June 16, 2020

PRODUCT CORRESPONDENCE – RESPONSE TO PREA NON-COMPLIANCE LETTER

DEFERRAL EXTENSION REQUESTED

Ann Farrell M.D., Director
Division of Hematology Products
Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

RE: ARIXTRA® (FONDAPARINUX SODIUM) SOLUTION FOR SUBCUTANEOUS INJECTION, 2.5MG/0.5ML, 5MG/0.4ML, 7.5MG/0.6ML, 10MG/0.8ML
NDA 021345
SEQUENCE NUMBER: 0117
(Response to PREA Non-Compliance Letter – Deferral Extension Requested)

Dear Dr. Farrell:

Reference is made to the New Drug Application (NDA 021345) for Arixtra (fondaparinux sodium injection) solution, approved on December 7, 2001 and to supplements -004 and -005 approved on May 28, 2004 for the treatment of acute deep vein thrombosis and acute pulmonary embolism when administered in conjunction with warfarin sodium. Study AR1116442 is a post-marketing commitment study to evaluate the safety, efficacy and pharmacokinetics of two doses of Arixtra™ (fondaparinux sodium versus standard of care in treatment of venous thromboembolism in paediatric patients). It was proposed to fulfil the Pediatric Research Equity Act (PREA) post-marketing requirements triggered by supplements -004 and -005 of approved NDA 021345 ARIXTRA™ (fondaparinux sodium) Injection and is to be conducted under IND 051126.

Reference is also made to the Notification of Non-Compliance with PREA, dated April 27, 2020. Mylan Ireland Limited (Mylan) submits this response to the Notification of Non-Compliance with PREA in accordance with the provisions of section 505B(d)(1) of the Federal Food, Drug, and Cosmetic Act [21 U.S.C. 355c(d)(1)].

Please note that ownership of this NDA was transferred from Sanofi-Synthelabo to GlaxoSmithKline (GSK) and from GSK to Aspen Global, Inc (Aspen) on May 14, 2014. Subsequently, on October 24, 2014, Aspen transferred ownership of the NDA to Mylan Ireland Limited (Mylan). Aspen is the current holder of the IND for the pediatric study associated with this NDA application (051126).

General Background

Arixtra is a single-dose prefilled syringe containing sterile solution of fondaparinux sodium to be administered subcutaneously. It is approved for use in the treatment of acute deep vein thrombosis (DVT) when administered in conjunction with warfarin sodium, treatment of acute pulmonary embolism (PE) when

administered in conjunction with warfarin sodium, and the prophylaxis of deep vein thrombosis in patients undergoing hip fracture surgery, hip replacement surgery, knee replacement surgery or abdominal surgery. While the Agency has granted a waiver of pediatric studies for the indication of prophylaxis of deep vein thrombosis, it is requiring pediatric studies for the other indications, i.e., treatment of acute DVT and PE.

The approved dosing for treatment of acute DVT and acute PE is based on body weight, with a recommended dose of 5 mg for patients <50 kg (110 lbs), 7.5 mg for patients between 50 and 100 kg (110 and 220 lbs), and 10 mg for patients who have a body weight >100 kg (220 lbs). As noted in its FDA-approved prescribing information, Arixtra increases the risk of bleeding in patients who weigh less than 50 kg (110 lbs) and in patients with renal impairment. Patients on Arixtra with risk factors for bleeding are at increased risk of hemorrhage. In the event of a major bleeding, there is no approved reversal agent for Arixtra, unlike most other anticoagulants. The absence of reversal agent is an important limitation of use considering the long half-life of the drug. In addition, Arixtra is only approved for use in patients who can transition to warfarin, and warfarin may not be appropriate for all patients with acute DVT or acute PE.

Historically, there have been significant challenges conducting a clinical study of Arixtra in pediatric patients. These challenges include the limited population of pediatric patients with acute DVT and PE where concomitant use of warfarin sodium is appropriate; technical challenges related to developing a formulation suitable for pediatric patients in a long-term, home-based care setting; and higher risk of bleeding in pediatric patients weighing less than 50 kg and non-availability of a reversal agent. In addition, the standard of care continues to evolve, which presents additional challenges with designing and conducting a safe and ethical study in pediatric patients. Importantly, the recent approval of dalteparin for treatment of VTE specifically in pediatric patients presents a treatment option that does not require concomitant use of warfarin sodium and has an available reversal agent.

Since our last communication with the Agency, we have continued to explore possible solutions to overcome these challenges. We would like to meet with the Agency to work toward a solution to these outstanding study requirements. Accordingly, we will be submitting a meeting request discuss a path forward with the Agency. The meeting request will be submitted by August 15, 2020. In addition, we respectfully request a one-year deferral extension to June 15, 2021. The requested extension should provide sufficient time to engage in a meaningful discussion with the Agency and provide additional clarity as to the full timeframe that may be needed to satisfy the requirement.

Sponsor Efforts to Satisfy PREA Requirements

Since approval of the supplements for treatment of DVT and PE, the application sponsor has been closely interacting with the Division of Hematology Products to reach agreement on the conduct and fulfilment of the PREA studies considering the difficulty in studying the drug in pediatric patients. Because of the challenges described above, the sponsor's efforts to complete a study in pediatric patients have thus far been unsuccessful.

The original post-marketing PREA studies, as described in the approval letter NDA 021345/S-004 and S-005 (May 28, 2004), were as follows:

- A study of the treatment of acute DVT when administered in conjunction with warfarin sodium in pediatric patients ages birth to 16 years; and
- A study the treatment of acute PE when administered in conjunction with warfarin sodium in pediatric patients ages birth to 16 years.

Due to the very small number of pediatric patients with DVT or PE, which made it difficult to complete the requested post-marketing studies, [redacted]. The Division acknowledged the incidence of pediatric VTE is low [redacted] stated that [redacted] more limited studies collecting pharmacokinetic, pharmacodynamic and safety information, with some documentation of clinical outcomes, could potentially provide useful labeling information and possibly inform dosing.

[redacted]
GSK submitted, on March 29, 2010, a pharmacokinetic (PK) study (FondaKids 1), which provided preliminary data on the safety of a 0.1 mg/kg per day dose for treatment of venous thromboembolism (VTE) in the pediatric population. [redacted]

Seeking to better understand the Agency's concerns and need for additional data, GSK met with the Division on September 8, 2011. The difficulty of conducting a pediatric fondaparinux study with the approved concomitant use of warfarin was discussed (i.e., difficulty in achieving and maintaining a therapeutic INR due to concomitant medications and dietary challenges). Despite these concerns, the Division suggested that GSK "continue to collect PK samples in patients receiving multiple-doses of fondaparinux" and conduct "a well-designed PK and pharmacodynamics (PD) and clinical outcomes study" in pediatric patients.

GSK began development of a new protocol following the September 2011 meeting in an attempt to conduct a multi-dose study in the subject population. In July 2012, a Special Protocol Assessment request was submitted to IND 051126 for a proposed pediatric study protocol [redacted] A No Agreement letter was received September 13, 2012 and additional Special Protocol Assessment (SPA) request amendments, meetings, and discussions with the Agency ensued over the next few years, with concentration on establishing acceptable parameters for the proposed study within the constraints and limitations of the population and indications to be evaluated. Agreement was reached on a final protocol, as submitted May 23, 2014, and documented in a June 30, 2014 "SPECIAL PROTOCOL – AGREEMENT" letter. Concurrent with the SPA agreement, a revised date for completion was established (December 15, 2019).

The new agreed upon study, however, brought on additional unanticipated challenges. To permit the weight-based dosing required under the protocol, the pediatric formulation had to be packaged [redacted] for the variable pediatric dosing. Between October 2014 and November 2015, GSK investigated multiple approaches to developing an appropriate pediatric formulation but encountered several significant technical challenges ([redacted]). GSK ultimately determined that it was not possible to develop a stable pediatric formulation and that any pediatric clinical study would need to be conducted with the current formulation and market presentation.

A meeting to discuss the progress, feasibility, and implementation of protocol [redacted] and the intent to [redacted] was requested, on April 5, 2016, by Lachman Consultant Services, Inc., US Agent for Aspen Global Inc. (AGI), the new owner of the IND for the study. During the meeting, held on June 16, 2016, the Sponsor explained the infeasibility of performing the clinical study as currently proposed under [redacted] including the following challenges:

- The lack of a stable formulation in a container-closure system that offers the desired dose ranging opportunity, despite extensive development efforts.
- The inability to translate study findings to clinical setting as any new viable pediatric formulation (if at all possible) will not be made commercially available. Further, the ability to correlate results to commercially available product will be limited as any pediatric formulation developed will have to differ significantly from that approved.
- Advances in Standards of Care with opportunity for other medications that offer potential for reversibility.

FDA acknowledged the challenges that had been encountered in conducting the studies since the product was approved, but explained that in the interest of keeping a level playing field amongst sponsors and obtaining pediatric use information for anticoagulants, [redacted (b) (4)]. The Agency was open to discussing re-direction of the development plan to satisfy the PREA requirement.

The Sponsor agreed to draft another proposal to address the PREA requirement based on the discussion with the Agency. The new proposal was based on the available information on clinical use of a formulation in pediatric patients using weight-based dosing (for patients 10-20 kg as needed). On November 21, 2017, Lachman Consultant Services, Inc., requested a meeting to discuss a proposed [redacted (b) (4)] study to evaluate the safety, efficacy, and pharmacokinetics of fondaparinux sodium in pediatric patients. A meeting was granted and scheduled for January 26, 2018.

FDA stated in Meeting Preliminary Comments received on January 22, 2018 that the proposed [redacted (b) (4)] study was not sufficient to satisfy the PREA requirement, and could only be considered as supportive data. Based on FDA's preliminary comments, and in an effort to reach agreement on how to satisfy the PREA requirement, the Sponsor opted to cancel the January 26, 2018 Meeting and engaged the Ombudsman, between January 25, 2018 and March 21, 2018, for further discussions with the Division.

Since then the Sponsor has continued to evaluate options on ways to satisfy FDA's request for a prospective study. This work included, for instance, [redacted (b) (4)]. This evaluation has continued to run into ethical concerns with conducting a prospective study of Arixtra in pediatric VTE patients.

Request for a Deferral Extension

Accordingly, we would like to meet with the Agency to work toward a solution to these outstanding study requirements and will be submitting a meeting request to discuss a path forward with the Agency. The meeting request will be submitted no later than August 15, 2020. In addition, we respectfully request a one-year deferral extension to June 15, 2021. The requested extension should1 provide sufficient time to engage in meaningful discussion with the Agency and provide additional clarity as to the full timeframe that may be needed to satisfy the requirement.

To facilitate review of the open PREA commitment, a copy of the Letter for Authorization filed by Aspen, on June 10, 2020 to authorize FDA to access IND 051126 is provided.

All files in this product correspondence have been scanned utilizing Symantec antivirus software and are free of known viruses. All inquiries regarding this correspondence should be directed to the responsible officials listed in Form FDA 356h.

Sincerely,

<Please see following page for signature manifestation.>

Robert Barto
Senior Director of Regulatory Affairs

RB/alm

SIGNATURE MANIFESTATION

Document Name : cover-letter-0117

Document Title : Cover Letter - 0117 - Product Correspondence - Response to PREA Non-Compliance Letter - Deferral Extension Request - 20200616

Document Version : 0.5; CURRENT; Most-Recent; In Approval

Date	Signed By	Reason for Signing
16-Jun-2020 01:34 PM EDT	Robert Barto	Approve

Object ID: 0901474e877467b8