APPLICATION NUMBER:

761078Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
<table>
<thead>
<tr>
<th>Application Type</th>
<th>BLA</th>
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<td>Application Number</td>
<td>761078</td>
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<thead>
<tr>
<th>Reviewer Name(s)</th>
<th>Elizabeth Everhart, MSN</th>
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<tr>
<td>Team Leader</td>
<td>Doris Auth, Pharm D</td>
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<td>Division Director</td>
<td>Cynthia LaCivita, Pharm D</td>
</tr>
<tr>
<td>Review Completion Date</td>
<td>April 13, 2017</td>
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<tr>
<td>Subject</td>
<td>Evaluation of Need for a REMS</td>
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<tr>
<th>Established Name</th>
<th>Avelumab</th>
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<tbody>
<tr>
<td>Trade Name</td>
<td>Bavencio</td>
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<tr>
<td>Name of Applicant</td>
<td>EMD Serono, Inc.</td>
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<tr>
<td>Therapeutic Class</td>
<td>Programmed death ligand-1 (PD-L1) blocking antibody</td>
</tr>
<tr>
<td>Formulation(s)</td>
<td>Injection</td>
</tr>
<tr>
<td>Dosing Regimen</td>
<td>10 mg/kg as intravenous infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity</td>
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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 avelumab is necessary to ensure the benefits outweigh its risks. EMD Serono submitted a Biologic Licensing Application (BLA #761078) for Avelumab with the proposed indication of the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy. The serious risks associated with avelumab are mainly immune-mediated adverse events (imAEs) that include pneumonitis, hepatitis, colitis, endocrinopathies, and nephritis. The applicant did not submit a proposed REMS, but submitted a European Risk Management Plan (EU RMP) which proposes to mitigate these risks with labeling and routine pharmacovigilance.

DRISK and the Division of Oncology Products 1 agree that a REMS is not needed to ensure the benefits of avelumab outweigh its risks. Metastatic urothelial cancer is a serious medical condition with very few treatment options and a poor outcome. As avelumab is dosed every two weeks, this provides an opportunity for patients to be evaluated for toxicities during these treatment visits. In addition, avelumab has recently received FDA accelerated approval for metastatic Merkel Cell carcinoma and joins three other drugs in the same class (nivolumab, pembrolizumab, and atezolizumab) with similar imAEs that are communicated via Warnings and Precautions in the label.

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) avelumab is necessary to ensure the benefits outweigh its risks. EMD Serono submitted a Biologic Licensing Application (BLA #761078) for Avelumab with the proposed indication of the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy. This application is under review in the Division of Oncology 1 (DOP 1). The applicant did not submit a proposed REMS, but submitted a European Risk Management Plan (EU RMP) which proposes to mitigate these risks with labeling and routine pharmacovigilance.

2 Background

2.1 PRODUCT INFORMATION

Avelumab, a new molecular entity (NME)\(^a\), is a programmed death ligand-1 (PD-L1) blocking monoclonal antibody proposed for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy. Avelumab is dosed at 10 mg/kg as an intravenous infusion over 60 minutes every 2 weeks until disease progression or unacceptable toxicity\(^b\). Avelumab received FDA accelerated approval for metastatic Merkel Cell Carcinoma in March, 2017 (BLA 761049).

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

\(^b\) Section 505-1 (a) of the FD&C Act: FDAAA factor (D): The expected or actual duration of treatment with the drug.
2.2 REGULATORY HISTORY
The following is a summary of the regulatory history for BLA/761078 relevant to this review:

- 10/06/2016: Pre-BLA meeting held; details of planned BLA submission discussed
- 12/27/2016: BLA 761078 submission for the treatment of patients with locally advanced or metastatic urothelial cancer (UC) with disease progression on or after platinum-based therapy received
- 03/09/2017: A Post 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 Avelumab

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION
Bladder cancer is the 6th most common cancer in the United States; in 2017, it is estimated that the number of new cases will 79,030 and will be associated with 16,870 deaths. \(^d\) Transitional cell carcinomas (also called urothelial carcinomas, (UC)) are the most common type of bladder cancer.

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS
Standard of care treatment options for patients with locally advance or metastatic UC that recurs after platinum-based chemotherapy includes chemotherapy regimens such as gemcitabine and cisplatin or methotrexate, vinblastine, doxorubicin, and cisplatin. Patients often do not respond well to these options\(^1\); National Comprehensive Cancer Network (NCCN) guidelines for locally advanced or metastatic disease also recommend participation in clinical trials of new agents.\(^2\)

In May, 2016, atezolizumab, a biologic agent in the same PD-L1 inhibitor class, received accelerated approval for the treatment locally advanced or metastatic urothelial carcinoma that had disease progression after prior platinum-containing chemotherapy. In February, 2017, nivolumab, another biologic in the PD-1 class, received accelerated approval for patients with locally advanced or metastatic urothelial carcinoma that have disease progression during or following platinum containing chemotherapy, or patients that have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing therapy. While these approvals have added options for this patient population, there remains an unmet medical need.

\(^c\) Section 505-1 (a) of the FD&C Act: FDAAA factor (A): The estimated size of the population likely to use the drug involved.

\(^d\) 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.
4 Benefit Assessment

The efficacy of avelumab in metastatic UC was demonstrated in the UC cohorts of Trial 2, an open-label, single-arm, multi-center study that enrolled 242 patients with locally advanced or metastatic UC with progression on or after platinum-based chemotherapy, or who had disease progression within 12 months of treatment with a platinum-based neoadjuvant or adjuvant chemotherapy regimen. The primary efficacy endpoint was confirmed objective response rate (ORR), with duration of response (DOR) as an important additional efficacy outcome. Efficacy evaluations were determined in the primary analysis in patients followed for a minimum of 13 weeks and 6 months at the time of analysis.

Table 1 below summarizes the results of Trial 2 of the 226 UC patients with a minimum of 13 weeks of follow-up.

Table 1: Efficacy results of Trial 2

<table>
<thead>
<tr>
<th>Efficacy Endpoints</th>
<th>≥ 13 Weeks Follow Up</th>
<th>≥ 24 Weeks Follow Up</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N=226</td>
<td>N=161</td>
</tr>
<tr>
<td><strong>Confirmed Overall Response Rate (ORR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall Response Rate n (%) (95% CI)</td>
<td>29 (12.8%) (8.8, 17.9)</td>
<td>25 (15.5%) (10.3, 22.1)</td>
</tr>
<tr>
<td>Complete Response (CR) n (%)</td>
<td>9 (4.0%)</td>
<td>9 (5.6%)</td>
</tr>
<tr>
<td>Partial Response (PR) n (%)</td>
<td>20 (8.8%)</td>
<td>16 (9.9%)</td>
</tr>
<tr>
<td><strong>Duration of Response (DOR)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median, weeks (range)</td>
<td>NE (6.1+ to 71.7+)</td>
<td>NE (6.1+ to 71.7+)</td>
</tr>
</tbody>
</table>

CI: Confidence interval; NE: Not evaluable; + denotes a censored value

5 Risk Assessment & Safe-Use Conditions

Avelumab is part of a class of immunomodulating antibodies called checkpoint inhibitors. There are two primary targets of checkpoint inhibitors, programmed cell death (PD-1) and the ligand associated with it PD-L1, and Cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Inhibiting these targets results in activation of the immune system, thereby attacking malignant cells; because of this immune system activation, these agents are associated with immune-mediated adverse events (imAEs). Avelumab is a PD-L1 inhibitor; two other PD/PD-L1 inhibitors approved for metastatic or locally advanced UC are

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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.

Reference ID: 4083933
nivolumab and atezolizumab; pembrolizumab is a third PD/PD-L1 inhibitor approved in other malignancies. These three agents are associated with similar imAEs as seen with avelumab.

In addition to the imAEs described below and communicated in the Warnings and Precautions section of the label, the risk of infusion-related reactions, which occurred in 29% (71/242) patients with locally advanced or metastatic UC, including one grade 3 reaction, and the potential for embryo-fetal toxicity will also be communicated in the Warnings and Precautions section of the prescribing information.

The safety information described in this review is from the pooled safety results of the clinical trial that enrolled 1738 with a variety of tumor types, including 242 patients with locally advanced or metastatic UC, who received avelumab at 10 mg/kg every two weeks. This review uses the label modified from the recently approved BLA #761049 for avelumab in patients with Merkel Cell carcinoma.

5.1 IMMUNE-MEDIATED PNEUMONITIS
In the clinical trial of avelumab, immune-mediated pneumonitis, including fatal cases, was seen. Immune-mediated pneumonitis was seen in 1.2% (21/1738) of patients in the clinical trial, including 1 CTCAE grade 5 (death), 1 grade 4, and 5 grade 3 cases of pneumonitis. Among all cases (21 in total) of immune-mediated pneumonitis of any grade, resolution occurred in 12 (57%) of the cases by the time of data cut-off.

5.2 IMMUNE-MEDIATED HEPATITIS
In the clinical trial of avelumab, immune-mediated hepatitis occurred in 0.9% (16/1738) patients treated with avelumab, with one case of CTCAE grade 5 (death) and 11 patients with CTCAE grade 3 immune-mediated hepatitis. Of the total of 16 patients with immune-mediated hepatitis of any grade, resolution of hepatitis occurred in 9 (56%) of patients at the time of data cut-off.

5.3 IMMUNE-MEDIATED COLITIS
Immune-mediated colitis was seen in patients in the clinical trial of avelumab, with 1.5% (26/1738) of patients receiving avelumab experiencing immune-mediated colitis, including 7 (0.4%) experiencing CTCAE grade 3 colitis. Resolution occurred in 18 (70%) of all patients with any grade colitis at the time of data cut-off.

5.4 IMMUNE-MEDIATED ENDOCRINOPATHIES
Several immune-mediated events affecting the endocrine system such as adrenal insufficiency, thyroid disorders, and type 1 diabetes mellitus occurred during the clinical trial of avelumab. They are described below.

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• **Adrenal insufficiency**: Avelumab can cause adrenal insufficiency; patients should be monitored and treated as appropriate. In the clinical trial, adrenal insufficiency occurred in 0.5% (8/1738) patients who received avelumab, including 1 CTCAE grade 3 event.

• **Autoimmune thyroid disorders**: Avelumab can cause thyroid disorders; in the clinical trial, 6% (98/1738) patients developed immune-mediated thyroid disorders, including 3 (0.2%) CTCAE grade 3 events.

• **Type 1 diabetes mellitus**: In study 001, type 1 diabetes mellitus without an alternative cause was seen in 0.1% (2/1738) patients in the clinical trial.

### 5.5 IMMUNE-MEDIATED NEPHRITIS AND RENAL DYSFUNCTION

Avelumab can cause immune-mediated nephritis and renal dysfunction; immune-mediated nephritis occurred in 0.1% (1/1738) patients in the clinical trial.

### 5.6 OTHER IMMUNE-MEDIATED ADVERSE REACTIONS

In study 001, there were cases of clinically significant immune-mediated adverse reactions occurring at an incidence of less than 1% of the 1738 patients in the clinical trial. Those adverse reactions included immune-mediated fatal cases of myocarditis, psoriasis, arthritis, exfoliative dermatitis, erythema multiforme, pemphigoid, hypopituitarism, uveitis, Guillain-Barre syndrome, pancreatitis, and systemic inflammatory response.

#### 5.6.1 Safe-Use Conditions

The adverse events described above are related to the immune system activation of PD-L1 blockade. The prescribing information includes recommendations for patient monitoring, dose modification/discontinuation, as well as corticosteroid administration as appropriate.

### 6 Expected Postmarket Use

Avelumab will be given in the outpatient clinic setting or infusion center by healthcare providers, typically medical oncologists, who should be familiar with the immune-mediated risks associated with avelumab. The avelumab will be given every 2 weeks, this dosing schedule also supports frequent monitoring of patients for the toxicities.

### 7 Risk Management Activities Proposed by the Applicant

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

### 8 Discussion of Need for a REMS

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 seriousness of the known or potential adverse events, and the likely prescribers. Locally advanced or metastatic urothelial cancer is a life-threatening condition.
with poor five-year median survival with few treatment options; the duration of response in the clinical studies is a clinically meaningful benefit to patients with advanced or metastatic UC.

The Clinical Reviewer recommends approval of avelumab on the basis of the efficacy and safety information currently available, including the durability of response to treatment. DRISK and the Division of Oncology Products (DOP)-I agree that a REMS is not necessary to ensure the benefits of avelumab outweigh its risks.

Similar to other drugs in this class, the imAEs of avelumab will be communicated through Warnings and Precautions section of labeling. To further mitigate these toxicities, the label also recommends monitoring, dose reductions, and treatment of imAEs with corticosteroids as appropriate. Additionally, as avelumab must be dosed every two weeks, this provides an opportunity for patients to be evaluated for toxicities during these treatment visits.

9 Conclusion & Recommendations

DRISK and DOP 1 agree that the benefit-risk profile for avelumab is favorable for the treatment of locally advanced or metastatic UC, and therefore, a REMS is not necessary for avelumab to ensure the benefits outweigh the risks. At the time of this review, label negotiations were ongoing. Please notify DRISK if new safety information becomes available that changes the benefit-risk profile so that this recommendation can be reevaluated.

10 Materials Reviewed

The following is a list of materials informing this review:

11 References


3 EMD Serono. Draft label for Avelumab, April, 2017.


5 Buchbinder, EI and Desai, A. CTLA-4 and PD-1 Pathways: Similarities, Differences, and Implications of Their Inhibition. American Journal of Clinical Oncology; Issue: Volume 39(1), February 2016, p 98–106

6 EMD Serono. Draft label for Avelumab, March, 2017
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIZABETH E EVERHART
04/13/2017

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04/15/2017
Concur