CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761040Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRISK)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761040
PDUFA Goal Date	August 20, 2017
OSE RCM #	2016-823, 2016-825
Reviewer Name(s)	Mei-Yean Chen, Pharm.D.
Team Leader	Doris Auth, Pharm.D., Acting Team Leader, Acting Associate Director
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	May 19, 2017
Subject	Evaluation of Need for a REMS
Established Name	Inotuzumab Ozogamicin
Trade Name	Besponsa
Name of Applicant	Pfizer Inc./Wyeth Pharmaceuticals, Inc., a subsidiary of Pfizer Inc.
Therapeutic Class	CD22-directed antibody (inotuzumab)-drug (ozogamicin) conjugate (b) (4)
Formulation(s)	mg single-dose vial administered by intravenous infusion
Dosing Regimen	Cycle 1: 1.8 mg/m^2 per 3-week cycle, given as 3 divided doses on Days 1, 8, and 15. Subsequent cycles: total dose is 1.5-1.8 mg/m^2 per 4-week cycle, given as 3 divided doses on Days 1, 8, and 15.

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Besponsa (Inotuzumab Ozogamicin) is necessary to ensure the benefits outweigh its risks. Pfizer, Inc., submitted a Biologic Licensing Application (BLA) 761040 for inotuzumab ozogamicin with the proposed indication for the treatment of relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL). The most serious risks associated with Besponsa are hepatotoxicity, including: 1) hepatic veno-occlussive disease/sinusoidal obstruction syndrome (VOD/SOS) and, 2) increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality. The applicant did not submit a proposed REMS or risk management plan with this application.

The risk of hepatotoxicity can be severe, life threatening and sometimes fatal VOD/SOS. VOS and infectious complications are the common causes for increased post-transplant non-relapse mortality. These risks will be included in the label as a boxed warning and the strategies to mitigate these risks will be communicated in Warnings and Precautions. Besponsa improved CR rate and improved MRD negativity rate. The improved outcomes translated to higher eligibility rate for HSCT, the only known curative option in this setting. Given that relapse/refractory ALL is a fatal disease and Besponsa provides an additional treatment option and the improved outcomes may allow patients to proceed to HSCT, DRISK and the Division of Hematology Products (DHP) agree that a REMS is not necessary for Besponsa to ensure the benefits outweigh the risks.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Besponsa (inotuzumab ozogamicin) is necessary to ensure the benefits outweigh its risks. Pfizer submitted BLA 761040 for Besponsa with the proposed indication for the treatment of relapsed or refractory B-cell precursor ALL. This application is under review in DHP. The applicant did not submit a proposed REMS or risk management plan with this application.

2 Background

2.1 PRODUCT INFORMATION

Besponsa (inotuzumab ozogamicin), an NME,[a] is an antibody-drug conjugate (ADC). The ADC consists of 3 components: 1) the recombinant humanized IgG4 kappa antibody inotuzumab, with the specific target human CD22, 2) N-acetyl-gamma-calicheamicin that causes DNA double strand-breaks, and 3) an acid-cleavable linker that covalently attaches N-acetyl-gamma-calicheamicin to inotuzumab. When Besponsa binds to the CD22 antigen on malignant B-cells, it is internalized into the cell, where the cytotoxic agent, calicheamicin, is released to destroy the cell. Besponsa is proposed for the treatment of relapsed or refractory B-cell precursor ALL. Besponsa is supplied as (b) (4) mg single-dose vial and administered through

[a] Section 505-1 (a) of the FD&C Act FDAAA factor (F): Whether the drug is a new molecular entity.

intravenous infusion over one hour. For the first cycle, the recommended total dose is 1.8 mg/m^2 per 3-4 week cycle, given as 3 divided doses on day 1, day 8, and day 15. For subsequent cycles, the recommended total dose is 1.5-1.8 mg/m^2 (depending on the patient's remission status) per 4-week cycle, given on days 1, 8, and 15. For patients proceeding to HSCT, the recommended duration of treatment with BESPONSA is 2 – 3 cycles. For patients not proceeding to HSCT (b) (4) additional cycles of treatment, up to 6 cycles, may be administered.[b] Besponsa is not currently approved in any jurisdiction.

2.2 Regulatory History

The following is a summary of the regulatory history for Besponsa BLA 761040 relevant to this review:

- March 25, 2013: Orphan Drug Designation granted.
- November 2014: pre-BLA meeting IND 065658
- October 15, 2015: Breakthrough Designation granted.
- December 20, 2016: BLA 761040 rolling review final module received.
- February 21, 2017: Priority Review Designation granted.
- April 5, 2017: A Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for Besponsa. There are no plans at this time for an Advisory Committee meeting.

3 Therapeutic Context and Treatment Options

3.1 Description of the Medical Condition

ALL is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs. In the United States, it is estimated there will be approximately 5,970 new cases and 1,440 deaths in 2017 (including both children and adults).[1] The median age of diagnosis for ALL is 14 years with 58% of patients diagnosed at younger than 20 years. The risk for developing ALL is highest in children younger than 5 years of age. The risk then declines slowly until the mid-20s, and begins to rise again slowly after age 50. About 11% of patients are diagnosed at 65 years or older. ALL represents about 20% of all leukemia among adults. In contrast to the more favorable outcomes with childhood ALL, in which the overall survival is more than 80% at 5 years, therapeutic progress has been slow in adult ALL with an average survival of 35% in patients age 18 years to 60 years.[2]

ALL can be classified into 3 distinct groups based on immune-phenotyping, which includes precursor B-cell ALL, mature B-cell ALL, and T-cell ALL. In adult patients with ALL, 25% are T-cell lineage ALL. Within the B-cell lineage, the profile of cell surface markers differs by different stages of B-cell maturation,

[b] Section 505-1(b) of the FD&C Act FDAAA factor (D): The expected or actual duration of treatment with the drug.

which include early precursor B-cell (early pre-B-cell), pre-B-cell, and mature B-cell. The CD22 antigen is present on B cells in most patients (>90%) with precursor B-cell ALL. Inotuzumab is a monoclonal antibody that binds to CD22 antigen.

Relapsed or refractory B-cell ALL is frequently a fatal disease. Older adult patients have the poorest outcome with a 5-year overall survival (OS) rate of 24% for patients between the ages of 40 and 59 years, and even lower rate of 18% for patients between the ages of 60 and 69 years. The median survival time in adults with relapsed or refractory B-cell was reported to be about 3-6 months.[c]

Complete response rates in the front-line treatment setting range from 60-85%; only 30-40% of adults achieve long-term disease-free survival with disease recurrence being the primary reason for failure.[2] Despite the associated mortality and morbidity, allogeneic HSCT after salvage therapy offers the best opportunity for long-term survival.

3.2 Description of Current Treatment Options

The primary goal of remission induction therapy in relapsed or refractory ALL (R/R ALL) is achievement of complete remission (CR) or sufficient cytoreduction to enable allogenic HSCT.

Options for remission induction therapy for R/R ALL include immunotherapeutic approaches such as the monoclonal antibody blinatumomab (Blincyto, approved by FDA December 2014), or cytarabine-based or other combination chemotherapies. By the use of intensive combination chemotherapies, CR is achieved in 25-46% of patients with R/R ALL. Long-term survival was less than 1% for patients treated with chemotherapy alone and only 36% for those who could proceed to HSCT.[3]

For most patients with R/R ALL, the current recommendation is blinatumomab rather than chemotherapy based approaches[3]s preference is based on a randomized, multicenter, international trial[5] which demonstrated that blinatumomab resulted in improved rates of CR, overall survival (OS), and event free survival (EFS) when compared with chemotherapy regimens (CR 34 % versus 16%; OS 7.7 months versus 4.0 months; EFS at 6 months 31% versus 12%). Similar outcomes were demonstrated in other trials of Blinatumomab in patients with R/R ALL.

Blinatumomab is a bispecific T cell engager monoclonal antibody directed at both CD19 on precursor B cell ALL tumor cells and CD3 on cytotoxic T cells. It was approved with a REMS in December 2014 to treat Philadelphia chromosome-negative relapsed or refractory B-cell precursor ALL. The REMS program is a communication plan. The goals of the REMS are to:

- Informing healthcare providers (HCP) about the risk of cytokine release syndrome (CRS) which may be life-threatening or fatal.

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

- Informing HCP about the risk of neurological toxicities which may be severe, life-threatening, or fatal.
- Informing pharmacists, who will prepare and dispense Blinatumomab, and nurses, who will administer Blinatumomab, about the risk of preparation and administration errors associated with use of Blinatumomab.

The Blinatumomab labeling includes boxed warnings of cytokine release syndrome and neurological toxicities, each of which may be life-threatening or fatal. Potential neurologic events include encephalopathy, convulsions, speech disorders, disturbances in consciousness, delirium, and coordination and balance issues.

4 Benefit Assessment[d]

The efficacy of Besponsa in patients with R/R ALL was evaluated in a randomized, open-label, international, multicenter, phase 3 study. Eligible patients were 18 years or older with Philadelphia chromosome-negative or Philadelphia chromosome-positive relapsed or refractory B-cell precursor ALL. 326 patients were randomized to receive Besponsa (N=164) or Investigator's choice of chemotherapy[e] (N=162). Sixty-six percent of patients had received one prior treatment and 33% of patients had received two prior treatments. The median age was 47 years (range: 18-79 years), 63% of patients had a duration of first remission <12 months and 18% of patients had undergone a HSCT.

The primary endpoints were complete remission (CR)/complete remission with incomplete hematologic recovery (CRi), for which 218 patients were randomized, and overall survival (OS). The secondary endpoints included minimal residual disease (MRD) negativity, duration of remission (DoR), HSCT rate, and progression–free survival (PFS). Besponsa improved CR rate (73% in the Besponsas arm versus 31% in the control arm) and improved MRD negativity rate (77% in the Besponsa arm versus 38% in the control arm). These improved rates of CR/CRi and MRD negativity made more patients eligible for HSCT which offers the best opportunity for long-term survival. There were 47% of patients in the Besponsa arm received HSCT compared to 20% of patients in the control arm. The mean duration of OS was 10.4 months in the Besponsa arm versus 8 months in the control arm. Medical reviewers concluded that Besponsa has clinically meaningful activity in R/R ALL. Even though OS failed to show statistical significance, the statistical review team concluded patients who received Besponsa had a better survival outcome than patients in the control arm after 18 months for those patients receiving HSCT. The summary of statistical review team[6] is:

[d] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[e] Investigator's choice of chemotherapy: FLAG (FLudarabine+Ara-C(cytarabine)+Granulocyte colony-stimulating factor), cytarabine +mitoxantrone, or high dose cytarabine (HIDAC).

- CR/CRi : Besponsa demonstrated a statistically significant improvement in the primary endpoint. This improvement was consistent across all pre-specified stratification subgroups.
- Improvement is consistent for all secondary endpoints.
- OS failed to show statistical significance, however, the statistics reviewer[6] observed the OS results were confounded by HSCT; no difference was found between the study arms in subjects not receiving HSCT. There were fewer early deaths in the control arm after HSCT, but patients in the Besponsa arm had a better survival outcome than patients in the control arm after 18 months.

5 Risk Assessment & Safe-Use Conditions[f]

The safety of Besponsa was evaluated in a randomized, open-label, international, and phase 3 study (Study 1). Among 326 patients, 164 patients were randomized to receive Besponsa and 143 patients received Investigator's choice of chemotherapy. [g] Nineteen patients in the control arm were not treated.

5.1 Deaths

The rate of all deaths was 74% in the Besponsa arm compared to 85% in the control arm. Overall post-transplant mortality is similar in the Besponsa arm (60%) to the control arm (58%). But non-relapse mortality was higher in the Besponsa arm (38%) versus the control arm (27%). In the Besponsa arm, there were 5 fatal VOD cases and 6 cases of VOD were ongoing at the time of death due to other mechanisms.[4] VOD with multi-organ failure (MOF) has mortality rate of 84%.[4] Deaths due to other mechanisms often included MOF. The additional 6 cases with VOD ongoing at time of death were likely caused by VOD leading to MOF and death. The medical reviewer concluded that hepatotoxicity and VOD/SOS are the primary factors in increased post-transplant non-relapse mortality in the Besponsa arm. [7]

5.2 Serious Adverse Reactions

1) Hepatotoxicity, including Veno-occlusive Liver Disease/Sinusoidal Obstruction Syndrome (VOD/SOS)

VOD/SOS was reported in 13% patients (N=22) in the Besponsa arm, compared to <1% patients (N=1) in the control arm, with grade ≥3 reactions in 11% patients (N=11) in the Besponsa arm versus <1% in the control arm. Grade 3/4 aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

[g] Investigator's choice of chemotherapy: FLAG (FLudarabine+Ara-C(cytarabine)+Granulocyte colony-stimulating factor), cytarabine +mitoxantrone, or high dose cytarabine (HIDAC).

bilirubin abnormal liver tests occurred in 4%, 4%, and 5% patients in both arms. Among all 164 patients, VOD/SOS was reported in 3% patients during therapy or in follow-up without a post-study HSCT. Among the 77 patients who proceeded to a subsequent HSCT, VOD/SOS event was reported in 23**%** patients. Five of 18 VOD/SOS events that occurred post-HSCT were fatal.

2) Myelosuppression/Cytopenia and Infections

Besponsa has serious adverse reactions (SARs) of myelosuppression, infection, and hemorrhage. These SARs are comparable to slightly better compared to the control arm as shown as Table 1.

Table 1

	Myelosuppression/ cytopenia	neutropenia	febrile neutropenia	infection	fatal infection	pneumonia	hemorrhage (epistaxis)	infusion related reactions
Besponsa	83%	49%	27%	49%	5%	8%	34% (15%)	2%
Control	89%	46%	19%	77%	5%	8%	29% (8%)	1%

6 Expected Post-market Use

Besponsa, if approved, will be administered in the inpatient and outpatient infusion settings and the likely prescribers will be oncologists/hematologists.

7 Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for Besponsa beyond routine pharmacovigilance and labeling**.**

8 Discussion of Need for a REMS

The Clinical Reviewer recommends approval of Besponsa on the basis of the efficacy and safety information currently available. They are recommending a boxed warning regarding hepatotoxicity, including VOD/SOS and increased risk of post-transplant non-relapse mortality, which the sponsor accepted. The proposed boxed warning is shown as below:

"Warning: hepatotoxicity, including hepatic veno-occlusive disease (VOD) also known as sinusoidal obstruction syndrome (SOS) and increased risk of post-hematopoietic stem cell transplant (HSCT) non-relapse mortality.

See full prescribing information for complete boxed warning.

- *Hepatotoxicity, including fatal and life-threatening VOD occurred in patients who received Besponsa.*

- *A higher post-HSCT non-relapse mortality rate occurred in patients receiving Besponsa, resulting in a higher day 100 post-HSCT mortality rate."*

When considering whether a REMS is necessary to ensure that the benefits outweigh the risks of a particular drug, DRISK considers factors such as the size of the patient population, the seriousness of the disease, the expected benefit of the drug, the expected duration of treatment, the seriousness of known or potential adverse reactions, and whether the drug is a NME. Relapsed or refractory B-cell ALL is frequently a fatal disease. Older adult patients have the poorest outcome with a 5-year overall survival (OS) rate of 24% for patients between the ages of 40 and 59 years and even lower rate of 18% for patients between the ages of 60 and 69 years. The median survival time in adults with relapsed or refractory B-cell was reported to be about 3-6 months.

The medical reviewers concluded that Besponsa has clinically meaningful activity in relapsed/refractory ALL. Besponsa improved CR rate (73% in the Besponsa arm versus 31% in the control arm) and improved MRD negativity rate (77% in the Besponsa arm versus 38% in the control arm). The improved outcomes translated to higher eligibility rate for HSCT, the only known curative option in this setting. Forty-seven percent of patients were able to proceed to transplant after receiving Besponsa, compared with 20% of patients with chemotherapy. [7] Even though OS failed to show statistical significance, the statistical review team concluded patients who received Besponsa had a better survival outcome than patients in control arm after 18 months for those patients receiving HSCT. The duration of Besponsa therapy is from 2 cycles to 6 cycles.

Besponsa has serious adverse reactions (SARs) of myelosuppression, infection, and hemorrhage. These SARs are comparable to slightly better compared to the control arm as discussed in Section 5.

Besponsa will likely be provided in treatment centers and hospitals and its use will be under the supervision of oncologists/hematologists who are expected to be familiar with the risks and managements of SARs.

The serious safety concern with Besponsa is heptatoxicity, including severe, life threatening and sometimes fatal VOD/SOS. VOS is also a primary factor in increased post-transplant non-relapse mortality as discussed in the during the mid-cycle presentation.[7]

The risk of VOD associated with cyclophosphamide, intravenous busulfan, clofarabine, and azathioprine is communicated in Prescribing Information of "Warnings and Precautions" or "Adverse Reaction". There is a boxed warning for dacarbazine: Hepatic necrosis has been reported (see Warnings). None of these drugs have required a REMS to address the VOD risk.

To mitigate the risks of VOD associated with Besponsa, the following strategies are communicated in the warnings and precautions section of the proposed prescribing information:

- Identification of patients most at risk for VOD. Risk factors for development of VOD are last bilirubin ≥ULN prior to follow-up HSCT, dual alkylators, busulfan containing regimen, prior HSCT, (b) (4), prior history of liver disease, and number of treatment cycles.
- In patients proceeding to HSCT, the recommended duration of treatment is 2 cycles; a third cycle may be considered for those patients who do not achieve a CR or CRi and MRD negativity after 2 cycles.
- Monitor closely for toxicities post HSCT, including signs and symptoms of infection and VOD.
- (b) (4)

The risks of hepatotoxicity, including heptatic VOD, and increased risk of post-HSCT non-relapse mortality associated with Besponsa will be included in the label as a boxed warning. In general, healthcare providers who treat R/R ALL are familiar with the risks of hepatic VOD and the importance of patient selection and monitoring. Given that R/R ALL is a fatal disease and the clinically meaningful activity of Besponsa, DRISK and DHP agree that a REMS is not necessary to ensure the benefits of Besponsa outweigh its risks.

9 Conclusion & Recommendations

Based on the available data, DRISK and DHP agree that a REMS is not necessary for Besponsa to ensure the benefits outweigh the risks. Should DHP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK so that the risk:benefit analysis can be reevaluated.

10 Appendices

10.1 References

[1] www.cancer.org/cancer/acute lymphocytic leukemia. Accessed online April 20, 2017.

2 www.emedicine.medscape.com, Acute Lymphoblastic Leukema, Mrch 30, 2016

3 Larson RA treatment of relapsed or refractory acute lymphoblastic leukemia in adults, UpToDate, updated March 13, 2017

4 Harper JL, Veno-occlusive hepatic disease, www.emedicine.medscape.com, updated March 21, 2016

5 Kantarjian H, Stein A, et al Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia, N Engl J Med 2017; 376(9):836

6 Xu, Q. Statistical mid-cycle presentation for Besponsa BLA 761040, March 21, 2017

7 Wroblewski, T. Clinical mid-cycle presentation for Besponsa BLA 761040, March 21, 2017

8. Cyclophosphoamide Prescribing Information, dated November 2013.

9. Busulfex (busulfan) for injection Prescribing Information, dated January 2015.4

10. Clolar (clofarabine) injection Prescribing Information, dated September 2014.

11. Azathioprine (Imuran) 50 mg tablets Prescribing Information, dated February 2014.

12. Dacarbazine for injection Prescribing Information, dated November 2014.

13. Blincyto Prescribing Information, dated December 2014.

14. Proposed Prescribing Information for Besponsa BLA 761040, updated April 19, 2017.

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/s/

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05/19/2017

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