CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125326

OFFICE DIRECTOR MEMO

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Date	October 22, 2009
From	Richard Pazdur, M.D. R Pazdur 10/26/09
Subject	Office 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. C b(4) D
Recommended Action for NME:	Approval

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 & Justin Earp
DDMAC consult review	Jeffrey Trunzo, RPh, MBA
Division Director Review	Patricia Keegan, MD
CDTL Review	Joseph E. Gootenberg, M.D.
OSE/DMEPA reviews	Tselaine Jones Smith
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
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

SUMMARY

On October 26, 2009 the U.S. Food and Drug Administration granted accelerated approval to ofatumumab (Arzerra®, GlaxoSmithKline) for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. The approval was based on a clinically meaningful and durable overall objective response rate (ORR) observed in a single-arm trial (study Hx-CD20-406). As a condition of accelerated approval, subsequent randomized trials are required to verify and describe the clinical benefit of ofatumumab in CLL.

Hx-CD20-406 was a single-arm, multicenter study in 154 patients with relapsed or refractory CLL. Accelerated approval was based on the results of a pre-specified subgroup of 59 patients who were refractory to both fludarabine and alemtuzumab. Drug refractoriness was defined as failure to achieve at least a partial response to, or disease progression within 6 months of, the last dose of fludarabine or alemtuzumab. The primary efficacy outcome was durable ORR determined by the 1996 National Cancer Institute Working Group (NCIWG) Guidelines for CLL.

In study Hx-CD20-406, patients received an initial 300 mg dose, followed 1 week later by 2,000 mg weekly for seven doses, followed 4-5 weeks later by 2,000 mg every 4 weeks for 4 doses (maximum of 12 doses). All doses were administered by intravenous infusion.,

In patients with CLL refractory to both fludarabine and alemtuzumab, the median age was 64 years (range 41 to 86 years), 75% were male and the median number of prior therapies was five. Eighty-eight percent received at least 8 ofatumumab infusions and 54% received 12 infusions.

The investigator-determined ORR in patients with CLL refractory to fludarabine and alemtuzumab was 42% (99% CI: 26, 60) with a median response duration of 6.5 months (95% CI: 5.8, 8.3). There were no complete responses. Supportive information included anti-tumor activity observed in a multicenter, open-label, dose-escalation study (Hx-CD20-402) conducted in patients with relapsed or refractory CLL and additional patients enrolled in Hx-CD20-406..

The safety of single-agent ofatumumab was evaluated in 181 patients with relapsed or refractory CLL enrolled in either Hx-CD20-406 and HD-CD20-402 studies. . Ofatumumab was administered at 2,000 mg beginning with the second dose for 11 doses in Hx-CD20-406 (154 patients) or 3 doses in Hx-CD20-402 (27 patients).

The most common adverse reactions (≥10%) in Hx-CD20-402 were neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections. The most common adverse reaction leading to drug discontinuation was infections

In Hx-CD20-406, infusion reactions occurred in 44% of patients on the day of the first infusion (300 mg) and 29% on the day of the second infusion (2,000 mg). The most common serious adverse reactions in this study were infections (including pneumonia and sepsis), neutropenia, and pyrexia. . A total of 45 patients (29%) experienced grade 3 or greater infections; 19 (12%) were fatal. Of 108 patients with normal baseline neutrophil counts, 45 (42%) developed grade 3 or greater neutropenia. Nineteen (18%) developed grade 4 neutropenia. One patient developed fatal progressive multifocal leukoencephalopathy after ofatumumab treatment.

Key Review Issues

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.

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

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.

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 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.

FDA has accepted durable objective tumor responses to be a surrogate endpoint that is reasonably likely to predict a clinically important effect on progression-free survival (PFS), which FDA has previously identified as a measure of clinical benefit for lCLL.

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.

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).

Objective response rate information as determined by clinical investigators, the IRC, and FDA, using a uniform set of criteria are provided below

Summary of Applicant's Revised ORR Results-Study 406 (Table Completed by Statistical Reviewer)

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%]	41% [25%, 59%]
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 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.

The applicant provided data from 154 patients who received the recommended dose and schedule, supplemented by 27 patients who received the approved dose with a shorter schedule. This database was supplemented by several hundred patients receiving lower doses and with different underlying primary diseases (e.g., rheumatoid arthritis).
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). .

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.

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.

Recommended Regulatory Action: Approval under Accelerated Approval Provisions.

This recommendation is consistent with the viewpoints expressed by the FDA review staff (exception of Dr. Rothman) and the ODAC vote. Please refer to Dr. Keegan's review who discusses Dr. Rothman's concerns. Please refer to Dr. Lemery's review for a discussion of post-marketing studies to provide evidence of clinical benefit.

Richard Pazdur
10/26/09