Office Director Decisional Memo

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<thead>
<tr>
<th>Date</th>
<th>(electronic stamp)</th>
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<tbody>
<tr>
<td>From</td>
<td>Edward Cox, MD MPH</td>
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<tr>
<td>Subject</td>
<td>Office Director Decisional Memo</td>
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<tr>
<td>BLA #</td>
<td>761046</td>
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<tr>
<td>Applicant</td>
<td>Merck Sharpe and Dohme</td>
</tr>
<tr>
<td>Date of Submission</td>
<td>November 22, 2015</td>
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<tr>
<td>PDUFA Goal Date</td>
<td>October 21, 2016</td>
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<tr>
<td>Proprietary Name</td>
<td>Zinplava</td>
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<tr>
<td>Dosage Form(s) / Strength</td>
<td>Intravenous 1000 mg/40 mL vial</td>
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<tr>
<td>Applicant Proposed Indication</td>
<td>Prevention of <em>Clostridium difficile</em> infection (CDI) recurrence in patients 18 years or older receiving antibiotic therapy for CDI</td>
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<tr>
<td>Action for NME:</td>
<td>Approval</td>
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<tr>
<td>Approved Indication/Population(s)</td>
<td>To reduce recurrence of <em>Clostridium difficile</em> infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence</td>
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</table>

<table>
<thead>
<tr>
<th>Material Reviewed/Consulted OND Action Package, including:</th>
<th>Names of discipline reviewers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Officer Review</td>
<td>Shrimant Mishra MD MPH</td>
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<td></td>
<td>Hiwot Hiruy MD PhD</td>
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<td>Statistical Review</td>
<td>Cheryl Dixon PhD</td>
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<td>Pharmacology Toxicology Review</td>
<td>Terry Miller PhD</td>
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<td>OPQ Review</td>
<td>Rashmi Rawat PhD</td>
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<tr>
<td>Microbiology Review</td>
<td>Kerian Grande Roche</td>
</tr>
<tr>
<td>Clinical Pharmacology Review</td>
<td>Yang He PhD</td>
</tr>
</tbody>
</table>
BLA 761046, Bezlotoxumab for injection

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<thead>
<tr>
<th>OPDP</th>
<th>Adam George PharmD</th>
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</thead>
<tbody>
<tr>
<td>OSI</td>
<td>John Lee MD</td>
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<tr>
<td>CDTL Review</td>
<td>Dmitri Iarikov MD PhD</td>
</tr>
<tr>
<td>OSE/DMEPA</td>
<td>Sevan Kolejian PharmD</td>
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<td>OSE/DRISK</td>
<td>Mona Patel PharmD</td>
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<tr>
<td>Office of Biotechnology Products</td>
<td>Jibril Abdus-Samad, PharmD</td>
</tr>
</tbody>
</table>

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE=Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
1. Benefit-Risk Assessment

**Benefit-Risk Summary and Assessment**

In my assessment, the Applicant has provided substantial evidence to support the effectiveness of bezlotoxumab in reducing recurrence of *Clostridium difficile* infection (CDI) in patients 18 years of age or older who are receiving antibacterial drug treatment for CDI and are at a high risk for CDI recurrence.

As noted in this review, there were a number of significant challenges in interpreting the data from the two Phase 3 trials conducted to demonstrate the safety and efficacy of bezlotoxumab. The pre-specified primary endpoint in both trials was the proportion of subjects with CDI recurrence during the 12-week (Day 85 ± 5 days) follow-up period after infusion of study drug. The Agency had raised concerns about the CDI recurrence endpoint prior to the commencement of the second trial while the first trial was still ongoing. The concern with the CDI recurrence endpoint is that it ignores the potential impact of the investigational drug on initial clinical cure and counts patients who do not have initial clinical cure of their presenting CDI episode as successes (i.e., not having a recurrence). The Agency had noted that if an imbalance in the initial cure rates is seen, the effect of the study drug on recurrence can be very difficult to interpret. The Agency recommended that the Applicant use a primary endpoint of global cure (sustained clinical response) defined as clinical cure of the initial CDI episode and absence of CDI recurrence.

In both Phase 3 trials, recurrence rates in the 12-week follow up period were lower in patients who received bezlotoxumab compared to those who received placebo in addition to SOC antibacterial drugs for treatment of CDI. However, the imbalance in initial cure rates, especially the lower cure rates seen in the bezlotoxumab arm in Study P001, make it difficult to interpret the efficacy of bezlotoxumab using recurrence rate as the primary endpoint. Global cure or sustained clinical response is a valid measure of the efficacy of bezlotoxumab and is the more interpretable endpoint because it considers both initial cure of the CDI and absence of recurrence. To be a success, a patient needs to achieve clinical cure of the CDI episode and not have a recurrence. While sustained clinical response was not the Applicant’s pre-specified primary endpoint, in both trials, there was a favorable treatment effect with bezlotoxumab for the pre-specified primary endpoint of reducing recurrences and in both trials, there was also an imbalance in the initial cure rate (one in favor of bezlotoxumab, the other against bezlotoxumab); in the setting of an imbalance in the initial cure rate the recurrence endpoint is not a sound endpoint, making it reasonable to evaluate the trials using sustained clinical response as the endpoint.
Additional post hoc analyses were performed to allow for a better assessment of the negative impact of bezlotoxumab, if any, on initial clinical cure, seen in Study P001. It does appear that the impact on clinical cure might be a reflection of the protocol-specified definition of clinical cure that stipulated the duration of SOC as no more than 14 days and required resolution of diarrhea in the two days immediately following the bezlotoxumab infusion. While a negative impact on clinical cure cannot be definitively ruled out based on the information available (e.g., a delay in achieving cure), it does not appear to cause a significant worsening of the baseline CDI episode. The difference in clinical cure between the treatment arms does resolve with extending the allowed duration of SOC to 3 weeks and the finding of reduction in recurrence rates remains significant. As there is no longer a difference in clinical cure rates using this expanded definition, the effect on global cure/sustained clinical response is also significant.

Based on the effect on sustained clinical response and the additional analyses that allow for an extended duration of SOC to 3 weeks post infusion, enabled by analyses of the primary endpoint in each of the two trials that achieved their pre-specified criteria (with the shortcomings described above), the evidence supports the efficacy of bezlotoxumab for the reduction of recurrence of CDI.

There are no currently approved therapies for reducing the risk of recurrences in patients with CDI. Recurrent CDI is a significant cause of morbidity and there is an unmet medical need for this condition. Approximately 20% of patients develop a recurrence after the resolution of the first episode of CDI and with a recurrent episode, the risk of subsequent recurrences is greater than that after the first episode.

Although the overall safety profile of bezlotoxumab was acceptable, it is important to note that the adverse reaction of heart failure was more common in patients who received bezlotoxumab, especially in those with congestive heart failure.

Given the uncertainties in assessing any potential negative impact on clinical cure and the safety signal for cardiac failure, it is prudent that bezlotoxumab only be indicated in patients at high risk for CDI recurrence. The Indications and Usage section of labeling will specify that bezlotoxumab is only approved for patients at high risk of recurrence of CDI and the Warnings and Precautions and the Adverse Reactions sections will include information regarding the risk of cardiac failure.

The following table has been adapted from the table in the CDTL and Division Director reviews.
### Analysis of Condition

**Clostridium difficile** infection (CDI) is a toxin mediated disease caused by the bacterium *C. difficile*. The clinical manifestations of the disease can vary from mild diarrhea to severe colitis that could result in intestinal perforation and death. A total of 453,000 cases of CDI resulting in 29,000 deaths are estimated to occur annually in the United States. About 20% of patients with CDI develop recurrence following resolution of the first episode and the risk of recurrence increases once the disease recurs.

### Current Treatment Options

Currently, there are no approved therapies to reduce or prevent CDI recurrence. There is an unmet medical need for this clinical condition.

### Benefit

Efficacy of bezlotoxumab in reducing CDI recurrence was supported by two Phase 3 trials in which bezlotoxumab was compared to placebo in addition to SOC in both arms (Studies P001 and P002). Bezlotoxumab was administered as a single 10 mg/kg infusion at any time during CDI SOC therapy. In both trials the proportion of patients who did not have CDI recurrence through 12 weeks after study drug infusion was higher in the bezlotoxumab arm in the full analysis set (FAS) population. However, interpretation of this endpoint was challenging as it was based on the FAS population and as such classified all clinical failures of the initial CDI episode as successes as they could not develop recurrences. In both trials, there was an imbalance in the initial cure rates of the baseline CDI. In Study P001, the cure rate was 77.5% in the bezlotoxumab and 82.8% in the placebo arm. In Study P002, cure rate of the initial CDI episode was 82.5% in the bezlotoxumab and 77.8% in placebo arm. Additional analyses showed that by week 3 post infusion, the cure rates in all study arms in both trials were similar and that the negative impact, if any on initial cure did not result in clinically significant worsening of the baseline CDI.

There are some uncertainties if bezlotoxumab can have a negative impact on clinical cure of the baseline CDI. However, data available so far do not suggest a significant clinical worsening of the baseline CDI episode and the finding may be related to the specific definitions used in the protocol. Both trials showed a benefit in reducing recurrence of CDI in patients who had received bezlotoxumab in addition to SOC.

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<thead>
<tr>
<th>Dimension</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
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<td>CDI is a serious disease that can be associated with mortality and significant morbidity. In addition to the initial episode of CDI, recurrent CDI is a cause of significant morbidity.</td>
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<td>Current Treatment Options</td>
<td>Currently, there are no approved therapies to reduce or prevent CDI recurrence.</td>
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<td>Benefit</td>
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<td><strong>Risk</strong></td>
<td>The overall rates of adverse events and deaths in patients who received bezlotoxumab were similar to that seen in placebo recipients. A higher number of serious adverse events (SAEs) related to heart failure were seen in the bezlotoxumab arm (2.2%) compared to the placebo arm (0.9%). These SAEs were mainly observed in patients with baseline congestive heart failure (CHF). There were also more deaths in patients with baseline CHF in the bezlotoxumab arm, 19.5% (23/118), compared to the placebo arm, 12.5% (13/104). The reason for this finding is unclear. Bezlotoxumab is a fully human monoclonal antibody and tissue cross-reactivity studies did not suggest any potential for cardiac toxicity. The finding also does not appear to be temporally related to bezlotoxumab administration or to volume overload.</td>
<td>Bezlotoxumab had an overall favorable safety profile. However, a higher number of adverse events related to heart failure and a higher number of deaths in subjects with baseline CHF were noted in bezlotoxumab-treated patients in comparison to placebo.</td>
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<tr>
<td><strong>Risk Management</strong></td>
<td>A risk of heart failure associated with bezlotoxumab use, especially in patients with underlying CHF cannot be ruled out based on the available data.</td>
<td>Labeling will include a warning about the risk of heart failure, especially in those with baseline CHF and a recommendation to reserve the use of bezlotoxumab in patients with CHF to situations when the benefit clearly outweighs the risk. No additional risk-mitigation measures except for routine postmarketing pharmacovigilance are considered necessary at this point.</td>
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2. Further discussion to support regulatory action

Background

Bezlotoxumab is a fully human monoclonal IgG1 antibody directed against *C. difficile* toxin B developed as a therapy to prevent recurrence of CDI. It is administered as a single 10 mg/kg infusion at any time during CDI antibacterial therapy.

The review team has reviewed the issues in detail in their respective disciplines with regard to the safety and efficacy of bezlotoxumab. For a detailed discussion of BLA 761046, the reader is referred to the individual discipline specific reviews. In addition, the Cross-Discipline Team Leader’s review and the Division Director’s review summarize key issues in the BLA submission. This memorandum will focus on select issues from the review.

Product Quality

The product quality reviewers recommend approval of the BLA for bezlotoxumab. Bezlotoxumab is produced from a [some additional testing of the master cell bank is warranted and will be addressed as a postmarketing commitment. The stability data in the BLA support a shelf life of 24 months for the drug product when stored at 2 - 8°C.]

Nonclinical Pharmacology / Toxicology

The pharmacology-toxicology reviewer recommends approval for this BLA. In single and repeat-dose studies in mice with IV bezlotoxumab administered for 14 days (5 doses/3 day interval) and 21 days (2 doses/14 day interval), no clinical signs or evidence of toxicity were seen at doses up to 50 and 125 mg/kg respectively, and at approximately 2.5 and 7 times greater exposure than that seen in humans after a single 10 mg/kg dose. No targets of bezlotoxumab toxicity were identified in any of the animal toxicology studies. Bezlotoxumab does not appear to be immunogenic, however there is potential interference noted in the anti-drug antibody (ADA) assay in the presence of high serum antibody levels. Tissue cross-reactivity studies conducted in vitro in at least 38 mouse and human tissues with bezlotoxumab showed no reactivity (positive staining) of tissue samples.

Clinical Pharmacology
The clinical pharmacology reviewer for this BLA recommends approval. The elimination half-life \((t½)\) of bezlotoxumab is approximately 19 days in CDI patients. Bezlotoxumab is degraded into small peptides and individual amino acids through protein catabolism. Bezlotoxumab can be detected in stools from a limited number of CDI patients after IV administration. No exposure-response relationship for efficacy or safety was seen. No dose adjustment is needed with renal or hepatic impairment or based on gender/age when using the proposed weight-based dosing.

**Clinical Microbiology**

The clinical microbiology reviewer for this BLA recommends approval. Bezlotoxumab binds to *C. difficile* toxin B. Bezlotoxumab does not bind to toxin A. In vitro studies in cell-based assays using Vero cells or Caco-2 cells, suggest that bezoitoxumab neutralizes the toxic effects of toxin B. Higher concentrations of bezlotoxumab were needed to neutralize purified toxin B of ribotypes 027 and 078 (hypervirulent ribotypes) compared to other ribotypes.

**Clinical / Statistical - Efficacy**

The clinical reviewer for this BLA recommends approval for this BLA. The statistics reviewer performed an excellent review and defers to the clinical team regarding approval. As described in the risk benefit summary, there were a number of significant challenges in interpreting the data from the two Phase 3 trials conducted to demonstrate the safety and efficacy of bezlotoxumab. The pre-specified primary endpoint in both trials was the proportion of subjects with CDI recurrence during the 12-week (Day 85 ± 5 days) follow-up period after infusion of study drug. The Agency had raised concerns about the CDI recurrence endpoint prior to the commencement of the second trial while the first trial was still ongoing. The concern with the CDI recurrence endpoint is that it ignores the potential impact of the investigational drug on initial clinical cure and counts patients who do not have initial clinical cure of their presenting CDI episode as successes (i.e. not having a recurrence). The Agency had noted that if an imbalance in the initial cure rate is seen, the effect of the study drug on recurrence can be very difficult to interpret. The Agency recommended that the Applicant use a primary endpoint of global cure (sustained clinical response) defined as clinical cure of the initial CDI episode and absence of CDI recurrence.

In both Phase 3 trials, recurrence rates in the 12-week follow up period were lower in patients who received bezlotoxumab compared to those who received placebo in addition to SOC antibacterial drugs for treatment of CDI. However, the imbalance in initial cure rates, especially the lower cure rates seen in the bezlotoxumab arm in Study P001, make it difficult to interpret the efficacy of bezlotoxumab using recurrence rate as the primary endpoint. Global cure or sustained clinical response is a valid measure of the efficacy of bezlotoxumab and is the more interpretable endpoint because it considers both initial cure of the CDI and absence of recurrence. To be a success, a patient needs to achieve clinical cure of the CDI episode and not have a recurrence. While sustained clinical response was not the Applicant’s pre-specified
primary endpoint, in both trials, there was a favorable treatment effect with bezlotoxumab for
the pre-specified primary endpoint of reducing recurrences and in both trials there was also an
imbalance in the initial cure rate (one in favor of bezlotoxumab, the other against
bezlotoxumab); in the setting of an imbalance in the initial cure rate, the recurrence endpoint is
not a sound endpoint making it reasonable to evaluate the trials using sustained clinical
response as the endpoint.

Additional post hoc analyses were performed to allow for a better assessment of the negative
impact of bezlotoxumab, if any, on initial clinical cure, seen in Study P001. These additional
analyses constituted a major amendment to the BLA and the review clock was extended by
three months. From these analyses, it does appear that the impact on initial clinical cure might
be a reflection of the protocol-specified definition of clinical cure that stipulated the duration
of SOC as no more than 14 days and required resolution of diarrhea in the two days
immediately following the bezlotoxumab infusion. While a negative impact on initial clinical
cure cannot be definitively ruled out based on the information available (e.g., a delay in
achieving cure), it does not appear to cause a significant worsening of the baseline CDI
episode. The difference in initial clinical cure between the treatment arms does resolve with
extending the allowed duration of SOC to 3 weeks post infusion and the finding of reduction
in recurrence rates remains significant. As there is no longer a difference in clinical cure rates
using this expanded definition, the effect on global cure/sustained clinical response is also
significant.

Based on the effect on sustained clinical response and the additional analyses that allow for an
extended duration of SOC to 3 weeks post infusion, enabled by analyses of the primary
endpoint that achieved their pre-specified criteria (with the shortcomings described above), the
evidence supports the efficacy of bezlotoxumab for the reduction of recurrence of CDI in
patients at high risk of recurrence.

Safety

The safety reviewer finds that the safety of bezlotoxumab has been adequately characterized.
A total of 1790 subjects received bezlotoxumab either alone or in combination with actoxumab
of whom 1741 were exposed to a bezlotoxumab dose of 10 mg/kg. Among all randomized
subjects, the proportions of subjects who discontinued the study and the reasons for
discontinuation were balanced between study arms. The mortality rate was similar between
the treatment arms and placebo; 7.1% (56/786), 6.6% (51/777), and 7.5% (59/781) in the
bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arms, respectively. The incidence
of Serious Adverse Events (SAEs) was similar between the treatment arms with the exception
of SAEs related to cardiac failure (includes the terms cardiac failure, cardiac failure acute,
cardiac failure congestive, and cardiac failure chronic) and were reported in 17/786 (2.2%),
patients in the bezlotoxumab arm and 7/781 (0.9%) in the placebo arm.
Additional analyses were performed on the subgroup of patients with CHF. Approximately 14% of patients had CHF across the three arms; 118/786 (15%), 103/777 (13.3%), and 104/781 (13.3%) in the bezlotoxumab, actoxumab plus bezlotoxumab, and placebo arms, respectively. In patients with CHF, the mortality rate was higher in the bezlotoxumab arm, 23/118 (19.5%), and actoxumab plus bezlotoxumab arm, 18/103 (17.5%), compared to the placebo arm, 13/104 (12.5%). The incidence of SAEs in subjects with CHF was also higher in the bezlotoxumab arm, 63/118 (53.5%) compared to actoxumab plus bezlotoxumab, 46/103 (44.7%), and placebo arm, 50/104 (48%).

The product labeling includes a Warning and Precaution statement on the risk of cardiac failure including a statement that in patients with CHF, bezlotoxumab should be reserved for use when the benefits clearly outweigh the risks.

**Advisory Committee Meeting**

This BLA was discussed at a meeting of the Antimicrobial Drugs Advisory Committee on June 9, 2016. The committee was asked to vote on the following question:

Has the applicant provided substantial evidence of the safety and effectiveness of bezlotoxumab for the prevention of *C. difficile* infection recurrence in patients aged 18 years and older?

There were 10 Yes votes, 5 No votes, and 1 abstention.

Many committee members were of the opinion that benefit with regard to recurrence had been demonstrated and some members expressed concerns regarding the potential negative impact on clinical cure. Some committee members noted that the trials were well conducted and that there was an unmet need for products that can reduce recurrence rates. Several committee members recommended that the product be labeled for use only in high-risk patients and that labeling should include a warning related to use in patients with underlying CHF. Among committee members who voted no, there was concern that the efficacy finding was not convincing and that there was a safety signal. Some committee members recommended that an additional trial should be conducted to better delineate the treatment effect.

**Pediatrics**

The Applicant requested deferral of pediatric studies because adult trials were completed and the product is ready for approval. The Applicant has proposed a PK and safety study in pediatric patients from ≥1 year to <18 years of age. A waiver will be granted in pediatric patients younger than a year of age as CDI is not common in pediatric patients less than a year of age making studies in this age group not feasible.
The pediatric study plan was discussed with the Pediatric Review Committee (PeRC) and found to be acceptable.

**Labeling**

The product labeling includes a Warning and Precautions statement on heart failure and notes that in patients with a history of congestive heart failure, bezlotoxumab should be reserved for use when the benefits outweigh the risks. Bezlotoxumab is indicated to reduce the recurrence of CDI in patients at high risk of CDI recurrence. There is also a Limitation of Use statement noting that bezlotoxumab is not indicated for the treatment of CDI and should only be used in conjunction with antibacterial treatment for CDI. For the reasons described in the Benefit-Risk Summary, the efficacy tables in the Clinical Studies section focus on sustained clinical response results but also provide some additional information on clinical failure and recurrence.

**Risk Evaluation and Mitigation Strategies (REMS)**

This application does not include a REMS. The product labeling including the package insert and patient package insert provides adequate information on the product, its risk and benefits, and recommendations on how to mitigate risks of adverse effects.

**Postmarketing Requirements and Commitments**

In addition to the required pediatric study, there are several postmarketing commitments (PMC) to obtain additional information related to product quality. These PMCs are enumerated in the approval letter.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

EDWARD M COX
10/21/2016