DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Memorandum

Food and Drug Administration
Center for Drug Evaluation and Research
CDER/ODE 2/DPARP

Addendum to Primary Clinical Review of Supplement 211

Date: March 24, 2017

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Product: abatacept (ORENCIA)

Subject: Review of interim study IM101240 report and additional safety data intended to support the request for pediatric exclusivity

Sponsor: Bristol-Myers Squibb

Application: BLA 125118

In 2008, abatacept was approved in the US for the treatment of juvenile idiopathic arthritis (JIA) in children ≥6 years of age. At the time of approval, the Sponsor agreed to the post-marketing requirement (STN 125118/045, PMR#5) of studying ≥500 JIA patients, which included intensive scrutiny for the initial 3 years, with annual follow-up visits assessing for the occurrence of malignancies, other autoimmune diseases, and serious infections, for a total of 10 years.

As agreed, the Applicant initiated Study IM101240 in June of 2009 to address PMR#5. The study is an observational, multicenter registry that will enroll ≥500 JIA patients from clinical pediatric rheumatology centers in countries where abatacept is approved for JIA and collect ≥10 years of follow-up safety data. An interim report of this study, together with study IM101301, was also included as part of a pediatric written request (PWR) initially issued on September 13, 2013.

In 2015, the PWR was amended to specify that the interim report should include information on 180 patients with JIA with ≥12 months of abatacept treatment. The current submission provides an interim report for Study IM101240 to fulfill that amended PWR. However, due to lower than expected patient recruitment into the Study IM101240 registry and a higher temporary discontinuation rate than expected, the Sponsor was unable to provide data on the previously agreed 180

patients with ≥12 months of treatment. Therefore, to comply fulfill the intent of with the PWR, the Sponsor utilized two other sources of data to supplement the data submitted in the IM101240 interim report: Truven Health MarketScan and a Swedish Pediatric Registry of Rheumatology. Both databases were observational retrospective studies and are described below.

Study IM101240

Study IM101240, entitled *"An Observational Registry of Abatacept in Patients with Juvenile Idiopathic Arthritis"* is an observational, multicenter registry to describe the long-term safety of IV abatacept treatment for JIA in routine clinical practice. Patients are recruited from clinical pediatric rheumatology centers in countries where abatacept is approved for the treatment of JIA and include the Pediatric Rheumatology Collaborative Study Group (PRCSG) centers in North America and Paediatric Rheumatology International Trials Organization (PRINTO) at centers outside of North America.

Approximately 900 patients who receive abatacept for JIA will be enrolled in the registry with the final goal of approximately 750 patients with ≥5 years of follow-up data and 500 of these patients with ≥10 years of follow-up data by the end of the study. Patients included in the study were required to meet the following inclusion criteria:

- Diagnosis of JIA
- Age ≤18 years at time of enrollment
- Receiving abatacept at time of enrollment
- Parent/Legal Guardian willing to participate in study and sign informed consent

The major outcomes include serious infections, infections of special interest, autoimmune disorders, and malignancies. The infections of special interest include EBV, CMV, HPV, HZ, TB and opportunistic infections. All statistical analyses are descriptive. Incidence rates are calculated as the # of new cases/1-person-years with 95% CI.

The submitted interim report contains tabular presentations and safety data up to a cutoff date of April 28, 2016 and included data on 226 JIA patients treated with IV abatacept of which a subset (n=134) have been treated for ≥12 months. However, the submission also provided descriptive safety as of August 31, 2016 at which point a total of 165 patients received abatacept for ≥12 months. The mean time of observation in the total IV group is 25 months (range: 0-77 months). The mean time of observation for the subgroup of subjects treated with abatacept ≥12 months was 36 months (range: 12-77 months). The total exposure to abatacept for the ≥12 month subgroup is 401 person-years.

Baseline demographics demonstrated that the average subject in the abatacept-treated ≥12 month subgroup was 13 years-old (±3), female (80%), and White

(84%). Only one of the subjects in this cohort was younger than 5 years of age. Disease history in the abatacept-treated ≥12 month subgroup showed an average disease duration of 79 months (±46) and that the most common JIA subtypes included RF(-) pJIA (54%), oligoarticular JIA (16%), undifferentiated (10%), RF(+) pJIA (8%), Psoriatic JIA (7%), and systemic JIA (4%). A total of 105/134 (78%) subjects in the abatacept-treated ≥12 month subgroup were receiving concomitant medications at baseline including methotrexate (57%), NSAIDS (44%), and corticosteroids (16%).

A total of 18/226 (8%) of the entire IV population reported 22 adverse events (AE), with 14 of the patients reporting serious adverse events (SAE). Most AEs were reported as a single occurrence except for three cases of hip pain. Two subjects discontinued treatment due to an AE including anaphylactic shock and an infusion reaction. In the abatacept-treated ≥12 month subgroup a total of 8 patients reported 12 AEs that were classified as serious. There were no reports of deaths, malignancies, or new onset autoimmune disorders.

A total of 6 patients reported 6 events of infection in the entire IV population (n=226) including asceptic meningitis, candidal esophagitis (≥12 month subgroup), foot infection (≥12 month subgroup), herpes simplex, post-traumatic would infection (≥12 month subgroup), and one infection with MRSA (≥12 month subgroup). Incidence rates for the for infections for the overall IV population was 3 (95% CI: 1, 6) and 2.5 (95% CI: 1, 6) for the abatacept-treated ≥12 month subgroup.

Of the 6 infections, 2 meet the criteria for serious infections: aseptic meningitis and MRSA wound infection. The MRSA infection presented as nasal cellulitis and was initially treated with IV antibiotics and then oral antibiotics. Both serious infections resolved completely and without sequelae. There was also one subject who reported an exacerbation of Type I diabetes mellitus.

Increased rates of hospitalization for bacterial infections in JIA patients not receiving methotrexate or TNF inhibitors have been reported with an adjusted Hazard Ratio of 2 (95% CI: 1.5, 2.5)[1]. JIA patients receiving methotrexate but not TNF inhibitors had an adjusted hazard ratio of 1.2 (95% CI 0.9-1.7). JIA patients receiving treatment with just TNF inhibitors but not methotrexate had a similar adjusted hazard ratio of 1.2 (95% CI 0.8-1.8). The authors of this study concluded that the risk of hospitalized bacterial infection was associated with JIA activity status and not associated with methotrexate or TNF inhibitor use. The incidence rate for the entire cohort was reported was reported as 2.8/100 person years (95% CI 2.5, 3.1). A German registry reported a low rate of serious infections ranging from 0.16/100 person-years in JIA patients on methotrexate without a biologic but increasing up to 0.97/100 person-years with adalimumab or

[1] Beukelman T, et al. Arthritis & Rheumatism. Aug 2012; 64(8): 2773-2780.

0.8/100 person-years with etanercept.[2]

Other published studies evaluating the risk of serious infections in JIA patients consistently reported increased risk of serious infections in JIA patients.[3][4][5]
Taken together, the scientific evidence suggests that JIA increases the risk of infection independent of treatment with use of immunosuppressant therapy modestly increasing in risk of infection among JIA patients.

The Applicant included a listing of AEs for an additional 31 patients who achieved ≥12 months of abatacept therapy after the April 2016 cutoff. One patient was hospitalized for nephrolithiasis. An additional five non-serious AEs in five subjects were reported and included post-traumatic wound infection, foot infection, laryngitis, pneumonia, and "pale skin".

Overall, the incidence rates observed in the interim report of Study IM101240 registry are within the range of published incidence rates. No new safety signals were identified.

Additional AEs of special interest included one patient from a North American site experienced an infusion-related reaction that included difficulty breathing, chest pain and lightheadedness. The patient was transported to the hospital and treated with epinephrine and the event resolved. A single case of anaphylactic shock was reported from a European site. Both events resulted in the patients discontinuing abatacept therapy. Of note, anaphylaxis is a well-recognized risk with biologic therapies and is a labeled warning in abatacept labeling.

Observational Registry Studies

Data from a US administrative healthcare claims data base (Truven Health MarketScan) and a Swedish JIA registry (the Swedish Pediatric Registry of Rheumatology) have been included by the Sponsor to supplement the IM101240 interim report. The analyses consist of an observational study of patients with JIA who were receiving abatacept.

The Truven MarketScan Commercial database is an administrative claims database with patient information dating from 2006. The commercial database provides detailed information for ≥70 million privately insured patients ≤65 years. The information in this database is projectable to the US population. Patients

[2] Becker I and Horneff G. Arthritis Care Res. 2016; Jul 7

[3] Prince FH, et al. Ann Rheum Dis 2009; 68(5): 635-41.

[4] Davies R, et al. Arthritis Rheumatol 2015; 67(9): 2487-94

[5] Giannini EH, et al. Arthritis Rheum 2009; 60(9): 2794-804

diagnosed with JIA who initiated abatacept between January 2006 and 30 September 2014 were eligible for inclusion in the study. Inclusion criteria included the following:

- Two diagnoses of JIA within 90 days
- Continuous enrollment in the health care plan of 180 days prior to the second diagnosis
- Age <18 years at the time of second of the two diagnoses
- Index date is the date of initiating treatment with abatacept
- Age < 18 years at the index date

The Swedish Pediatric Registry of Rheumatology contains patient information dating from 2009 with the primary goal to follow all children on biologics and cytokine modulators and later expanded to all JIA patients with/without antirheumatic drugs. This registry offers caregivers details on patient level data in clinical settings and involves patients and parents as partners in the process. The study population includes patients with JIA who are treated with abatacept. Inclusion criteria included the following:

- Age < 18 years at the time of enrollment
- Receiving abatacept at the time of enrollment as per the treating physician's decision

Two groups of abatacept treated patients were identified in both databases: an overall abatacept treated population and a subgroup of patients treated with abatacept for ≥12 months. Patients could have had ≤90 days of interruption and still be considered as continuous treatment.

There were a total of (b) (4) in the Truven MarketScan database and (b) (4) patients who received IV abatacept for ≥12 months in the Swedish JIA Registry. Baseline demographics for the Truven MarketScan database demonstrated (b) (4) . Demographic data from the Swedish JIA Registry (b) (4) .

The mean time on abatacept therapy for the subgroup of subjects treated ≥12 months from the Truven MarketScan was (b) (4) The total exposure to abatacept for the ≥12 month subgroup from the Swedish JIA Registry was (b) (4) .

The most common concomitant medications for all JIA patients treated with abatacept, and those treated ≥12 months, in the Truven MarketScan were

(b) (4)

No data was provided from the Swedish JIA Registry.

A total of 6 patients from the Truven MarketSca (b) (4)

Review of the literature described a study that found zero cases of brain cancer among 3,605 JIA paitients[6], while Beukelman[7] et al reported three cases of brain cancer among 4,617 JIA patients.

The Swedish JIA Registry only reported (b) (4)

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Overall, the analyses of these observational retrospective studies demonstrate that the subjects enrolled in the two databases were similar to each other as well as those patients enrolled in Study IM101240. Moreover, the hospitalized infection rate in the database was similar to that reported in the scientific literature for JIA as well as the rates observed in Study IM101240. There was a single malignancy reported from the US registry.

Summary

To fulfill the requirements of the PWR, the Applicant submitted interim data from Study IM101240 on 226 JIA patients treated with IV abatacept of whom 165 were treated with abatacept ≥12 months. Of note, the PWR states the following requirement: "*Interim report containing a minimum of 180 patients treated for at least 12 months is due September 30, 2016.*" However, due to slow enrollment despite good faith efforts, the Applicant was unable to achieve that goal. The Division considered this in the context of the overall objectives of the abatacept pediatric program. The PWR-specified number was not selected based on statistical considerations, i.e. ruling out a specific risk, rather it was intended to provide a descriptive assessment of safety.

In addition, to supplement the data, the Sponsor analyzed an additional 115 JIA patients treated with abatacept for ≥12 months from the Truven MarketScan and Swedish JIA Registry databases. These patients were similar in baseline demographics and disease characteristics as those enrolled in Study IM101240. Overall, analyses of the data from these additional sources did not suggest any new safety signals and is supportive of the safety observed in Study IM101240.

[6] Nordstrom BL, et al. Arthritis Care & Research 2012; 64(9):1357-364.

[7] Beukelman T, et al. Arthritis & Rheumatism 2012; 64(4): 1263-271.

Given these considerations, the safety profile from this submission, and the overall known safety profile of abatacept, the Division concluded that the data submitted in this supplement, while not technically meeting the specifics of the PWR, are adequate and fulfills the intent of the Pediatric Written Request.

The Division's assessment and recommendations, as detailed above, were discussed at the Pediatric Exclusivity Board on January 24, 2017.

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/s/

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03/24/2017

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