR group (n=59) with a median duration of 7.1 months and 48% overall response rate in the BFR group (n= 79) with a median duration of 5.6 months. GSK proposed to submit the results from Hx-CD20-406, supported by the results

of Study Hx-CD20-402, and to verify clinical benefit through study, Protocol OMB110913, a randomized, open-label, multicenter trial of fludarabine plus cyclophosphamide with or without ofatumumab in patients with relapsed B-cell CLL, with the primary endpoint of progression-free survival.

FDA did not agree that results would support labeling for BFR group, which did not have an unmet medical need since durable tumor responses have been demonstrated with alemtuzumab in patients with bulky, fludarabine-refractory CLL. FDA stated that GSK/Genmab would need to provide additional data in order to strengthen their argument that ofatumumab therapy demonstrates superior efficacy or similar efficacy with superior safety to alemtuzumab in the bulky, fludarabine-refractory CLL patient population. The ultimate decision regarding this issue will be a review issue. FDA stated that the Independent Response Committee assessment was viewed as an audit of investigator-reported response determination because the committee utilized the tumor measurements made by the investigators. GSK disputed this interpretation, however FDA did not revise this assessment of the IRC evaluation.

The application was submitted on Jan 30, 2009. Orphan drug designation was granted on March 10, 2009. In response to multiple requests for CMC information to address issues relating to particulate formation and facilities inspectional findings, multiple submission were submitted to address these issues. The June 5, 2009 response to FDA's information requests on outstanding CMC issues was characterized as a major amendment, thus extending the PDUFA goal date to October 31, 2009. The application was presented to the Oncologic Drugs Advisory Committee on May 29, 2009. A summary of the outcome of that presentation will be discussed under Section 9 of this review.

2. Background

The application is based on demonstration of durable objective tumor responses of a clinically meaningful magnitude in patients with CLL that was refractory to both fludarabine and alemtuzumab. The data were derived from a pre-defined subpopulation of patients with an unmet medical need enrolled in a single, multicenter, fixed-dose, open-label study (Study Hx-CD20-406) and were supported by evidence of durable tumor responses in less-heavily pretreated patients with CLL in enrolled in the same study (406) and in a Phase 1-2 study with a shorter, but similar treatment regimen (Study Hx-CD20-402) a single-arm, multicenter study. FDA considered the subpopulation of patients with CLL that was refractory to both alemtuzumab and to fludarabine, with a median of 5 prior treatment regimens, in which more than 90% received prior alkylating agent-containing treatment and approximately 50% received prior rituximab, to be a patient population with an unmet medical need.

FDA has stated (REGO Initiative 1996) that durable tumor shrinkage is an endpoint that may be reasonably likely to predict clinical benefit in settings where there is no available therapy and the magnitude of the effect is clinically important. A key issue in the review of this BLA is the uncertainty regarding the precise magnitude of the treatment effect (overall response rate and duration) due to the small sample size studied (n=59) and lack of objectively verifiable tumor measurements which preclude an independent, unbiased verification of the treatment effect reported in this open-label trial.

A second issue is whether overall response rate (ORR) observed in study Hx-CD20-406 is of sufficient magnitude to be reasonably likely to predict clinical benefit, the evidentiary standard for benefit in the accelerated approval regulations as set out in 21 CFR 601.40. FDA has accepted durable objective tumor responses to be a surrogate endpoint that is reasonably likely to predict a clinically important effect for the entire population on progression free survival (PFS), which FDA has previously identified as a direct measure of clinical benefit for chronic lymphocytic leukemia. The basis for the initial approvals of fludarabine and alemtuzumab was durable tumor responses of a clinically meaningful magnitude in a population with unmet medical need. Although the population did not receive bendamustine, an alkylating agent that received approval for initial treatment of CLL in 2008, more than 90% of the efficacy population received prior alkylating agents. There is no evidence that treatment with bendamustine as third-line (as opposed to first-line) therapy of CLL is beneficial and may in fact be harmful as the risks of secondary leukemia/myelodysplasia is expected to increase with multiple courses of alkylating agents. Thus the population studied was considered to have an unmet need.

Data from drugs approved for the treatment of CLL since 1990 have a consistent correlation between an improvement in progression-free survival and evidence of durable objective tumor responses with new drugs administered as monotherapy. Based on recent experience, durable objective tumor responses of a clinically meaningful magnitude is reasonably likely to predict an improvement in progression-free survival, an accepted measure of clinical benefit in patients with CLL. No approved agent has been shown to improve overall survival in CLL, which as direct evidence of clinical benefit.

In the past decade, regular approval for the treatment of CLL has been based on demonstration of superior progression-free survival (PFS), while accelerated approval has been granted based on demonstration of durable objective tumor responses in patients with CLL that has progressed following available therapy.

- Approval of fludarabine occurred prior to the establishment of the accelerated approval regulations in April, 1992. Fludarabine received regular approval in 1991 based on demonstration of durable response rates in two single arm, open-label studies conducted in 48 and 31 patients, respectively with CLL refractory to at least one prior standard alkylating-agent containing regimen. In these studies, the ORRs were 48% and 32%, with median durations of response of 1.75 and 1.25 years, respectively. In the published results of a three- arm trial comparing fludarabine alone, chlorambucil alone, or fludarabine plus chlorambucil, there was a significantly higher overall response rate (63% vs. 37%, $p<0.001$) and significantly longer progression-free survival (25 months vs. 14 months, $p<0.001$) among patients randomized to receive fludarabine monotherapy compared to chlorambucil monotherapy.

- Alemtuzumab received accelerated approval in 2001 based on the results of three single-arm studies enrolling 149 patients with CLL and progressive disease following alkylating agents and fludarabine. The overall response rate (ORR) in the three studies ranged from 21% to 33% with median durations of response of 7 to 11 months. Alemtuzumab was

granted regular approval in 2007, on the basis of superior PFS [HR 0.58 (95% CI 0.43, 0.77), p<0.0001 stratified log-rank test] in a randomized active-controlled study comparing alemtuzumab to chlorambucil in previously untreated patients with CLL. Alemtuzumab also demonstrated an improvement in ORR (83% and 55%) compared to chlorambucil.

- Bendamustine was granted regular approval in 2008 on the basis of superior PFS [HR 0.27 (95% CI 0.17, 0.43) p<0.0001] in a randomized active-controlled study comparing bendamustine to chlorambucil in previously untreated patients with CLL. Bendamustine also demonstrated an improvement in ORR (59% vs. 26%) compared to chlorambucil.

- The ODAC did not recommend approval for oblimersen sodium, which was presented to the ODAC in September 2006. Oblimersen was studied in a randomized trial of fludarabine and cyclophosphamide (FC) versus FC plus oblimersen in 230 patients with relapsed or refractory CLL. The addition of oblimersen to FC did not improve the overall response rate (41% vs. 45%), time-to-progression, or survival.

The magnitude of the objective response rate (ORR) in this application was dependent upon the assessor, with a higher response rate as determined by the independent review committee than by the investigators (58% vs. 42%) in the DR subgroup of study HxCD20-406. FDA's review of the case report forms yielded an ORR which was similar to that of the investigators. Furthermore, because radiographs were not required for documentation of response, the independent review committee (IRC) did not conduct an independent assessment of tumor measurements in lymph nodes, spleen, or liver but instead relied on investigator-reported tumor measurements. The difference between the investigator-reported response rate and that of the IRC appears to arise from the consensus process which inflated the response rate. Therefore, FDA will rely on the investigator-reported ORR and response duration as the basis for approval and for labeling claims.

3. CMC/Device

Ofatumumab is a fully human, IgG kappa monoclonal antibody with a molecular weight of 149 kDa, directed against the CD-20 molecule present on normal and malignant B-cells. The product will be marketed at in cartons of 3 or 10 vials containing 100 mg of ofatumumab solution at a strength of 20 mg/mL.

Ofatumumab was generated via transgenic mouse and hybridoma technology and is produced in a recombinant murine cell line (NS0) using standard mammalian cell cultivation and purification technologies. The potency of this product is determined complement-mediated cytotoxicity against a CD20-expressing cell line, as measured against a reference standard. Ofatumumab is also able to mediate antibody-dependent cellular cytotoxicity.

I concur with the conclusions reached by the chemistry reviewer and DMPQ reviewers regarding the acceptability of the manufacturing of the drug product and drug substance. Manufacturing site inspections were acceptable. Stability testing supports an expiry of 18 months at 2-8°C. There are no outstanding issues that preclude approval, however multiple post-marketing commitments have been agreed upon to provide additional data on long-term

stability testing and characterization of product quality. In addition, the applicant has agreed to develop and market a new strength which is more appropriate for use with the recommended dose.

4. Nonclinical Pharmacology/Toxicology

The application contained "proof-of-concept" studies conducted with SCID-mouse/human CD20-tumor bearing xenograft models, which exhibited evidence of anti-tumor activity. Pivotal toxicology studies were conducted in non-human primates, which were determined to be relevant animal species based on similar binding affinity of ofatumumab to monkey CD20 as compared to human CD20; no other relevant species, as ofatumumab does not bind to CD20 in other species tested. The toxicologic effects observed in the pivotal toxicology study in cynomolgus monkeys was predicted based on binding and represented exaggerated pharmacologic effects, with the exception of delayed onset anemia that was observed in cynomolgus monkeys but not in clinical studies. Reproductive toxicology studies conducted in cynomolgus monkeys demonstrated that ofatumumab crosses the placenta and exhibits expected pharmacologic effects, including prolonged B-cell depletion of >100 days post-natally. There are no data regarding secretion of ofatumumab in milk of lactating primates.

The nonclinical studies do not support dose-selection for the recommended human dose. Studies were conducted in normal, non-tumor bearing primates. Doses of 20 and 100 mg/kg appeared to saturate theCD20 receptors on normal B-cells in cynomolgus monkeys and the magnitude of the pharmacologic effect did not increase with increasing doses.

I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval. No additional studies are recommended for this indication and all labeling recommendations have been incorporated into product labeling.

5. Clinical Pharmacology/Biopharmaceutics

The dose-response relationship and rationale for clinical dose selection is extremely limited and supported only by a sequential dose-escalation study (Protocol Hx-CD20-402), which was not adequate in design to determine the optimal dose or range of doses for anti-tumor activity. Details regarding this study are included in section 7 below.

The data from major efficacy study, Protocol Hx-CD20-406, utilized a fixed dose beyond dose 1; the analysis relating anti-tumor activity to AUC is confounded by the inverse relationship between ofatumumab levels and tumor burden, with a reduction in ofatumumab levels due to the "tumor sink" of CD20 on persistent tumor. The higher AUC present in responding patients is likely to result from, rather than predict, tumor response. The apparent large therapeutic index for this product is large, with no maximum tolerable dose established and little evidence of a substantial or sharp increase in toxicity with increasing dose. Therefore, I concur that the recommended dose as study in Hx-CD20-406 is reasonable and should be the recommended dose in product labeling, reflecting the clinical study in which efficacy was established. .

The pharmacokinetic data show continued accumulation of ofatumumab after 8 doses (as compared to the first 4 doses), with target-mediated clearance correlated with depletion of normal B-cells in all patients and malignant in responding patients. Although clearance was dose-dependent, as expected given the high degree of variability in patients' tumor load and response to treatment, the clearance of ofatumumab exhibited large inter-subject variability. There were no pharmacokinetic data available from patients with renal or hepatic impairment, however given the known clearance mechanisms (target-mediated) and metabolic pathway (proteolytic enzymes with degradation to inactive peptides and amino acids), additional studies to investigate pharmacokinetics in patients with hepatic or renal failure will not be required. No drug interactions studies were performed. Since ofatumumab will be indicated for use as monotherapy for the treatment of CLL and based on the low potential for drug interactions with proteins, as a class, drug interactions studies will not be required.

The assessment of the development of anti-drug antibodies (ADA) to ofatumumab was not adequately evaluated in the efficacy study due to the small size of the clinical development program (143 total patients assessed pre-treatment) and limitations of the assay, which precluded the ability to detect an ADA response in the presence of circulating levels of ofatumumab, coupled with the limited follow-up of patients on clinical studies

I concur with the conclusions reached by the clinical pharmacology, pharmacometrics, and pharmacogenomics reviewers that there are no outstanding clinical pharmacology issues that preclude approval. The application did not contain an adequate characterization of the impact of ofatumumab on QTc intervals in humans (ECG assessments in nonclinical studies did not reveal drug-related adverse effects). Therefore, in conjunction with the QT-IRT consultant, two required post-marketing trials will be conducted to assess for large ofatumumab-related effects on QTc. The first trial, OMB12855, will assess QTc in 12 patients receiving the approved dose and a modified schedule (all doses beyond first cycle will be monthly). The second trial, OMB110913, a randomized, controlled trial, will assess QTc in 25 ofatumumab-treated and 25 control patients. In this second trial, the doses of ofatumumab will be 1000 mg, rather than the 2000 mg used in Hx-CD20-406. This trial is requested because of the inclusion of a control arm, which will provide greater ability to distinguish drug effects from background noise in this elderly population.

6. Clinical Microbiology

No clinical microbiology data were submitted in this application and none were required for this review.

7. Clinical/Statistical-Efficacy

This application relies primarily on a subgroup of 59 patients enrolled in a single, multicenter, open-label trial (Protocol Hx-CD20-406, double-refractory [DR] subgroup), supported by activity in less-heavily pre-treated patient subgroups in the same trial and a limited dose-escalation, activity exploring trial using a shorter treatment duration (Protocol Hx-CD20-402, n-33). The original IND sponsor, Genmab, was advised that this clinical development strategy was suboptimal in terms of number of patients studied for either safety or efficacy and limited

in dose exploration. Despite FDA's advice on several separate occasions to conduct additional studies to confirm optimal dose and randomized trial design to obtain more reliable characterization of safety and efficacy, Genmab and GSK opted to submit an application based on the interim results of this single, historically-controlled trial.

Protocol Hx-CD20-406

The trial was an open-label, multicenter, historically-controlled trial intended to investigate the activity, as determined by the objective response rate (ORR), and safety of ofatumumab in patients with CLL who required additional treatment following fludarabine and alemtuzumab. Twenty-six percent of the 154 patients were enrolled in the United States, with most of the remaining patients enrolled at European sites.

Patients were scheduled to receive a total of 12 doses of ofatumumab as follows: 300 mg during week; 2,000 mg weekly from weeks 1 to 7; then 2000 mg weeks 12, 16, 20, and 24. Prior to receiving ofatumumab, all patients were to receive premedication with an antihistamine, acetaminophen (1,000 mg or equivalent), and IV corticosteroids at doses according to a prespecified protocol.

In the final version of the protocol, key eligibility criteria relating to the double-refractory (DR) efficacy group were ≥18 years of age, B-cell CLL with an indication for treatment as defined by NCI Working Group (1996 NCIWG) guidelines, and disease refractory to both fludarabine and alemtuzumab. Patients were required to be refractory to an adequate course of fludarabine (minimum of two cycles) as defined by one of the following: failure to achieve at least PR to a fludarabine-containing regimen; disease progression during fludarabine treatment; or disease progression in responders within 6 months of the last dose of a fludarabine containing regimen. Patients were also required to either be refractory to alemtuzumab (a minimum of 12 administrations), designated as "double refractory" (DR), or have bulky lymphadenopathy with at least one lymph node > 5 cm, designated as "bulky fludarabine refractory" (BFR). ECOG performance status was to be ≤2.

The sample size assumptions for the final version of the protocol were based on a predicted overall response rate (complete plus partial response rates) of 30%. The protocol-specified primary analysis of ORR was based on the IRC-determined response assessment. The final efficacy analyses were to be conducted separately for the DR and the BFR subgroups when data for 100 patients were available for each group. The protocol was amended on October 31, 2007 (Amendment 4) to include an interim analysis when the primary endpoint data were available for 66 patients in the DR subgroup. The data monitoring committee (DMC) conducting the interim analysis would notify Genmab if the lower limit of the 99% CI excluded a response rate of 15% or less.

Based on the October 31, 2007 amendment to the protocol, the DMC conducted an interim analysis when 66 patients in the DR population were assessable for overall response rate with a data cut-off of May 19, 2008. Genmab conducted an internal review and questioned the IRC's grouping classification (DR, BFR, or other) for 19 patients. As a result of Genmab's query, 10 patients were re-classified by the IRC into a different population

group; thus, the final DR population consisted of 59 patients. The results of the interim analysis met the specified criteria for efficacy based on an overall response rate in the DR for which the lower limit of the confidence interval exceeded 15%.

The total study population contained in the interim study report was 154 patients, which also included 79 patients with bulky (>5cm nodal involvement), fludarabine-refractory disease (BFR) and an additional 16 patients, characterized as "other" who did not meet the criteria for inclusion in the DR or BFR subgroups. Eighty-eight percent of 59 patients in the DR subgroup received at least 8 infusions of ofatumumab and 54% received 12 infusions.

The characteristics of the overall study population and of specific subgroups are summarized in the following tables obtained from Dr. Lemery's review:

Table 17: Demographics

Baseline variables and demographic variables	DR n=59	BRF n=79	other n=16	Total n=154
Sex				
Male	75%	72%	62%	72%
Age				
Median (yr)	64	62	63	63
≥ 65 yrs	46%	42%	38%	43%
Race				
White	95%	99%	94%	97%
Black	0	1%	0	<1%
Hispanic	2%	0	0	<1%
Asian	2%	0	6%	1%
Median time from CLL diagnosis (yrs)	6.0	5.9	7.5	6.3
Rai stage at screening				
0	2%	0	0	1%
1	19%	9%	13%	13%
2	25%	22%	25%	23%
3	17%	14%	25%	16%
4	37%	56%	38%	47%

Table 18: Prior Treatment History

Type of prior Regimen	DR n=59	BRF n=79	other n=16	Total n=154
Alkylating agent	93%	92%	100%	94%
Alkylating agent other than chlorambucil alone or combination regimen	88%	85%	100%	88%
Bendamustine alone or bendamustine-containing regimen	3%	6%	13%	6%
Fludarabine	100%	100%	100%	100%
Combination therapy that includes fludarabine plus at least one other drug*	85%	82%	63%	81%
Alemtuzumab	100%	19%	63%	55%
Rituximab alone or rituximab-containing regimen	59%	54%	63%	57%

*the other drug could include a monoclonal antibody, steroid, or chemotherapy (or a combination of different therapies)

In an attempt to address issues of potential bias regarding investigator-determined responses in an open-label trial, the applicant conducted a post-hoc evaluation of objective responses based on review by an independent review committee (IRC). . The IRC in study Hx-CD20-406 was blinded only to investigator response assessment and did not evaluate radiographs because these were not required for response other than confirmation of complete response and were generally not obtained during the course of the trial. Therefore, IRC determination of response for involved disease sites was based solely on investigator-determined lymph node, spleen, and liver measurements.

A blinded independent review of the primary efficacy endpoint (ORR or PFS) using objective records (radiographs, laboratory, and pathologic reports) was undertaken to minimize bias in the assessment of ORR and response duration. However, due to the manner in which the trial was conducted and lack of objective measurements of tumor status, FDA considers that the IRC review was not an independent radiological confirmation of disease sites and that possible investigator bias in the measurements of lymph nodes or hepatosplenomegaly could not be adequately controlled. The finding that serial hematologic assessment of peripheral blood counts was not a major driver of response determination (as it frequently is for initial therapy) was not appreciated by FDA or Genmab at the time of study design. In addition, this limitation was either not considered or ignored by the DMC and Genmab based on information obtained during the conduct of the study.

The FDA clinical reviewer performed a case-by-case review of laboratory data, CRFs, and electronic case report forms for all patients in the DR patient subgroup. To be consistent with the IRC's methods, the clinical reviewer's case-by-case analysis did not consider additional data obtained from CT scan reports, which were available for a limited number of patients.

The point estimate for the FDA clinical review was similar to that of the investigators (41% versus 42%). The FDA clinical reviewer also noted that, if CT scan information had been considered as available in the determination of response rate, five responding patients might have been classified as non-responders. Removing these five patients as responders yields an objective response rate of 32%.

Objective response rate as determined by clinical investigators, the IRC, and FDA, using a uniform set of criteria are provided below (abstracted from information in Table 22 of the joint clinical/statistical review).

Summary of Applicant's Revised ORR Results-Study 406

Protocol HX-CD20-406 Analysis Subgroup and Outcomes	Investigator-determined	IRC-determined	FDA-determined
Primary efficacy subgroup	(n=59)	(n=59)	(n=56)
Double refractory (DR) Overall Response Rate [99% CI] Median response duration (mos)	42% (25/59) [26%, 60%] 6.5	54% (32/59) [37%, 71%] 7.1	41% (23/56) [25%, 59%] 6.5
Supportive subgroup	(n=79)	(n=79)	----
Bulky, fludarabine-refractory (BFR) Overall Response Rate [99% CI]	34% (42/59) [25%, 60%]	44% (35/79) [30%, 59%]	-----

The IRC response rates were 58% and 47% in the DR and BFR groups, respectively, notably higher than the 42% and 34% rates determined by the investigators. This finding is different than that generally found when an IRC is utilized in an open-label study. FDA also noted the requests by Genmab for re-assessments by the IRC as described in the paragraph above. For both these reasons, FDA closely evaluated the IRC dataset containing response assessments for readers 1 and 2, the adjudicator, and the final IRC determination. In that review, the clinical and statistical reviewers noted differences between the individual readers, the adjudicator, and the final IRC determination that did not appear to conform to the IRC charter. In addition, as noted by the clinical reviewer, the IRC did not utilize the criteria for response duration as stated in the protocol. In the May 19, 2009, amendment to the BLA, GSK stated that the IRC calculated response duration from the date of onset of response to the assigned date of progression, rather than the latest date of confirmed response. As noted by the medical reviewer, since response assessments occurred every four weeks, using the IRC's criteria, a patient who progressed shortly after the first confirmatory four week visit could be considered a responder if he/she was assigned as progressing at the next month's visit. Due to concerns regarding the manner of the IRC-determination and considering the IRC's reliance on investigator's measurements rather than primary data, in this instance, use of investigator-assessed response rates and durations of response are more appropriate for inclusion in product labeling than the IRC-determined values.

Protocol Hx-CD20-402

The results of Protocol Hx-CD20-406 are supported by a single dose-escalation and activity estimating study at a single dose level in Protocol Hx-CD20-402. This trial evaluated three different initial/subsequent dose combinations,as follows: level 1 - 100 mg dose 1/500 mg doses 2-4 (n=3); level 2 - 300 mg dose 1/ 1000mg doses 2-4 (n=3); and level 3 - 500 mg dose 1/ 2000 mg doses 2-4 [n=27(1 additional patient dropped out after a single dose due to an SAE and is not included in efficacy or PK analyses)]. The size of the third cohort was based on the assumption that 50% of the patients would achieve an objective response, with two-sided 95% confidence intervals of 31% and 69%. The lower limit of the confidence interval would be greater than 30%, which was considered to be the lowest response level which was clinically relevant.

Because the enrollment was sequential rather than parallel, the dose groups were not well-balanced with regard to relevant prognostic factors, such as proportion of patients with bulky disease, Binet stage at entry, and presence/absence of constitutional symptoms. In study Hx-CD20-402, there was one response in the low-dose group [ORR 33% (95% CI 1%, 91%)], no responses in the mid-dose group, and 13 responses [ORR 50% (95% CI 30%, 70%)]. This level of dose-exploration is suboptimal and clearly does not rule out that lower doses may also be effective.

I concur with the conclusions reached by the review team members (with the exception of the statistical team leader) and the advice of the Oncologic Drugs Advisory Committee that, while a precise determination of activity cannot be made for the reasons discussed above, the objective tumor response rate estimated in patients with fludarabine- and alemtuzumab-refractory disease is of sufficient clinical magnitude and durability to be reasonably likely to predict an effect on clinical benefit. Verification of clinical benefit, through the conduct and submission of the results of the postmarketing trial requirement under 21 CFR 601.70, will be based on the results Protocol OMB110911, as amended on August 21, 2009 and as outlined in the following commitment from the applicant:

After receipt of the protocol amendment, GSK agreed to the following postmarketing requirement under 21 CFR 601.70:

> "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 Arzerra (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 as amended (Amendment 2) with submission to FDA on August 21, 2009; and began patient accrual on December 22, 2008. "

The applicant has also agreed to provide the final results of Protocol HX-CD20-406 under a 506B that includes information on all patients enrolled and within the DR subgroup. This PMC, to submit the final results of study Hx-CD20-406 to FDA by December 31, 2011, will

provide additional information in order to more accurately characterize the effect size for ORR, contained in the interim report submitted in this BLA.

8. Safety

Limitations of the safety database in this application were the limited number of patients who were treated at the proposed recommended dose and schedule as well as the uncontrolled nature of the data, which made ascertainment of causal relationship to drug difficult. The size of the safety database was deemed sufficient only because of the prior extensive experience with other agents in this class, such that target-mediated toxicities are generally well-understood.

The applicant provided data only from 154 patients who received the recommended dose and schedule, supplemented by 27 patients who received the approved dose with a shorter schedule. The original application contained safety data from 648 patients, primarily derived from studies in which patients received lower doses and had different underlying primary diseases (e.g., rheumatoid arthritis). The safety database was expanded to include information on a total of 1138 patients in the 120-day safety update. The data from the 154 patients enrolled in Study Hx-CD20-406 was utilized for characterization of the incidence rates of specific toxicities and the larger database of 1138 patients contained in the 120day safety update was utilized for identification of serious adverse events.

The most common adverse reactions (≥10%) of 154 patients enrolled under Protocol Hx-CD20-406 were neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections.

The most common serious adverse reactions in 154 patients enrolled under Protocol Hx-CD20-406 were infections (including pneumonia and sepsis), neutropenia, and pyrexia. Infections were the most common adverse reactions leading to drug discontinuation in this trial.

The incidence of infusion reactions, characterized by fever, chills/rigors, dyspnea and/or bronchospasm, arrhythmias, rash, urticaria, or hypotension, occurring during or within 24 hours of infusion, was highest during the first infusion (41%) and gradually decreased to 5-15% with later infusions. This incidence rate occurred with a regimen that had been optimized to reduce this toxicity, specifically by premedication with acetaminophen, antihistamines, and corticosteroids, slow initial infusion rate with gradual escalation as tolerated, and an initial dose that was substantially lower than the remainder of the recommended dosing regimen (300 mg rather than 2000 mg). Deviations from this approach are likely to result in higher rates and more severe infusion reactions. Based on the overall safety database, the incidence rates of infusion reactions were higher in patients with non-malignant diseases and more severe in patients with significant underlying pulmonary disease.

The incidence of infections also appears to be substantial, however given the extent of prior myelosuppressive chemotherapy and the underlying disease, CLL, in which defective lymphocyte function is often present as part of the malignant process, it is difficult to

accurately characterize the extent to which ofatumumab increases the risks of infection. The incidence of fatal infections in Hx-CD20-406 was 17% and serious infections involved bacterial, fungal, or viral pathogens. A single case of progressive multifocal leukoencephalopathy (PML) was reported following ofatumumab, however the patient had extensively prior treatment with multiple anti-neoplastic drugs that also increase the risk of PML, so that the contribution of ofatumumab to the risk of developing PML is unclear.

The overall per-patient incidence of adverse reactions and the incidence of severe or life-threatening adverse reactions occurring in ≥ 5% of the 154 patients enrolled in Protocol Hx-CD-406 and in the 59 patients in the DR subgroup are displayed in the following table.

Body System/Adverse Event	Total Population (n = 154)		Fludarabine- and Alemtuzumab-Refractory (n = 59)	
	All Grades %	Grade ≥3 %	All Grades %	Grade ≥3 %
Infections and infestations				
Pneumonia[a]	23	14	25	15
Upper respiratory tract infection	11	0	3	0
Bronchitis	11	<1	19	2
Sepsis[b]	8	8	10	10
Nasopharyngitis	8	0	8	0
Herpes zoster	6	1	7	2
Sinusitis	5	2	3	2
Blood and lymphatic system disorders				
Anemia	16	5	17	8
Psychiatric disorders				
Insomnia	7	0	10	0
Nervous system disorders				
Headache	6	0	7	0
Cardiovascular disorders				
Hypertension	5	0	8	0
Hypotension	5	0	3	0
Tachycardia	5	<1	7	2
Respiratory, thoracic, and mediastinal disorders				
Cough	19	0	19	0
Dyspnea	14	2	19	5
Gastrointestinal disorders				
Diarrhea	18	0	19	0
Nausea	11	0	12	0
Skin and subcutaneous tissue disorders				
Rash[c]	14	<1	17	2
Urticaria	8	0	5	0
Hyperhidrosis	5	0	5	0
Musculoskeletal and connective tissue disorders				
Back pain	8	1	12	2
Muscle spasms	5	0	3	0
General disorders and administration site conditions				
Pyrexia	20	3	25	5
Fatigue	15	0	15	0
Edema peripheral	9	<1	8	2
Chills	8	0	10	0

[a] Pneumonia includes pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.
[b] Sepsis includes sepsis, neutropenic sepsis, bacteremia, and septic shock.
[c] Rash includes rash, rash macular, and rash vesicular.

A potential safety concern identified early in the review by the review team and DRISK consultant was that delivery of the recommended dose of 2000 mg required the use of 20 vials. This is an unusual approach that raised concerns regarding the possibility of medication errors. The review team notes that GSK evaluated this risk through a survey of pharmacists and has adjudged the risk to be low. In addition, GSK committed to develop a more appropriate strength given the recommended dose. Based on this commitment, the clinical review staff considers this concern to have been adequately addressed.

I concur with the review team' and consultants' conclusion that a REMS is not required for this application. I also concur that the applicant should conduct additional trials, under Section 505(o) of the Federal Food, Drug, and Cosmetic Act (FDCA), to assess as recommended by the review team. These post-marketing requirements are:

> To conduct a sub-study in OMB110911 to evaluate QTc effects. Specifically GSK must conduct an assessment of QTc intervals in patients who have been administered Arzerra (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 Arzerra (ofatumumab) per the approved prescribing information. Thenumber 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 Arzerra (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.

9. Advisory Committee Meeting

This application was presented to the Oncologic Drugs Advisory Committee on May 29, 2009. The majority (10 yes; 3 no) of the ODAC members agreed that the results of Protocol Hx-CD20-406 supported the accelerated approval of Arzerra®, as a single agent, for the treatment of patients with chronic lymphocytic leukemia. This recommendation was based on an objective response rate of 42% (99% CI: 26%, 60%) with an estimated median duration of 6.5 months in 59 patients with CLL that was refractory to both fludarabine and alemtuzumab [double-refractory (DR) subgroup].

Those members who voted "no" felt that the data was not robust enough, given the small number of patients envaluated and uncertainty regarding the true response rate, since CT scan measurements were not obtained, thus the response rate was likely to be an over-estimation. These members agreed that there was anti-drug activity but were concerned about the over-estimation of the treatment effect, in adequate evaluation of toxicity of the proposed regimen, and inability to assess the effect on survival. These members recommended awaiting the results of the randomized trial.

Those members who voted "yes" considered that the level of activity and the manner in which it was assessed was similar to that used to support approval of other drugs and that even given the uncertainty of the treatment effect, the applicant met the criterion discussed with FDA (ORR >20%). Despite uncertainty regarding the estimated treatment effect, these members stated that a response rate of 20-40% would be likely to predict benefit in this population of heavily pre-treated patients.

The committee was discussed considerations for optimal trial design for studies intended to support marketing approval of drugs for the treatment of CLL. All members generally agreed that CT scans and other objective members should be incorporated into disease assessments, noting that this is the current recommendation in the 2008 NCIWG guidelines. An additional recommendation was for taking into account concurrent hematopoietic growth factor use in determining tumor responses. Several members also recommended randomized trials in less refractory patients in future trials.

10. Pediatrics

The applicant's January 22, 2009 request for Orphan Drug designation was granted on March 10, 2009. Based on this designation, the requirements of the PREA (Pediatric Research Equity Act) do not apply to this application. Because chronic lymphocytic leukemia would be rare in children, studies with this product in children would likely be infeasible.

11. Other Relevant Regulatory Issues

There are no other unresolved relevant regulatory issues.

12. Labeling

- Proprietary name
  I concur with the evaluation by the DMEPA reviewers that the proposed proprietary name ARZERRA is not likely to lead to medication errors and is not promotional in nature.

- Physician labeling: All outstanding issues regarding physician labeling have been resolved. Labeling recommendations from all consultants were considered except where noted below. Substantive changes to the proposed labeling from the applicant are summarized as follows:

  Indications and Usage
  - The indication was limited to the population of patients with an unmet need, rather than the broadly worded indication proposed by the applicant.
  - Added wording to provide basis for accelerated approval (durable objective responses) and lack of information on improvements in disease related symptoms or survival.

Dosage and Administration

- Revised for brevity and clarity (e.g., infusion rates placed in table rather than text)
- Separate subsection created for recommended dose modifications for emphasis and clarity
- The timing of the administration of the 5th ofatumumab dose was written as a range in the clinical protocol (Hx-406-CD20); this dose could be administered 4 or 5 weeks following the 4th dose. However, in the trial, this was most commonly administered 4 weeks after the 4th dose. Since the exact timing is unlikely to be critical to efficacy and to limit confusion, (b(4)

Warnings and Precautions

- [redacted]
- [redacted] b(4)
- [redacted]
- [redacted]

Adverse Reactions

- Introductory section modified to reference all subsections in Warnings and Precautions and to add a summary of the most common adverse reactions and most common serious adverse reactions, as recommended in FDA Guidance on this section of product labeling.
- Clinical Trials Experience subsection
  - Description of data source modified for brevity and limited to characterization of safety data sources as described in FDA Guidance
  - Table containing adverse events moved up and modified to exclude events from the ( ) b(4)
  - FDA recommended addition of subsection entitled Neutropenia, due to the frequency of this event.
- Immunogenicity subsection revised to include standard language, as proposed by FDA, to put information in this subsection in context, to include number of patients evaluated for immunogenicity after 8 doses, and to remove promotional language ( ) when, in fact, this risk has been inadequately characterized. b(4)

Use in Special Populations

- Section 8.1 revised in accordance with information to be included in this section per FDA Guidance and recommendations of Maternal/Fetal Health Staff (MFHS); change to Pregnancy Category C [redacted] based on findings in animals. Removes misleading information regarding [redacted] b(4)
  - FDA requested modifications to Section 8.3 to include available information about [redacted] b(4)
  - Section 8.5 (Geriatric Use) modified for consistency with 21 CFR 201.57.
  - New sections (8.6 and 8.7) on use in patients with renal and hepatic insufficient added to clarify lack of information and for consistency with current FDA recommendations for inclusion of information in product labeling.

Overdosage

- FDA requested removal of the statement [redacted] as it is vague and not informative. b(4)

Clinical Pharmacology

- Section 12.1 (Mechanism of Action) revised to limit extraneous information
- Section 12.2 (Pharmacodynamics), revised to provide data relevant to the indicated population. The statement [redacted] was replaced with the more accurate statement "The time to recovery of lymphocytes, including CD19-positive B cells, to normal levels has not been determined." b(4)
- Section 12.3 (Pharmacokinetics) revised to delete subsections on [redacted] b(4)

Nonclinical Toxicology

- Subsection 13.3 (Reproductive Toxicology) added to product labeling; contains information described under Subsection 8.1 in original proposed labeling and described in greater detail in 13.3.

Clinical Studies

- [redacted] labeling now notes only that the data in this study and in other subgroups b(4)

b(4)

within Hx-CD20-406 are supportive.

- Description of study population revised to reflect the DR subgroup only.
- Deleted descriptions of

b(4)

References section (section 15) deleted.
Patient Counseling

- Section 17.1 (General Counseling Information): revised to include direct language regarding advice to be provided to patients
-

b(4)

- Carton and immediate container labels
  There are no outstanding issues regarding carton and container labeling.

- Patient labeling/Medication guide

b(4)

I concur that a Medication Guide is not required to ensure safe use of this product as it is intended to be administered by oncologists managing the treatment of patients with CLL. Patient labeling is unnecessary since the drug will be administered by intravenous infusion under medical supervision; counseling of patients is part of the standard medical care for patients with cancer who are beginning a new chemotherapy course. Such counseling should be adequate to inform patients of expected toxicities/risks of this product.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

  I recommend approval for this product with the labeling, including revised indication, recommended by the review team.

  The recommendation for approval was supported by all disciplines except the statistical review team, where the primary statistical reviewer recommended approval and the statistical team leader recommended that the application not be approved. The clinical review team's and primary statistical reviewer's recommendations were based on a finding of that durable tumor shrinkage of sufficient magnitude to be reasonably likely to predict clinical benefit. A range of potential response rates, based on the investigator-reported rate, the FDA clinical reviewer's assessment of each patient's case report forms and other clinical information, a strict mathematical determination of response rate derived from the response algorithm defined in the protocol using

investigator-assessed tumor measurements and laboratory data, along with multiple sensitivity analyses, were considered in evaluating the magnitude of the effect. Dr. Rothmann's recommendation relies partly on the uncertainty of the magnitude of the effect given the small sample size and lack of independent verification; these concerns are valid. Dr. Rothmann's recommendation is also based on his conclusion that durable tumor shrinkage is not reasonably likely to predict clinical benefit. As discussed above, I disagree with this conclusion. I believe that based on prior experience in CLL, durable tumor responses of this magnitude (25% or higher) with single agents have been shown to predict improvements in progression-free survival.

- Risk Benefit Assessment
  I concur with the recommendation of the clinical reviewer and the majority of the ODAC members that this drug should be approved. The benefits of durable tumor shrinkage include the potential for improved symptom control and delay in time to disease progression or mortality. This is weighed against commonly reported toxicities of therapeutic proteins and standard chemotherapy for the treatment of CLL. The magnitude of the reported benefit (ORR 42% and median duration of response of 6.5 months) is consistent with observed degree of benefit reported for the applications supporting the initial approvals for fludarabine and alemtuzumab. Although there is some uncertainty regarding this estimated effect size, given the small number of patients studied and the absence of radiographic imaging of non-palpable disease sites, even if the effect size is modestly over-estimated, this magnitude of effect is acceptable given the extensive degree of prior treatment and remains likely to predict clilnical benefit. The toxicity, which may also be underestimated, is acceptable in light of the reported benefit.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  I concur with the recommendations of the review team that a REMS is not required for this application. The risks of ofatumumab, although incompletely charactized in the single-arm studies supporting this application, appear to be qualitatively and quantitatively similar to other agents indicated for the treatment of CLL. Oncologists are familiar with identification and management of the common toxicities of infusion reactions, infections, and cytopenias, thus a REMS is not considered necessary to enhance safe use of this product for the proposed indication.

- Recommendation for other Postmarketing Requirements and Commitments

  I concur with the following post-marketing requirements and commitments for this application
  - Submission of the results of the randomized, controlled 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" to verify the clinical benefit of ofatumumab, as required under 21 CFR 601.40 (Subpart E).

PMRs under Section 505(o) of the FDCA

- 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.
- 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.
- To conduct clinical trial OMB112855, a trial of QTc intervals in patients who have been administered ofatumumab.
- 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).

PMCs reportable under Section 506B

- 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.

PMC's not reportable under 506B

- To reassess release and stability specifications for ofatumumab drug substance and drug product through August 31, 2011.
- 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.
- 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.
- To submit a Prior Approval Supplement (PAS) for the introduction of a ( ) ofatumumab single-use vial, 20 mg/mL, to reduce the number of vials needed for the 2000 mg dose. b(4)
- 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 and a revised potency assay SOP will be submitted in the annual report or the robot format of the potency assay will be removed.
- To perform leachables studies to characterize the potential presence of volatile leachables from the elastomeric stopper and the presence of ( ) 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. b(4)

- 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.
- 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.
- To confirm the lack of a deleterious effect on the stability of drug substance of reprocessing at the ( ) 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. b(4)
- To update the bioburden test for cell culture, primary recovery, and purification samples from ( ) 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. b(4)
- To validate drug substance intermediate hold times for microbial control at commercial scale. A final report containing the validation data will be submitted.

Signature Page

/Patricia Keegan/s/ October 20, 2009

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OND/CDER/FDA