U.S. FOOD & DRUG ADMINISTRATION

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (CBER)
Division of Epidemiology (DE)

MEMORANDUM

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To: Wilson Bryan, MD
Director, Office of Tissues and Advanced Therapeutics

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Director, DE, OBE

Subject: Review of Pharmacovigilance Plan

Sponsor: CSL Behring

Product: Haegarda; C1 esterase inhibitor subcutaneous (Human)

Application Type/Number: BLA/STN 125606/0

Proposed Indication: Routine prophylaxis to prevent hereditary angioedema attacks in adolescent and adult patients (b) (4)

Submission Date: June 30, 2016

Action Due Date: June 30, 2017

1. **Objective**
   The purpose of this review is to assess the adequacy of the pharmacovigilance plan (PVP) based on the safety profile of Haegarda®.

2. **Product Information**
   a. **Product description**
   Haegarda is a concentrated, (b) (4) formulation of human plasma-derived C1 esterase inhibitor (C1-INH) for prophylaxis against exacerbations of hereditary angioedema (HAE). The sponsor currently markets Berinert, an intravenous (IV) plasma-derived C1-INH indicated for treatment and pre-procedure prevention of acute attacks of HAE. Both products contain the same active substance (b) (4) in the same facilities.

b. Proposed dosing regimen(s) and formulation(s)

Haegarda is a subcutaneous formulation labeled for self-administration at a dose of 60 IU/kg twice weekly in adolescents and adults (b) (4)

3. Materials Reviewed

Materials reviewed in support of this assessment include:

- Sponsor's Pharmacovigilance plan (PVP) (Section 1.16 of 125606/0 in GSReview)
- Sponsor's Proposed label (Section 1.14 of 125606/0 in GSReview)
- Sponsor's Clinical Summary of Safety (Section 2.7.4 of 125606/0 in GSReview)
- Sponsor's Clinical Summary of Safety 4-Month Safety Update (Section 2.7.4 of 125606/0 in GSReview)
- Safety issues identified by Clinical reviewer (email)
- Review memo Nov 10, 2015 on final report of post-marketing requirement (PMR) for (b) (4)) by Faith Barash, MD
- Periodic Safety Update Report (PSUR) for Berinert/CSL830 (Oct 21, 2016)
- Literature search in PubMed

4. Summary of Prior Marketed Experience

- Haegarda has not been approved for use in the US or any other country, so there is no post-marketing experience data. However, since Haegarda and Berinert are both derived from human plasma and manufactured in the same facilities (b) (4) , the post-marketing experience of Berinert is relevant to the safety of Haegarda.
- The PMR for Berinert was a registry (Study CE1145_5002) which collected data on 15,000 infusions in 318 patients for four years post-approval. Adverse events were mostly mild or moderate such as injection site reactions. No cases of hypersensitivity or anaphylactic reactions were seen. There were two cases of thromboembolic events, with one possibly related to Berinert, as assessed by the investigator. No cases of blood-borne viral transmission were reported, but there was no requirement to conduct viral testing. There were 18 patients who were younger than 12 years of age, and the adverse event rate in that population was lower than the entire population, and there were no serious adverse events in that group of patients younger than 12.
- Berinert was initially approved in 1979 in Germany. It has been given to 47,982 patients (b) (4) doses), and the following is a safety summary for the cumulative duration from 1985 to January 2016:
    - Hypersensitivity and anaphylactic reactions: 458 total events; most frequent being swelling, swelling of the face, swollen tongue, dyspnea, and urticaria (many of these findings are also part of HAE). There were four events of anaphylactic reaction and one of anaphylactic shock. One death from generalized edema.
    - Thromboembolic events: 68 total events; most frequent being thrombosis, vena cava thrombosis, cerebrovascular accident, deep vein thrombosis, pulmonary embolism, and venous thrombosis. 19 total deaths, 14 of which were for off-label use during cardiac surgery, which does not apply to Haegarda, since it is self-administered.
    - Transmission of infectious agents: 20 total events; no confirmed cases of infectious agents due to the administration of Berinert.
- Results of literature search:

- Search terms used: “c1 esterase inhibitor”, “c1 inhibitor”, “berinert”, “safety”, “hereditary angioedema treatment” (in different combinations)
- No articles showed new safety concerns that were not already mentioned in one of the above sources.

5. Sponsor’s Pharmacovigilance Plan

	Safety Concern	Pharmacovigilance Action
Important identified safety concerns		
1	Hypersensitivity and anaphylactic reactions	Routine PV
Important potential safety concerns		
2	Thromboembolic events (TEE)	Routine PV; expedited reporting of all TEE case reports
3	Transmission of infection agents	Routine PV; expedited reporting of all possible virus transmissions[1]
Important missing information		
4	Limited experience in pregnancy/lactation	Routine PV
5	Limited experience in pediatric population	Routine PV
6	Limited experience in geriatric population	Routine PV

(Sequence 0000, module 1.16.1 Pharmacovigilance plan, pages 40-45, tables 19-26)

6. Analysis of Sponsor’s Pharmacovigilance Plan

- Hypersensitivity and anaphylactic reactions:
  - Clinical trials: 8 out of 184 subjects experienced 16 events: 2 rash, 9 urticaria, 1 pruritus, 1 cough, 1 conjunctivitis, 1 injection site urticaria, and 1 drug hypersensitivity, 1 hypotension related to analyphylaxis. No deaths.
  - Comment: Routine PV is appropriate.
- Cardiovascular Events
  - Clinical trials: 1 case of acute myocardial infarction (found to be unrelated to Haegarda) No deaths.

[1] Reviewer comment: Per regulation, all suspected transmissions of any pathogen will undergo expedited reporting, and as such, this represents routine PV

    - Comment: Routine PV is appropriate; expedited reporting is in accordance with current regulatory requirements.
- Transmission of Infectious Agents
    - Clinical trials: 1 possible case of Epstein-Barr transmission, which was later determined to be unrelated.
    - Comment: All clinical trial data and decades of post-marketing data for Berinert have not shown any proven cases of virus transmission. In clinical trials, the investigators were able to rule out viral transmission in suspected cases for both Haegarda and Berinert. In post-marketing experience for Berinert, suspected cases either lacked full information to determine if viral transmission had occurred or had lab data showing it was unrelated to Berinert. Routine PV is appropriate; expedited reporting is in accordance with current regulatory requirements.
- Pregnancy/Lactation missing data:
    - One pregnant woman was included in the trials for Haegarda, and reported no adverse events. (This subject became pregnant during the clinical trial, and was discontinued from the study when the investigators were notified.) No lactating women were included, and there is a general lack of data about Haegarda in both of these populations, given the rarity of HAE. However, in the Berinert registry, there were 20 pregnant women ranging from 20-35 years of age who received repeated doses and reported no complications during delivery and no harmful effects to the 34 neonates that were born. The label states that Haegarda should only be given to women in these populations if clearly needed.
    - Comment: Routine PV is appropriate
- Pediatric Population missing data:
    - The safety of Haegarda was evaluated in a subgroup of six pediatric patients 12 to <17 years of age. Results of subgroup analysis by age were consistent with overall study results.
    - Comment: Routine PV is appropriate
- Geriatric Population missing data:
    - The safety of Haegarda was evaluated in a subgroup of seven geriatric patients (age ≥65). Results of subgroup analysis by age were consistent with overall study results.
    - Comment: Routine PV is appropriate
- No additional safety concerns were identified by either the DE reviewer or by the clinical reviewer.

7. Recommended Pharmacovigilance Actions

DE agrees with the pharmacovigilance activities proposed by the sponsor in the PVP (as noted in section 5), with adverse event reporting as required under 21 CFR 600.80. Periodic adverse event reports should include details of the potential risks and missing information identified in this safety review. The reviewed safety data do not substantiate the need for a post-marketing study or Risk Evaluation and Mitigation strategy (REMS).