CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761049Orig1s000

MEDICAL REVIEW(S)

Office of Hematology and Oncology Products Memorandum

BLA	761049
Applicant	EMD Serono
Link to EDR	\\CDSESUB1\evsprod\BLA761049\761049.enx
Submission Date(s)	7/06/2016, 9/02/2016, 9/23/2016
Submission Type	New Molecular Entity
Priority or Standard	Priority
Proposed Trade Name	BAVENCIO
Established Name	Avelumab
Dosage Form and Strength	10 mg/kg every two weeks
Route of Administration	Intravenous
Proposed Indication	Treatment of patients with metastatic Merkel cell carcinoma
Associated INDs	119394; 115747
Regulatory Project Manager	Idara Udoh
Clinical Reviewer	Denise Casey
Cross Discipline Team Leader	Suzanne Demko

The clinical review of safety and efficacy is complete and has been added to the BLA Multi-disciplinary Review and Evaluation, which will be uploaded to DARRTS when it is finalized. The clinical review team recommends accelerated approval under Subpart E (21CFR601.41) for avelumab for the treatment of patients with metastatic Merkel cell carcinoma at a dose of 10 mg/kg intravenously every two weeks. Please refer to the Multi-disciplinary Review and Evaluation for additional details.

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/s/

DENISE A CASEY
02/23/2017

SUZANNE G DEMKO
02/23/2017
I concur with the action proposed in this memo by the clinical reviewer and the content of the referenced review.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 761049 **Applicant: EMD Serono** **Stamp Date: September 23, 2016**

Drug Name: Avelumab **NDA/BLA Type: 1**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic common technical document (eCTD).	X			
2.	Is the clinical section legible and organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
LABELING					
6.	Has the applicant submitted a draft prescribing information that appears to be consistent with the Physician Labeling Rule (PLR) regulations and guidances (see http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm	X			
SUMMARIES					
7.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
8.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
9.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
10.	Has the applicant submitted a benefit-risk analysis for the product?	X			Section 6 of the Clinical Overview (Module 2.5)
11.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).				505 (b)(1)
505(b)(2) Applications					
12.	If appropriate, what is the relied upon listed drug(s)?			X	
13.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the listed drug(s)/published literature?			X	
14.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSAGE					
15.	If needed, has the applicant made an appropriate attempt to determine the correct dosage regimen for this product (e.g., appropriately designed dose-ranging studies)? Study Number: EMR 100070-001 Study Title: A Phase I, open-label, multiple-ascending dose trial to investigate the safety, tolerability, pharmacokinetics, biological and clinical activity of avelumab (MSB0010718C) in subjects with metastatic or locally advanced solid tumors and expansion to selected indications	X			Module 5.3.5.2 contains CSR for Study EMR100070-01. (Study 001) Sections 11.3 and 11.4 of the CSR provide descriptions of the pharmacokinetic and pharrmacodynamic evaluations of avelumab.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	Sample Size: 1490 (53 in dose-escalation; 1437 across 16 expansion cohorts) as of data cut-off date November 20, 2015 Treatment Arms: Dose-escalation with expansion cohorts Location in submission: Module 5.3.5.2				
EFFICACY					
16.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1:Study EMR100070-003 (Part A) Indication: Metastatic Merkel Cell carcinoma (mMCC) after failing at least one line of chemotherapy	X			Merkel Cell Carcinoma is a rare tumor. The single pivotal study includes safety and efficacy data for 88 patients. Study 001 will provide supportive safety data.
17.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			EMD Serono is seeking accelerated approval based on durable objective response rate.
18.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
19.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
20.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
21.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			
22.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
23.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dosage (or dosage range) believed to be efficacious?			X	
24.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			
25.	Has the applicant submitted the coding dictionary[2] used for	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted

	Content Parameter	Yes	No	NA	Comment
	mapping investigator verbatim terms to preferred terms?				
26.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
27.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
28.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
29.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
30.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Avelumab was granted orphan drug designation for the treatment of patients with Merkel Cell Carcinoma and is exempt from the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c).
PREGNANCY, LACTATION, AND FEMALES AND MALES OF REPRODUCTIVE POTENTIAL USE					
31.	For applications with labeling required to be in Pregnancy and Lactation Labeling Rule (PLLR) format, has the applicant submitted a review of the available information regarding use in pregnant, lactating women, and females and males of reproductive potential (e.g., published literature, pharmacovigilance database, pregnancy registry) in Module 1 (see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307 htm)?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			

as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

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	Content Parameter	Yes	No	NA	Comment
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?		X		For Study 003, there were seven sub-investigators for whom no disclosure information was submitted and there is no Form 3454 stating that the sponsor acted with due diligence but was unable to obtain the information. An Information Request was sent to the Sponsor on November 8, 2016, to obtain this information.
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. None

Reviewing Medical Officer Date

Clinical Team Leader Date

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/s/

DENISE A CASEY
11/14/2016