CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125557Orig1s000

OFFICE DIRECTOR MEMO

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	125557
Applicant Name	Amgen
Date of Submission	September 19, 2014
PDUFA Goal Date	May 19, 2015
Proprietary Name / **Established (USAN) Name**	Blincyto (blinatumomab) for Injection
Dosage Forms / Strength	35 mcg of lyophilized powder in a single use 4 mL vial
Proposed Indication(s)	for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)
Action/Recommended Action for NME:	Accelerated Approval

Material Reviewed/Consulted OND Action Package, including:	
Division Director	Ann Farrell, MD
RPM	Kris Kolibab
Medical Officer Review	Donna Przepiorka, MD/Albert Deisseroth, MD, PhD
CDTL Review	Albert Deisseroth, MD, PhD
Statistical Review	Chia-wen Ko, PhD, Lei Nie, PhD
Pharmacology Toxicology Review	Brenda J. Gehrke, PhD, Haw-Jyh Chiu, PhD, Tiffany K. Ricks, PhD/Christopher Sheth, PhD
CMC Review/OBP Review	Qing Zhou, PhD/Deborah Schmiel, PhD/Rashmi Rawat, PhD, Sarah Kennett, PhD/Laura Salazar-Fontana, PhD/Susan Kirshner, PhD/ Jibril Abdus-Samad, PharmD
Microbiology Review	Candace Gomez-Broughton, PhD/Maria Candauchacon, PhD/Patricia Hughes, PhD
Clinical Pharmacology Review	Pengfei Song, PhD, Ping Zhao, PhD,Vikram Sinha, PhD Qi Liu, PhD, Nitin Mehrotra, PhD
OPDP	Adam George, PharmD/Morgan Walker
OSI	Anthony Orencia, MD, FACP/Janice Pohlman, MD, MPH/Kassa Ayalew, MD, MPH
OSE/DMEPA	Neil Vora, PharmD, MBA/Yelena Maslov, PharmD/Luban Merchant, PharmD/Kellie Taylor, PharmD, MPH
OSE	Carolyn Yancey, MD, Naomi Redd, PharmD, Cynthia LaCivita, PharmD

1. Introduction & Background

On September 19, 2014, Amgen submitted a BLA for Blincyto (blinatumomab) a bi-specific CD-19 directed CD-3 T-cell engager—the first submitted bi-specific antibody to OHOP. Blinatumomab was granted breakthrough therapy designation on June 30, 2014 for the treatment of adult patients with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia (ALL).

This application seeks approval of blinatumomab for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). Philadelphia chromosome-negative relapsed and/or refractory ALL is a rapidly fatal disease with few available treatment options. Two other products have received accelerated approval for a similar indication: Marqibo (vincristine sulfate liposome injection) and Clolar (clofarabine injection).

For the Marqibo approval, a 4.6% complete remission rate with a documented duration of response of 28-56 days from a single arm trial supported an accelerated approval. For the Clolar approval, a complete remission rate less than 20% from a single arm trial supported approval.

2. CMC/Device

There are no issues that preclude approval from a product quality perspective. The product quality reviewers have concluded:

The data submitted in this Biologics License Application support the conclusion that the manufacture of Blincyto (blinatumomab) and IV solution stabilizer is well-controlled and leads to a product that is pure and potent. The blinatumomab product and the IV solution stabilizer are free from endogenous and adventitious infectious agents sufficient to meet the parameters recommended by the FDA.

A 36-month expiration dating period is granted for the drug product when stored at 5 ± 3 C and protected from light. This BLA is recommended for approval from a product quality perspective with postmarketing commitments as outlined in the action letter.

3. Nonclinical Pharmacology/Toxicology

There are no issues that preclude approval from a nonclinical perspective. The following is an excerpt from nonclinical reviews:

Blinatumomab (Blincyto) is a bispecific T-cell engager antibody construct that binds to CD19 (expressed on B cells) and CD3 (expressed on T cells)…In mice, the surrogate decreased lymphocytes including total B cells and T cells and the CD4+ and CD8+ T lymphocyte subsets in the blood, spleen, and lymph node. Following daily administration of the surrogate for 4 or 13 weeks in mice, lymphoid tissues were the target organs of toxicity with decreased spleen weights and decreased cellularity or germinal center development observed in the lymph nodes, Peyer's patches, and spleen. In chimpanzees, infusion with blinatumomab decreased lymphocyte levels including B cells (CD19+ and CD20+) and T cells (CD3+/CD4+ and CD3+/CD8+) and increased the expression/levels of T cell activation markers sCD25, CD69, and HLA-DR. Increases in cytokines IL-2, IL-6, and INFγ were also observed following infusion with blinatumomab in chimpanzees, a finding consistent with the cytokine release syndrome observed in the clinical trial in patients with ALL. … neurologic adverse events were observed in approximately half of the patients in the clinical trial, clear evidence of CNS toxicities was not observed in the general toxicology or CNS safety pharmacology studies.

The Applicant conducted embryo-fetal development studies in mice with the murine

surrogate of blinatumomab. The surrogate molecule failed to show embryo-fetal toxicity or teratogenicity in mice but did cross the placental barrier. Fetal exposure occurred at pharmacologically active concentrations, suggesting the potential for lymphocyte depletion. There are no reproductive and developmental toxicology studies with blinatumomab, and it is not known if blinatumomab can cause fetal harm. Based on the mechanism of action of B cell depletion and to be consistent with the labels of other B cell targeting agents, the Pharmacology/Toxicology team recommends Pregnancy category C.

4. Clinical Pharmacology/Biopharmaceutics

There are no issues that preclude approval from a clinical pharmacology perspective. The following text is from the review:

Blinatumomab demonstrated linear pharmacokinetics (PK) in terms of dose proportionality at a dose range from 5 to 90 µg/m2/day and time-independent clearance. The mean clearance (CL), volume of distribution (Vz), and elimination half-life (T1/2) are 2.92 L/hr, 4.52 L, and 2.1 hours, respectively. The pharmacokinetics of blinatumomab is highly variable, with a 97% coefficient of variation (CV) in CL and a 64% CV in Vz. Body weight does not affect the pharmacokinetics in adult patients. Negligible amount of blinatumomab was detected in urine samples at steady state from subjects who received the 60 µg/m²/day dose. Based on PK, safety and efficacy data, no starting dose adjustment is needed in patients with baseline mild or moderate renal impairment. There is no information available in patients with severe renal impairment or patients on hemodialysis.

Pharmacodynamic assessments focused primarily on the evaluation of dynamic changes to T cells, B cells, and cytokines during the treatment of blinatumomab. T-cell kinetics showed characteristic redistribution after start of infusion and any increase in dose; circulating T-cells disappeared within the first 6 hours and returned to baseline during the subsequent 2 to 7 days; Redistribution of NK cells and monocytes exhibited kinetics similar to those observed for T cells. In most subjects, cytokine levels of IL-2, IL-6 and IL-10 increased immediately after the start of blinatumomab infusion and returned to baseline levels within 1 to 2 days.

5. Microbiology

No issues that would preclude approval were identified.

6. Clinical-Efficacy

This application is supported by a multicenter single-arm trial (Protocol MT103-211) that enrolled 185 patients with R/R ALL with results demonstrating an achievement of durable complete remission (CR) and response with a reduction in minimal residual disease (MRD) to less than 10^{-4}. Blinatumomab was administered by continuous infusion for 4 weeks of a 6-week cycle. Up to two cycles were used for induction and three cycles for consolidation.

In Protocol MT103-211, 32% (95% CI, 26% - 40%) of patients with R/R ALL attained CR with 2 cycles of treatment with single-agent blinatumomab, and the response was durable (median 6.7 months; range, 0.46 - 16.5 months). Furthermore, 31% (95% CI, 25%-39%) of the patients in the study had a CR with or without complete hematological recovery but with reduction in MRD to $<10^{-4}$.

7. Clinical-Safety

Safety was evaluated in 212 patients with R/R ALL treated with blinatumomab. The most common adverse reactions (greater than or equal to 20%) were pyrexia (62%), headache (36%), peripheral edema (25%), febrile neutropenia (25%), nausea (25%), hypokalemia (23%), rash (21%), tremor (20%), and constipation (20%). A

neurological toxicity occurred in approximately 50% of patients and was a frequent reason for interruption of therapy.

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that activates endogenous T cells when bound to the CD19-expressing target cell. Activation of the immune system results in release of inflammatory cytokines. Cytokine release syndrome, including life-threatening or fatal events, was reported in 11% of the patients. A Boxed Warning regarding cytokine release syndrome and neurological toxicities is provided in the product labeling. In addition, blinatumomab is being approved with a Risk Evaluation and Mitigation Strategy (REMS) which consists of a communication plan to inform health care providers about the serious risks and the potential for preparation and administration errors.

8. Advisory Committee Meeting

This application did not require discussion at an ODAC meeting due to the fact that trial results were superior to other products for a similar disease indication and the risk/benefit was thought to be favorable.

9. Pediatrics

The Applicant is conducting trials for pediatric patients with relapsed ALL.

10. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action: Accelerated approval

- Risk Benefit Assessment
  In patients with relapsed and/or refractory ALL, Blincyto (blinatumomab) produces durable complete responses and minimal residual disease negativity (less than 10^{-4}) in a single arm trial. Blincyto use is associated with significant toxicities. The following adverse reactions (ARs): cytokine release syndrome and neurological toxicities (including seizures) were associated with fatalities. The following ARs were described as warnings in the labeling: infection observed in approximately 25%, tumor lysis syndrome, neutropenia and febrile neutropenia, effects on ability to drive and use machines, elevated liver enzymes, leukoencephalopathy, and preparation and administration errors. Although the toxicities are significant and include two boxed warnings, this product is proposed to be used in those patients who have no other effective alternatives. Due to the significant toxicities this approval will have a REMS communication plan.

  The risk-benefit profile was deemed favorable by Drs. Farrell, Deisseroth, and Przepiorka, and I concur with their assessment. Furthermore, all review team members recommend approval.

- Recommendation for Post marketing Risk Management Activities
  A REMS is necessary.

- Recommendation for other Post marketing Study Requirements/ Commitments
  See action letter.

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/s/

TAMY E KIM
12/03/2014

RICHARD PAZDUR
12/03/2014