Midcycle Review Meeting - April 16, 2009 - Gammaplex

M E M O R A N D U M

Meeting DATE/Time: April 16, 2009 1:00PM
FROM: Debbie Cordaro DBA/RPM
Kelly Lewis, DBA/RPM
THROUGH: Malgorzata (Margaret) Mikolajczyk
RE: 125329/0
Attendees: Michael Kennedy, Debbie Cordaro, Kelly Lewis, Malgorzata (Margaret) Mikolajczyk, Pei Zhang, Evi Struble, Ann Gaines, Craig Zinderman, Tony Hawkins, Hon Sum Ko, Xue Lin, Lisa Stockbridge, Doug Frazier, Dorothy Scott, Iftekhar Mahmood, Mahmood Farshid
SPONSOR: BPL
Product: IGIV 5%
Action Due date: September 17, 2009
To: 125329/0 File
SUBJECT: Midcycle Review Meeting
Discussion:

- The items on the Midcycle Checklist were reviewed
- The members were asked if they had any comments on their portion of the submission:
  - BIMO: Tony Hawkins - Four (4) clinical sites to inspect. Target date for completion: June 25, 2009. No major issues so far.
  - Pharmacovigilance: Ann Gaines/Craig Zinderman – The PVP included plans to provide, in PSURs, a detailed analysis an discussion of AEs reported for each of a list of specified AE types known to be associated with IVIGs in general. No specific serious safety signals were identified in the clinical trial or PK study with this product and no additional PV activities beyond routine AE reporting are planned.
  - Clinical: Hon Sum – We need an IR for the submission of analysis for adverse events and comparison for use of product after patient has reached steady state.
  - For both IgG2 and IgG4, the median changes from trough levels during prior IGIV therapy in those who had available data showed decrease, particularly with IgG4. Please (a) present an analysis of the pharmacokinetics of IgG subclasses, and (b) account for the decline of both subclasses, particularly IgG4, over Gammaplex® therapy, as this product is purported to provide normal distribution of IgG subclasses for replacement.
  - IgG subclass levels in Gammaplex – IgG4 levels? Doug checked and provided the normal subclass percentages to compare with Gammaplex subclass distribution

IgG SUBCLASS	AVERAGE %	GAMMAPLEX %
1	66	-(b)(4)-

IgG SUBCLASS	AVERAGE %	GAMMAPLEX %
2	23	-(b)(4)-
3	7	-(b)(4)-
4	4	-(b)(4)-

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  - Pharm/Tox: Evi Struble – No issues
  - Statistics: Mary Lin – The primary endpoint was met but the applicant needs to indicate why a N/A was reported instead of a calculated value. The statistical plan is not applicable to the data. IR for one letter ready comment. 5 subjects discontinued, 3 from adverse events. We need more information on the 2 patients who discontinued.
  - Clinical Pharmacology: Iftekhar Mahmood –will provide issues for an IR.
  - CMC: Michael, Margaret, Doug, and Pei
    - Michael is reviewing reworking, reprocess, and recovery. He will have an IR.
    - Doug – stability is adequate. For the -(b)(4)- assay, there is variation at the -(b)(4)- end. Is PS80 derived from plants or animals? *Post meeting note: PS80* -(b)(4)- *derived.*
    - *Margaret – PS80: Storage of PS80, storage and expiration date determination after opening. – IR. ----(b)(4)----- study needs to be completed as a possible PMC.* Post meeting note: Decided with Michael not to ask for this. ----------(b)(5)----------. Are the bioburden and endotoxin alert and action limit excursions processed as deviations? Validate the upper limits on -(b)(4)- times and -(b)(4)-. Describe rationale for study design for filtration of -------(b)(4)---------- solution after ----------(b)(4)----------. We do not agree with use of -(b)(4)- instead of -(b)(4)- solution or with a ----(b)(4)------ measurement in future temperature control for ----------(b)(4)---------- studies.
    - Pei – Viral Validation, no major issues, but need an IR for the calculation of ---(b)(4)---. B19 testing – -(b)(4)- screening, NAT. Will check for cutoff.
  - DMPQ: Jim Crim – The inspection has been scheduled for May 15-27, 2009. There will be 2 inspectors from DMPQ and 2 OBRR reviewers participating. Will look at container closure issue.

  Action Items:
- Hon Sum needs to complete PREA forms
- Lisa Stockbridge is aware that she needs to re-review the proprietary name submitted to IND. She asked to be updated as to the anticipated review completion date so she can complete the review within 90 days of the approval.
- Dot Scott will provide to Margaret/Michael:
  - an example of the memo to justify why this review did not go to BPAC. This document needs to be signed by Dov, Jay and Bob Yetter.
  - an example of the CBER lot release testing plan so they can draft a plan for this submission.
- Margaret/Michael will follow up on the requirement for a lot release protocol.
- IR for clinical, statistical, and CMC issues.

  The committee was reminded that under FDAAA we will now be expected to do our extensive label review approximately 2 weeks after the mid-cycle meeting. The members were advised to begin their extensive editing of the label as soon as possible to be prepared to participate in the extensive labeling discussion.