CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761036Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management Review

Application Type	BLA
Application Number	761036
Submission #	1, June 5, 2015
OSE RCM #	2015-1326
Reviewer Name(s)	Joyce Weaver, Pharm.D., Risk Management Analyst (RMA) Division of Risk Management (DRISK)
DRISK Team Leader	Naomi Redd, Pharm.D., Acting RMA Team Leader, DRISK
Division Director	Cynthia LaCivita, Pharm.D., Acting Division Director, DRISK
Review Completion Date	October 19, 2015
Subject	Review of an NME to determine if a REMS is necessary
Established Name	Daratumumab
(Proposed) Trade Name	Darzalex
Applicant	Janssen Research and Development, LLC
Therapeutic Class	IgG1κ human monoclonal antibody (mAb) that binds to CD38 protein
Formulation(s)	100mg/5mL and 400mg/20mL (20mg/mL) Injection
Dosing Regimen	16mg/kg body weight weekly weeks 1 to 8, every 2 weeks, weeks 9 to 24, then every 4 weeks onwards
Proposed Indication(s)	Treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent

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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 (NME) daratumumab is necessary to ensure the benefits of this product outweigh its risks. Janssen submitted a Biologic Licensing Application # 761036 for daratumumab with the proposed treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent. The applicant did not submit a proposed REMS with this application but proposed voluntary risk management activities.

DRISK and the Division of Hematology (DHP) agree that a REMS is not needed to ensure the benefits of daratumumab exceed its risks.

1 Introduction

Janssen submitted a Biologic Licensing Application # 761036 for Darzalex (daratumumab) for the proposed treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent (IMiD) or who are double refractory to a PI and an immunomodulatory agent. The applicant did not propose a REMS with this application but proposed voluntary risk management activities.

2 Background

2.1 PRODUCT INFORMATION

Daratumumab is a first-in-class new therapeutic biological product subject to Agency review as an NME. Daratumumab was granted breakthrough therapy designation for the treatment of multiple myeloma. The proposed indication is for treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody (mAb) that binds to CD38 protein expressed at high levels on cells in multiple myeloma tumor cells.

The proposed dosage regimen is 16 mg/kg body weight administered by intravenous infusion weekly for weeks 1 to 8, every 2 weeks for weeks 9 to 24, and then every 4 weeks onward until disease progression. Administration is intended to be carried out in any healthcare facilities able to administer infusions and manage infusion reactions.[1]

Daratumumab is not currently licensed in any jurisdiction.

[1] Draft labeling, section 2.1

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for BLA 761036 relevant to this review:

- 04/01/2013: Fast Track designation granted
- 05/01/2013: Breakthrough Therapy designation granted
- 05/06/2013: Orphan drug designation granted
- 07/31/2013: Multidisciplinary Breakthrough Therapy meeting to gain agreement on requirements across disciplines for the initial BLA
- 12/12/2014: Pre-BLA format and content meeting
- 03/31/2015: Pre-BLA topline clinical results meeting
- 04/24/2015: Agreement on rolling submission schedule
- 06/05/2015: Clinical Study Reports and Datasets for Studies MMY2002 and GEN501 submitted
- 9/24/2015: Mid-cycle communication meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data a REMS was not needed for daratumumab.

3 Medical Condition and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Multiple myeloma, an incurable malignancy of plasma cells, is the most prevalent hematologic malignancy in patients over 65 years of age. The expected number of new cases in the United States in 2015 is 26,850, with 11,240 expected deaths due to the disease.[2] About one-half of newly diagnosed patients survive beyond 5 years.[3] Advanced multiple myeloma tumors can invade bone, causing bone pain and fractures. Other complications include frequent infections, anemia, and bleeding.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

Often patients with multiple myeloma are treated with drug therapy. Some patients receive high-dose drug therapy and peripheral blood or bone marrow stem cell transplantation. Numerous drugs are FDA-approved for treatment of multiple myeloma (bortezomib, carfilzomib, carmustine, cyclophosphamide, doxorubicin, lenalidomide, panobinostat, plerixafor, pomalidomide, thalidomide). The 2015 National Comprehensive Cancer Network (NCCN) guidelines for multiple myeloma list the following combinations as preferred regimens for primary induction therapy in patients who are not candidates for transplantation:

- Lenalidomide/low-dose dexamethasone
- Melphalan/prednisone/bortezomib

[2] SEER data provided by NCI at http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed October 2, 2015.

[3] SEER data provided by NCI at http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed October 2, 2015.

- Melphalan/prednisone/lenalidomide
- Melphalan/prednisone/thalidomide

New treatment regimens with PIs (bortezomib, carfilzomib) and immunomodulatory agents (lenalidomide, pomalidomide, and thalidomide) have improved outcomes for patients with multiple myeloma, but the disease remains incurable. Most patients relapse after treatment with PIs and immunomodulatory agents and ultimately die of the disease. The median overall survival of patients refractory to PIs and immunomodulatory agents is less than a year. The ultimate failure of treatment regimens points to the need for additional therapy options to treat patients with relapsed disease.[4]

Lenalidomide, pomalidomide, and thalidomide have REMS to mitigate the risk of teratogenicity.

4 Benefit Assessment

The efficacy of Darzalex for the treatment of patients with relapsed and refractory multiple myeloma was explored in two open-label studies, in 148 total patients with relapsed and refractory multiple myeloma who received the proposed dose of 16 mg/kg.

In the first study, 106 patients with relapsed and refractory multiple myeloma received 16 mg/kg Darzalex until disease progression. The median patient age was 63.5 years (range, 31 to 84 years), 49% were male and 79% were Caucasian. Patients had received a median of 5 prior lines of therapy. Eighty percent of patients had received prior autologous stem cell transplantation. Prior therapies included bortezomib (99%), lenalidomide (99%), pomalidomide (63%) and carfilzomib (50%). Ninety-five percent of patients were refractory to both a PI and an immunomodulatory agent.

Thirty-one of 106 patients (29%) had a response to daratumumab. Most of the responses were categorized as having a very good partial response (10 patients) or a partial response (18 patients). The median time to response was 1 month. The median duration of response was 7.4 months. The lower end of the 95% confidence interval was 5.5 months, and the upper end of the 95% confidence interval had not been reached at the time of submission.

In the second study, 42 patients with relapsed and refractory multiple myeloma received 16 mg/kg Darzalex until disease progression. The median patient age was 64 years (range, 44 to 76 years), 64% were male and 76% were Caucasian. Patients in the study had received a median of 4 prior lines of therapy. Seventy-four percent of patients had received prior autologous stem cell transplantation. Prior therapies included bortezomib (100%), lenalidomide (95%), pomalidomide (36%) and carfilzomib (19%). Sixty-four percent of patients were refractory to both a PI and an immunomodulatory agent. Thirty-six percent of patients responded to Darzalex. The median duration of response was not reached; over one-half of patients who initially responded remained progression–free at 12 months.

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4 Mohty B, El-Cheikh J, Yakoub-Agha I, et al. Treatment strategies in relapsed and refractory multiple myeloma: a focus on drug sequencing and 'retreatment' approaches in the era of novel agents. Leukemia 2012;26(1):73-85.

5 Risk Assessment

The most frequently reported adverse reactions with daratumumab in clinical testing were infusion reactions, fatigue, nausea, back pain, anemia, neutropenia, and thrombocytopenia. The most frequently reported Grade 3 or higher adverse reactions were anemia, neutropenia, thrombocytopenia, and infusion reactions.[5]

The most important safety issues known at this time with daratumumab are infusion reactions and interference with serological testing (see section 5.2).

5.1 Infusion Reactions

Infusion reactions were reported in about one-half of the patients who received daratumumab in clinical testing. Most (91%) reactions occurred with the first infusion. Infusion reactions commonly manifested as nasal congestion, chills, cough, rhinitis, throat irritation, dyspnea, and nausea. In more severe cases (4%), more severe manifestations occurred, including bronchospasm, hypertension, and hypoxia.

Pre-treatment is recommended with antihistamines, antipyretics, and corticosteroids to prevent infusion reactions. Interruption of the infusion is recommended to manage the events. Treatment of all patients with corticosteroids on the two days following an infusion is recommended to prevent delayed infusion reactions.

5.2 Interference with Serological Testing

Red blood cells have surface CD38. Daratumumab binds with CD38 on red blood cells and causes a positive indirect Coombs test that can persist for 6 months following the last infusion. Daratumumab binding can interfere with the detection of antibodies to minor antigens. The determination of the patients ABO blood type and Rh type are not impacted by the binding.

There is also interference with monitoring response to treatment. This interference can impact the determination of complete response in patients with IgG kappa myeloma protein. There is no interference with determination of other response (partial response and very good partial response).

6 Expected Postmarket Use

Daratumumab will likely be used in settings that administer infusions to treat cancer; e.g., hospitals, cancer infusion centers. The settings in which daratumumab will be administered and the healthcare professionals that will administer daratumumab have the knowledge, training as well as other resources to deal with infusion reactions.[6]

Healthcare providers and blood bank personnel need to know of the capacity of daratumumab to interfere with serological testing. This capacity to interfere with serological testing is not unique to

[5] Data from the 120-day safety update report are not available

[6] Draft labeling, section 2.1

daratumumab, and blood banks deal with other drugs that cause positive indirect Coombs tests. Daratumumab's capacity to interfere with serological testing is clinically important in that the patient population receiving daratumumab is subject to frequent serological testing to manage their disease and treatment. Recent articles published in the medical literature have highlighted this issue.[7]

The interference with determination of complete response to treatment with daratumumab will require prescribers to use other findings, in addition to serological testing, to determine response.

7 Discussion of Need for a REMS

DRISK believes a REMS is not needed to ensure the risks of daratumumab outweigh its risks. Results from clinical testing to date show an acceptable safety profile and clinically important antitumor activity in a pre-treated population of multiple myeloma patients. The most important risk observed with daratumumab is infusion reactions. While these reactions can be severe, they are manageable, and are within the knowledge and expertise of the HCPs treating patients with cancer. This safety issue will be communicated through labeling (i.e., inclusion of the event in *Warnings and Precautions*), and additional requirements are not necessary to maintain a favorable benefit–risk balance.

The interference with serological testing does not present a sufficient risk to outweigh the benefits of daratumumab. This safety issue will be communicated through labeling (i.e., inclusion of the event in *Warnings and Precautions*), and additional requirements are not necessary to maintain a favorable benefit–risk balance. We note that articles have already appeared in the medical literature regarding this interference. A REMS is not necessary to ensure the benefits outweigh this risk for daratumumab. We do not oppose the sponsor's proposal to communicate with stakeholders, including outreach to the oncology community and to blood bank personnel (not part of a REMS).

8 Risk Management Activities Proposed by the Applicant

[7] Chapuy C, Nicholson R, Aguad M, et al. Resolving the daratumumab interference with blood compatibility testing. Transfusion. 2015 Jun;55(6 Pt 2): 1545–54.

Oostendorp M, Lammerts van Bueren JJ, Doshi P, et al. When blood transfusion medicine becomes complicated due to interference by monoclonal antibody therapy. Transfusion. 2015 Jun;55(6 Pt 2):1555-62. doi: 10.1111/trf.13150. Epub 2015 May 18.

8.1 Other Proposed Risk Management Activities for Infusion Reactions

The sponsor did not propose any risk management activities beyond routine measures for infusion reactions. The sponsor believes that proposed labeling and routine reporting/pharmacovigilance are sufficient to mitigate the risks and preserve benefits in the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a PI and an immunomodulatory agent or who are double refractory to a PI and an immunomodulatory agent.

8.2 Other Proposed Risk Management Activities for Interference with Serologic Testing

The applicant proposed the following voluntary risk management activities for interference with serologic testing:

Healthcare Professional Communication

The sponsor's oncology sales specialists will distribute a brochure describing the biologic basis and mitigation strategies for interference with serologic testing to relevant health care professionals (HCPs, e.g., medical oncologists, hematologists, oncology nurses). The brochure will also be available on the product website (Darzalex.com).

Blood Bank Communication

Information about the interference with serologic testing will be presented at a meeting in late October of the Biomedical Excellence for Safer Transfusion (BEST) Collaborative. The meeting is attended by blood bank directors, laboratory supervisors and administrators, transfusion specialists, cellular therapy and blood banking professionals, medical technologists and donor recruiters. The sponsor will also present an educational session at the American Association of Blood Banks (AABB) Annual Meeting in late October 2015 to inform the larger transfusion medicine community on interference with serologic testing and potential mitigation strategies. A summary of the session will be sent to all AABB members. The sponsor is working with AABB to disseminate a separate bulletin containing information regarding interference and mitigation with all blood banks. The sponsor's oncology medical science liaisons will distribute information about the interference with serologic testing and potential mitigation strategies to blood bank HCPs to ensure awareness in the transfusion medicine community. To facilitate comprehensive outreach to blood bank HCPs, oncology medical science liaisons will use a listing of AABB-accredited blood banks and communication from oncology sales specialists regarding other blood bank sites.

Patient Materials

HCPs treating patients with daratumumab will be supplied with cards for distribution to patients at treatment initiation identifying them as daratumumab-treated patients. These wallet-sized cards can be carried by patients to facilitate red blood cell transfusion support if such intervention is needed at locations where their treating health care professional may not practice. The patient information leaflet also alerts and reminds patients to notify HCPs when in need of a blood transfusion that they are currently receiving daratumumab.

9 Conclusion & Recommendations

Based on the available data, the benefit–risk profile is acceptable and a REMS is not necessary for daratumumab to ensure the benefits outweigh the risks. DRISK does not object to the communication (not part of a REMS) planned by the sponsor to provide information to stakeholders about interference with serologic testing. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRISK if new safety information becomes available that changes the benefit–risk profile; this recommendation can be reevaluated.

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/s/

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