CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

207924Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)
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<td>Reviewer Name(s)</td>
<td>Bob Pratt, Pharm.D.</td>
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<td>Team Leader</td>
<td>Donella Fitzgerald, Pharm.D.</td>
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<tr>
<td>Deputy Division Director</td>
<td>Jamie Wilkins Parker, Pharm.D.</td>
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<td>Review Completion Date</td>
<td>May 10, 2018</td>
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<td>Subject</td>
<td>Evaluation of Need for a REMS: Resubmission after Complete Response</td>
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<td>Established Name</td>
<td>Baricitinib</td>
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<td>Trade Name</td>
<td>Olumiant™</td>
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<td>Name of applicant</td>
<td>Eli Lilly and Company</td>
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<tr>
<td>Formulation(s)</td>
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<tr>
<td>Proposed Dosing Regimen</td>
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1 Introduction

This is the second addendum to the Division of Risk Management (DRISK) review of baricitinib, New Drug Application (NDA) 207924, dated January 6, 2017. The original review concluded a REMS is not necessary to ensure the benefits of the drug outweigh the risks. The first addendum, dated April 11, 2017, provided information and comments related to the risk of thrombosis that were not addressed in the original review and which changed the recommendation that no REMS is necessary to a deferral. The decision to defer was made after the Office of New Drugs determined additional information was needed to clarify the benefit-risk profile before the drug can be approved. The focus of the risk assessment in this addendum will be on the risk of thromboembolism.

Eli Lilly and Company (Lilly) submitted NDA 207924 for baricitinib, a Janus kinase (JAK) inhibitor, on January 15, 2016, for the proposed indication of treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. The application received a Complete Response on April 12, 2017 due to the Agency's conclusion that the benefit-risk assessment of baricitinib 2 mg and 4 mg is not favorable given the potential serious risk of thrombosis, and that there is a lack of consistent efficacy advantage of the 4 mg dose over the 2 mg dose. At the time, the Agency did not recommend approval with risk management because the finding of serious thrombotic events, some fatal, has not been observed with another JAK-inhibitor for the treatment of RA and baricitinib offers no obvious benefit over available therapies. Lilly resubmitted NDA 207924 on December 4, 2017. The resubmission includes the following: an update of the safety data through April 1, 2017 that characterizes the potential risks based on an increase in patient-years of exposure and two newly completed studies; an epidemiologic analysis of venous thromboembolic risk in patients with rheumatoid arthritis; and additional post-hoc analyses to support new dosing recommendations. On April 23, 2018, the application was discussed at a meeting of the Arthritis Advisory Committee.

2 Background

2.1 PRODUCT INFORMATION

Baricitinib is a Janus kinase (JAK) inhibitor with a proposed indication for the treatment of moderately to severely active rheumatoid arthritis in adults who have had an inadequate response or intolerance to methotrexate. Janus kinases are a family of tyrosine kinases that play an important role in cytokine signal transduction. Many of the pro-inflammatory cytokines implicated in the pathogenesis of rheumatoid arthritis, including interleukin-6 (IL-6) and granulocyte macrophage colony-stimulating factor (GMCSF), use cell signaling that involves the JAK signal transducers and activators of transcription (STAT) pathways.

Baricitinib is supplied as an oral tablet and is to be administered as a chronic therapy in a single daily dose of 2 mg. Baricitinib is currently approved in the European Union, Japan, and Australia.

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*a The Agency’s review of the Dosage and Administration section of the label is ongoing at the time of this addendum. The final approved language related to dosage is subject to change.
2.2 REGULATORY HISTORY

- January 15, 2016: NDA 207924 submission for the treatment of moderately to severely active rheumatoid arthritis in adults received.
- November 23, 2016: Lilly submitted a major amendment to the application.
- April 12, 2017: The Agency issued a Complete Response letter to Lilly for deficiencies related to the potential thrombotic risk, inadequate safety exposure at the baricitinib 2 mg dose, the efficacy of baricitinib 4 mg versus 2 mg dose, and other dose-ranging considerations.
- August 11, 2017: Lilly submitted a Formal Dispute Resolution Request.
- August 23, 2017: Lilly withdrew the Formal Dispute Resolution Request after agreeing with the Agency to provide a resubmission of the NDA that includes new data and analyses.
- December 4, 2017: Class 2 Resubmission of NDA 207924 received for the treatment of moderately to severely active rheumatoid arthritis in adults who have had an inadequate response or intolerance to methotrexate.2
- April 23, 2018: The Arthritis Advisory Committee Meeting was convened to discuss the efficacy, safety (including the risk of thromboembolic adverse events), dose selection, and overall benefit-risk considerations. The Committee voted 10 to 5 that the benefit-risk profile of baricitinib 2 mg once daily is adequate to support approval for the treatment of moderately to severely active rheumatoid arthritis in patients with an inadequate response or intolerance to methotrexate. The Committee voted 5 to 10 that the benefit-risk profile of baricitinib 4 mg once daily is adequate to support approval. A REMS proposal was not discussed.

3 Benefit Assessment

The clinical benefit of baricitinib was briefly summarized in the original DRISK review dated January 6, 2017. For additional details regarding the development program, see the Clinical Review of NDA 207924 dated January 9, 2017, the Cross-Disciplinary Team Leader (CDTL) Review dated January 5, 2017, the Division Director Review dated February 6, 2017, the respective addendums to the CDTL and Division Director Reviews dated March 28, 2017 and March 17, 2017, and the Deputy Office Director Decisional Memo dated April 12, 2017.

In the resubmission, Lilly presented the results of the newly completed Study JAGS, which was a 52-week, randomized, double-blind, placebo-controlled foreign study to assess the efficacy and safety of baricitinib 4 mg daily in 290 patients with moderately to severely active RA who had an inadequate response to methotrexate (MTX). The study did not include a baricitinib 2 mg dose group; however, this dose had been evaluated earlier in the clinical development program. The primary efficacy endpoint was ACR20 response at Week 12, which showed a statistically significant improvement in response rate for the baricitinib group (59% of patients) compared with placebo (28% of patients) (p≤0.001). Several secondary

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b The American College of Rheumatology's 20% response in RA (ACR20) is calculated as a ≥20% improvement in tender joint count and swollen joint count, as well as 3 of 5 ACR core set measures including physician and patient global assessments, patient-reported pain, patient assessment of physical function, and acute phase reactant.
efficacy endpoints also showed statistically significant improvements from baseline for the baricitinib 4 mg group compared to placebo.

4 Thromboembolic Risk Assessment

The Applicant's resubmission included an update of the integrated safety database through April 1, 2017 that accounted for the increase in patient-years of exposure (PYE) to baricitinib. The increase in exposure is based primarily on the enrollment of patients in a long-term, open label extension study. Table 1 below shows a summary of venous and arterial thromboembolic adverse events from the safety update of four multicenter, double-blind, randomized, controlled Phase 3 studies and the extension study.

Table 1: Thromboembolic events from the baricitinib safety database update

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<th>Exposure Weeks 0-16</th>
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<tr>
<td></td>
<td>Placebo n (IR)</td>
<td>Baricitinib 2mg n (IR)</td>
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<tr>
<td>No. Patients</td>
<td>892</td>
<td>403</td>
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<tr>
<td>Patient-Years Exposure</td>
<td>267</td>
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<td>Venous thromboembolism</td>
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<tr>
<td>Arterial thromboembolism</td>
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IR = Incidence rate per 100 patient-years


In Study JAGS, no serious adverse events of deep vein thrombosis or pulmonary embolism were reported. However, one patient in the baricitinib group died during the study due to ischemic stroke 247 days after first receiving the study drug. In addition to Study JAGS, a newly completed Phase 2 study of 75 patients with atopic dermatitis (Study JAHG) was included in the resubmission. None of the patients experienced a thromboembolic adverse event in this study.

Baricitinib was associated with a small increase in mean platelet count from baseline in patients who either experienced a venous thrombotic event or who did not have an event. The venous thrombotic events did not have a clear temporal relationship to the elevation in platelet count.

The Applicant submitted an epidemiologic analysis of baseline venous thromboembolic risk in patients treated with other approved RA therapies. The incidence of venous thromboembolism (VTE) per 100 patient-years (PY) was 1.34 and 1.05 in two commercial claims databases. The rate of VTE for the patients exposed to baricitinib in the ALL BARI RA dataset was 0.53 per 100 PY. However, an analysis of the submission by the Division of Epidemiology could not conclude the VTE, deep vein thrombosis, and pulmonary embolism rates within the baricitinib clinical population are comparable to the background rates due to limitations in the population data of the commercial claims databases. For additional details regarding this analysis, see the Division of Epidemiology Review dated February 22, 2018³ and the FDA Briefing Document for the Arthritis Advisory Committee Meeting dated April 23, 2018.⁴
5 Discussion of Need for a REMS

The Arthritis Advisory Committee discussed the NDA on April 23, 2018 and concluded that the benefit-risk profile of baricitinib is adequate to support approval of the 2 mg daily dose for the treatment of moderately to severely active rheumatoid arthritis in patients with an inadequate response or intolerance to methotrexate. The Agency's review of the Indications and Usage section of the label is ongoing at the time of this addendum. The final approved language related to the Indication statement is subject to change.

Baricitinib appears to be associated with an increased risk of venous thrombosis. Although platelet counts in patients who received baricitinib were increased over baseline, there was not a clear temporal relationship between the increase in platelet count and the thrombotic events observed. Lilly has proposed that the risk of thrombosis be managed by the addition of a Warning and Precaution to the baricitinib labeling.

The risk of thrombosis with baricitinib is unique in the class of small molecule or biologic disease-modifying anti-rheumatic drugs. Tofacitinib is a JAK inhibitor approved in 2012 for the treatment of rheumatoid arthritis that did not show such a risk in the clinical studies supporting approval. Ruxolitinib is another JAK inhibitor approved in 2011 for the treatment of myelofibrosis and polycythemia vera, but ruxolitinib is also not associated with a risk for thrombosis. However, it is noted the family of Janus kinase enzymes targeted by tofacitinib and ruxolitinib are somewhat different from those targeted by baricitinib.

Patients with rheumatoid arthritis appear to have an increased baseline risk of venous thromboembolism. A retrospective cohort study conducted using U.S. insurance claims data found the risk of incident VTE is increased by 40% (hazard ratio 1.4, 95% CI 1.1–1.7) in patients with RA compared to non-RA patients using an adjusted analysis that accounted for more than 20 different potential confounders such as cardiovascular disease, surgery, hospitalization, medications, and acute phase reactants. A population cohort study in Olmstead County, Minnesota also found that patients with RA had a higher cumulative incidence of venous thromboembolism in 1995 to 2007 compared to non-RA subjects (cumulative incidence % ± SE: 6.7 ± 1.7 versus 2.8 ± 1.1, respectively).

Although thrombosis in association with baricitinib is a unique risk in the class of disease modifying anti-rheumatic drugs, the likely prescribers of these drugs are specialists that prescribe a multitude of products that have many risks which require frequent monitoring and follow-up with patients. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) will require a Boxed Warning to address venous thromboembolism and the labeling will include a Medication Guide (MG) to inform patients of this risk. Additionally, information about the risk of thrombosis (as well as other serious risks) associated with baricitinib will be further obtained in a postmarketing safety study requirement. A Boxed Warning and MG will communicate this risk to prescribers and patients, and the postmarketing study will further clarify the risk. For these reasons, this reviewer is not recommending a REMS for management of the risk of thrombosis at this time.

Reference ID: 4261038
6 Conclusion & Recommendations

Based on the available information, a REMS is not necessary to ensure the benefits of baricitinib outweigh the risk of thrombosis. We expect healthcare providers who treat moderate to severe rheumatoid arthritis should be appropriately informed about the risk of thrombosis via the Boxed Warning in the approved baricitinib labeling. Should DPARP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

7 Appendix

7.1 REFERENCES

1 Thanh Hai MT. Office of Drug Evaluation II. Baricitinib NDA 207924, Office Deputy Director Decisional Memo, April 12, 2017.


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/s/

ROBERT G PRATT
05/10/2018

JAMIE C WILKINS PARKER
05/10/2018
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**Reviewer Name(s)**: Bob Pratt, Pharm.D.

**Team Leader**: Donella Fitzgerald, Pharm.D.

**Deputy Division Director**: Jamie Wilkins Parker, Pharm.D.

**Review Addendum Completion Date**: April 10, 2017

**Subject**: Addendum to Review

**Established Name**: Baricitinib

**Trade Name**: Olumiant™

**Name of applicant**: Eli Lilly and Company

**Therapeutic Class**: Janus kinase (JAK) inhibitor

**Formulation(s)**: Oral tablets 4 mg, 2 mg

**Proposed Dosing Regimen**: 4 mg once daily; 2 mg once daily may be acceptable for some patients
1 Introduction

This document is an addendum to the Division of Risk Management (DRISK) review of baricitinib, New Drug Application (NDA) 207924, dated January 6, 2017, which concluded in DRISK’s opinion a REMS is not necessary to ensure the benefits of the drug outweigh the risks.

The addendum provides an evaluation of the risk of thrombosis, which was not discussed in the original DRISK review as the strength of signal was unclear to this reviewer at that time. Eli Lilly and Company (Lilly) submitted NDA 207924 for baricitinib, a Janus kinase (JAK) inhibitor, on January 15, 2016 for the proposed indication of treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who have had an inadequate response or intolerance to methotrexate. On November 23, 2016, Lilly submitted a major amendment to the application, and the Agency sent a Review Extension - Major Amendment letter to the applicant on January 13, 2016, extending the PDUFA goal date to April 15, 2017. This application is under review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP).

2 Risk Assessment & Safe-Use Conditions

The primary safety analysis set is comprised of six placebo-controlled studies (three Phase 2 studies and three placebo-controlled Phase 3 studies) and includes 1070 patients in the placebo arms, 997 patients in the baricitinib 4 mg arms, 479 patients in the baricitinib 2 mg arms, and 1476 patients in the combined baricitinib 2mg/4mg group. 3464 patients received baricitinib in the Phase 1, 2, and 3 RA studies (the ALL BARI RA safety set).

2.1 Thrombosis

In the primary safety set, there was a numeric imbalance and a higher rate [per 100 person-years of exposure] of serious and non-serious thrombosis adverse events in patients who received baricitinib compared with placebo over Weeks 0 – 16 and Weeks 0 – 52. See Table 1 below, which is adapted from the Cross-Disciplinary Team Leader Review (NDA 207924, J. Maynard, January 5, 2017).

| Table 1. Thrombosis adverse events associated with baricitinib in the primary safety set |
|-----------------------------------------------|---------------|---------------|---------------|----------------|----------------|
| Treatment Group | Incidence rate difference (95% CI) | | | | |
| No. Patients | Placebo | Baricitinib 2mg/4mg | Baricitinib 2mg | Baricitinib 4mg | Baricitinib 4mg vs. Placebo | Baricitinib 4mg vs. 2mg |
| 0 – 16 Weeks | | | | | | |
| No. patients with ≥1 thrombotic event, N (rate) | 1 (0.3) | 8 (1.8) | 2 (1.4) | 6 (2.0) | 1.31 (-0.10, 2.71) | 1.39 (-2.02, 4.80) |
| No. patients with ≥1 venous thrombotic event, N (rate) | 0 | 4 (0.9) | 0 | 4 (1.4) | 0.94 (0, 1.88) | 1.44 (-0.55, 3.42) |
| No. patients with ≥1 arterial thrombotic event, N (rate) | 1 (0.3) | 4 (0.9) | 2 (1.4) | 2 (0.7) | 0.37 (-0.68, 1.42) | -0.04 (-2.81, 2.72) |
| 0 – 52 Weeks | | | | | | |
| No. patients with ≥1 thrombotic event, N (rate) | 2 (0.5) | 15* (1.1) | 5 (1.5) | 9 (1.0) | 0.67 (0.13, 1.22) | 0.01 (-1.12, 1.13) |
| No. patients with ≥1 venous thrombotic event, N (rate) | 0 | 9* (0.7) | 2 (0.6) | 6 (0.7) | | |
| No. patients with ≥1 arterial thrombotic event, N (rate) | 2 (0.5) | 6 (0.5) | 3 (0.9) | 3 (0.3) | | |

Rate is per 100 patient-years.
* It is unclear why the combined 2mg/4mg count does not equal the sum of the individual 2mg and 4mg counts.
There were a total of 20 patients in the ALL BARI RA safety set who reported one or more venous thrombotic adverse events while on treatment or during post-treatment follow-up. Fifteen of the 20 cases were serious, including one fatal outcome associated with pulmonary embolism. There were a total of 11 adverse event reports of pulmonary embolism. The time to diagnosis of the thrombosis event after initiation of baricitinib treatment ranged from 37 – 1063 days with a median value of 277.5 days.

Arterial thrombotic events from Week 0 – 16 in the primary safety set included thrombosis of the basilar and vertebral arteries, which resulted in a fatal outcome, myocardial infarction, peripheral arterial occlusive disease, and retinal vascular thrombosis. Other arterial events reported include brachial artery thrombosis and lower extremity arterial occlusive disease.

### 2.2 INCREASED PLATELET COUNTS

In the Phase 2 and 3 studies, baricitinib was associated with an increase in platelet count from baseline in the group of patients (n=20) who experienced a venous thrombotic event, defined as a treatment-emergent deep vein thrombosis and/or pulmonary embolism. The platelet count also increased in baricitinib-treated patients (n=2729) who did not have a thrombotic event. Figure 1 shows the median platelet counts through Week 52 in the two groups of patients. Platelets increased during the first two weeks of treatment and then decreased toward baseline, though counts remained elevated. In the placebo group of the primary safety set, the median platelet counts ranged from 274 – 285 x10^3/µL through Week 24.

Figure 1. Median platelet counts (x10^3/µL) at baseline and through Week 52 in baricitinib treated patients with and without venous thrombotic events and in placebo group patients

The applicant defined the Week 40 time-point as Weeks 36-40, and the Week 52 time-point as Weeks 48-52.


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a One Phase 2 study and one Phase 3 study were not included in the analysis because there were no thrombotic events for patients who received baricitinib.
For the group of 20 patients who experienced a venous thrombotic event, the increase in mean platelet count was approximately $78 \times 10^3 / \mu L$ using the higher value of the maximum platelet count either prior to or concurrent with the event.

3 Discussion

Baricitinib was associated with a numeric imbalance and a higher rate of serious and non-serious thrombosis adverse events compared with placebo in the primary safety analysis. Although platelet counts in patients who received baricitinib were increased over baseline, there was not a clear temporal relationship between the increase in platelet count and the thrombotic events observed. The risk of thrombosis with baricitinib appears to be unique in the class of small molecule or biologic disease-modifying anti-rheumatic drugs. Tofacitinib is a JAK inhibitor approved in 2012 for the treatment of rheumatoid arthritis that did not show such a risk in the clinical studies supporting approval. Ruxolitinib is another JAK inhibitor approved in 2011 for the treatment of myelofibrosis and polycythemia vera, but ruxolitinib is also not associated with a risk of thrombosis. Of note, the family of Janus kinase enzymes that tofacitinib and ruxolitinib target is somewhat different from baricitinib.

As noted in the addendum to the DPARP Division Director review dated March 17, 2017, the risk of thrombosis is of concern. Deep vein thrombosis and pulmonary embolism occurred with both baricitinib 2 mg and 4 mg at comparable rates and at rates higher than placebo. There were also cases of arterial thrombosis. There will need to be further safety data generated to understand the thrombosis risk for baricitinib, and it would be reasonable to obtain the data and address this safety risk pre-approval. The thrombosis safety finding applies equally to the baricitinib 2 mg and 4 mg doses.

The original recommendation from this reviewer was that a REMS was not necessary to ensure the benefits of baricitinib outweigh the risks in the proposed indication. Upon further review of the data, the review team is uncertain that the benefit-risk profile of baricitinib supports approval at this time, and the application will receive a complete response. Because benefit-risk has not been established and additional data is necessary to support approval, this reviewer defers a REMS recommendation until there is sufficient data to ensure an accurate benefit-risk assessment.

4 Conclusion & Recommendations

The benefit-risk profile of baricitinib for the treatment of adult patients with moderately to severely active rheumatoid arthritis has not been established. Therefore, we are unable to formulate a REMS recommendation at this time.

5 Materials Reviewed

The following is a list of materials informing this review:


5. Chowdhury B. Division of Pulmonary, Allergy, and Rheumatology Products. Baricitinib NDA 207924, Division Director Review Addendum, March 17, 2017.
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/s/

ROBERT G PRATT
04/10/2017

JAMIE C WILKINS PARKER
04/11/2017
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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Olumiant (baricitinib) is necessary to ensure the benefits of this drug outweigh its risks. Eli Lilly and Company (Lilly) submitted a New Drug Application (NDA 207924) for baricitinib on January 15, 2016, for the proposed indication of treatment of adult patients with moderate to severe rheumatoid arthritis. Baricitinib is a disease-modifying antirheumatic drug that belongs to the class of Janus kinase inhibitors. The risks associated with the use of baricitinib for which a REMS is being evaluated include serious infections and malignancies. The applicant did not submit a REMS with this application, but the submission includes a risk management plan that proposes routine risk minimization measures through the use of the labeling.

DRISK and the Division of Pulmonary, Allergy, and Rheumatology Products agree that a REMS is not needed to ensure the benefits of baricitinib outweigh its risks. There have been a number of communication plan REMS required, completed and released for disease-modifying antirheumatic drugs (including for a Janus kinase inhibitor) for the treatment of rheumatoid arthritis that have serious risks similar to baricitinib. Therefore, we expect that healthcare providers who treat rheumatoid arthritis are familiar with the risks associated with baricitinib for the proposed indication.

1 Introduction

This review by the Division of Risk Management (DRISK) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Olumiant (baricitinib) is necessary to ensure the benefits of this product outweigh its risks. Lilly submitted a New Drug Application (NDA 207924) for baricitinib on January 15, 2016, for the proposed indication of treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to methotrexate. This application is under review in the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP). The applicant did not submit a REMS with this application, but the submission includes a risk management plan that proposes routine risk minimization measures through the use of the labeling.

2 Background

2.1 Product Information

Olumiant (baricitinib), a new molecular entity, is a Janus kinase (JAK) inhibitor proposed for the treatment of moderately to severely active rheumatoid arthritis in adults. Janus kinases are a family of tyrosine kinases that play an important role in cytokine signal transduction. Many of the pro-inflammatory cytokines implicated in the pathogenesis of rheumatoid arthritis, including interleukin-6 (IL-6) and granulocyte macrophage colony-stimulating factor (GMCSF), use cell signaling that involves the JAK signal transducers and activators of transcription (STAT) pathways.

The class of Janus kinase inhibitors includes Jakafi (ruxolitinib) and Xeljanz (tofacitinib). Jakafi was approved in November 2011 for the treatment of intermediate or high-risk myelofibrosis and polycythemia vera. Xeljanz was approved in November 2012 with a communication plan REMS for the

\[\text{FDAAA factor (F)}: \text{Whether the drug is a new molecular entity.}\]
treatment of moderate to severe rheumatoid arthritis (RA) in adult patients. The goal of the Xeljanz REMS was to mitigate the risk of serious infections, malignancies, lymphoproliferative disorders, increased cholesterol, and low blood cell counts, by informing healthcare prescribers and pharmacists about these risks. The REMS was released in February 2016 after the Agency determined the communication plan was no longer necessary because it had been completed and the most recent REMS assessment demonstrated the communication plan had met its goals.

Baricitinib is supplied as an oral tablet and is to be administered as a chronic therapy in a single daily dose of 4 mg. For some patients, a dose of 2 mg once daily may be acceptable. As an oral therapy, the drug will typically be self-administered in the outpatient setting. Baricitinib is not currently approved in any country.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for NDA 207924 relevant to this review:

- 09/02/2015: Applicant informed at pre-NDA meeting that the need for a REMS for baricitinib will be determined during the review.
- 01/15/2016: NDA 207924 submission for the treatment of moderately to severely active rheumatoid arthritis in adults received.
- 06/30/2016: A post mid-cycle meeting was held between the Agency and the applicant via teleconference. The Agency informed the applicant that as the review of the application continues Lilly will be informed of any major safety concerns or need for a REMS for baricitinib.
- 10/4/2016: A post late-cycle meeting was held between the Agency and the applicant. The Agency informed the applicant that there are disagreements regarding the safety analyses and the presentation of safety data, and that the safety review is ongoing and additional analyses may be requested. There was no discussion of the need for a REMS during the meeting.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves synovial joints. The annual incidence of RA has been reported to be approximately 40 per 100,000. The disease prevalence is about 1 percent in Caucasians but varies between 0.1 percent in rural Africans to 5 percent in certain Native American tribes. Women are affected two to three times more often than men. The peak onset of RA is between the ages of 50 and 75, and because of the consistently higher rates in females, the prevalence in females over age 65 is as high as 5 percent. The onset of RA is usually insidious, with the predominant symptoms being pain, stiffness, and swelling of many joints. The arthritis is typically symmetrical and usually leads, if uncontrolled, to destruction of joints due to erosion of cartilage and bone, causing joint deformities. However, the disease shows variation of clinical

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b FDAAA factor (D): The expected or actual duration of treatment with the drug.

c FDAAA factor (A): The estimated size of the population likely to use the drug involved.
expression in individual patients, including the number of involved joints and pattern of joint involvement, fluctuations in disease activity and ability to achieve remission, and the rate of progression and extent of structural damage. RA usually progresses from the periphery to more proximal joints and results in significant disability within 10 to 20 years in patients who do not fully respond to treatment. In patients with severe joint disease, non-articular organs can become involved. Involvement of the musculoskeletal system (other than joints) and of organs not considered part of the musculoskeletal system (e.g., skin, eye, lung, heart, kidney, blood vessels) occurs in about 40 percent of patients with RA over a lifetime of disease and is associated with increased disease severity, morbidity, and premature mortality. 

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS 4

Pharmaceutical treatment options in RA include nonsteroidal anti-inflammatory drugs (NSAIDs), selective NSAID COX-2 inhibitors, corticosteroids, conventional disease-modifying antirheumatic drugs (DMARDs) such as methotrexate, biologic DMARDs such as tumor necrosis factor [TNF] inhibitors, interleukin (IL) inhibitors, T-cell costimulation modulators, B-cell depletion therapies, and the new class of Janus kinase DMARDs. Anti-inflammatory drugs, including NSAIDs and corticosteroids, are used primarily as adjuncts for temporary control of disease activity. DMARDs are a diverse group of therapeutic agents that reduce signs and symptoms of RA as well as slow disease progression.

Table 1 below shows a list of the DMARDs recently approved in the U.S. since the late 1990s. Of this group of products, TNF inhibitors, the IL-6 inhibitor tocilizumab, and the Janus kinase inhibitor tofacitinib all required communication plan REMS that were approved during the period from 2008 to 2012. All of the REMS have been released because the communication plans have been completed and the REMS assessments showed that each REMS had met its goals. In several of the REMS that included a Medication Guide as a required element, it was determined to maintain the Medication Guide as part of labeling under CFR 208 was sufficient to communicate the risks.

\[\text{\textsuperscript{d}}\text{ FDAAA factor (B): The seriousness of the disease or condition that is to be treated with the drug.}\]
<table>
<thead>
<tr>
<th>Product Name (Trade Name)</th>
<th>Year of Approval</th>
<th>Mechanism of action</th>
<th>Indications</th>
<th>REMS History</th>
<th>• Boxed Warnings</th>
<th>Risks addressed by REMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leflunomide (Arava)</td>
<td>1998</td>
<td>Anti-metabolite</td>
<td>Rheumatoid arthritis</td>
<td>No REMS</td>
<td>Embryo-fetal toxicity, Hepatic toxicity</td>
<td></td>
</tr>
<tr>
<td>Anakinra (Kineret)</td>
<td>2001</td>
<td>IL-1 inhibitor</td>
<td>Rheumatoid arthritis, Cryopyrin-associated periodic syndromes</td>
<td>No REMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adalimumab (Humira)</td>
<td>2002</td>
<td>TNF inhibitor</td>
<td>Rheumatoid arthritis, Juvenile idiopathic arthritis, Psoriatic arthritis, Adult Crohn’s disease, Pediatric Crohn’s disease, Ulcerative colitis, Plaque psoriasis, Hidradenitis suppurativa, Uveitis</td>
<td>(REMS Approved 2010) Communication Plan REMS Released December 2011</td>
<td>Serious infections, Malignancy</td>
<td>Serious fungal infections</td>
</tr>
<tr>
<td>Abatacept (Orencia)</td>
<td>2005</td>
<td>T cell activation inhibitor</td>
<td>Rheumatoid arthritis, Juvenile idiopathic arthritis</td>
<td>No REMS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>2006</td>
<td>Anti-CD 20 B-cell depletion</td>
<td>Non-hodgkin’s lymphoma, Chronic lymphocytic leukemia, Rheumatoid arthritis, Granulomatosis with polyangitis and microscopic polyangitis</td>
<td>No REMS</td>
<td>Fatal infusion reactions, Severe mucocutaneous reactions, Hepatitis B reactivation, Progressive multifocal leukoencephalopathy</td>
<td></td>
</tr>
<tr>
<td>Golimumab (Simponi)</td>
<td>2009</td>
<td>TNF inhibitor</td>
<td>Rheumatoid arthritis, Psoriatic arthritis, Ankylosing spondylitis, Ulcerative colitis</td>
<td>Medication Guide Communication Plan REMS Released March 2011</td>
<td>Serious infections, Malignancy</td>
<td>Serious infections, malignancies, congestive heart failure, demyelinating disorders</td>
</tr>
<tr>
<td>Tocilizumab (Actemra)</td>
<td>2010</td>
<td>IL-6 inhibitor</td>
<td>Rheumatoid arthritis, Polychravid juvenile idiopathic arthritis, Systemic juvenile idiopathic arthritis</td>
<td>Communication Plan REMS released August 2015</td>
<td>Serious infections, Malignancy</td>
<td>Serious infections, gastrointestinal perforations, hepatic effects, decreased neutrophil or platelet counts, elevations in lipid parameters, demyelinating disorders, malignancies</td>
</tr>
<tr>
<td>Tofacitinib (Xeljanz)</td>
<td>2012</td>
<td>Janus kinase inhibitor</td>
<td>Rheumatoid arthritis</td>
<td>Communication Plan REMS released February 2016</td>
<td>Serious infections, Malignancy</td>
<td>Serious infections, malignancy, increase in cholesterol, and decrease in blood counts</td>
</tr>
</tbody>
</table>
4 Benefit Assessment

The clinical development program for baricitinib included four multicenter, double-blind, randomized, placebo- or active-controlled Phase 3 studies of patients with moderate to severe RA.

- Study JADV evaluated 1,305 patients with insufficient response to MTX. Patients received treatment with baricitinib 4 mg daily, adalimumab 40 mg SC every other week, or placebo. All treatments were added therapy to MTX. The primary efficacy endpoint was ACR20\(^e\) (American College of Rheumatology 20% response in RA) response at Week 12.
- Study JADW evaluated 527 patients with insufficient response to TNF inhibitors and receiving stable doses of conventional DMARD therapy. Patients received treatment with baricitinib 4 mg daily or 2 mg daily or placebo. The primary efficacy endpoint was ACR 20 at Week 12.
- Study JADX assessed 684 patients with insufficient response to conventional DMARD therapy. Patients received treatment with baricitinib 4 mg daily or 2 mg daily, or placebo. Background DMARD therapy was continued. The primary efficacy endpoint was ACR 20 at Week 12.
- Study JADZ evaluated 584 patients with limited to no treatment with MTX. Patients received baricitinib 4 mg daily, baricitinib 4 mg daily plus MTX, or MTX alone. The primary efficacy endpoint was ACR 20 at Week 24.

Multiple secondary endpoints were also evaluated in the studies, including the HAQ-DI\(^f\) (Health Assessment Questionnaire-Disability Index), the modified Total Sharp Score (mTSS)\(^g\) at 24 weeks, the Simplified Disease Activity Index (SDAI)\(^h\), and the DAS28-hsCRP\(^i\) (Disease Activity Score in 28 joints), among other endpoints.

In Study JADV, a statistically significant improvement in the ACR20 response rate was observed at Week 12 for the baricitinib 4 mg group (70% of patients) compared to placebo (40%) (p ≤ 0.001). Baricitinib was also superior to adalimumab (61%) based on ACR20 at Week 12 (p=0.014). Secondary endpoints including HAQ-DI, mTSS at 24 weeks, SDAI, and DAS28-hsCRP also showed statistically significant improvements for the baricitinib 4 mg group from baseline compared to placebo.

Study JADW found that a statistically significant improvement in ACR20 response rate was observed at Week 12 for the baricitinib 4 mg group (55%) (p ≤ 0.001) and the baricitinib 2 mg group (49%) (p ≤ 0.001) compared to placebo (27%). Compared to placebo, improvements in the HAQ-DI change from baseline and DAS28-hsCRP change from baseline were statistically significant at Week 12 for baricitinib 4 mg. Statistical significance for SDAI remission endpoints were not met for either dose group compared with placebo.

In Study JADX a statistically significant improvement in ACR20 response rate was observed at Week 12 for the baricitinib 4 mg group (62%) (p ≤ 0.001) and the baricitinib 2 mg group (66%) (p ≤ 0.001) compared with placebo (40%). Statistically significant improvement for each baricitinib dose group was observed in the change from baseline in HAQ-DI score, DAS28-hsCRP, and SDAI response rate compared with placebo.

\(^e\) The American College of Rheumatology’s 20% response in RA (ACR20) is calculated as a ≥20% improvement in tender joint count and swollen joint count, as well as 3 of 5 ACR core set measures including physician and patient global assessments, patient-reported pain, patient assessment of physical function, and acute phase reactant.

\(^f\) Health Assessment Questionnaire-Disability Index. Higher scores indicate greater disability.

\(^g\) A scoring system used to quantify the radiological changes in patients with rheumatoid arthritis.

\(^h\) Determines the severity of rheumatoid arthritis using clinical and laboratory data.

\(^i\) Disease Activity Score in 28 joints calculated with the value of high sensitivity C-reactive protein.
Study JADZ showed that baricitinib 4 mg plus MTX (78%) was superior to MTX monotherapy (62%) with respect to ACR20 response rates at Week 24 (p=0.001). Baricitinib 4 mg monotherapy (77%) was also significantly superior to MTX monotherapy (62%) at Week 24 (p=0.003). The change from baseline in HAQ-DI score, DAS28-hsCRP, and SDAI response rate compared with MTX monotherapy were statistically significant for the baricitinib 4 mg group. The change in mTSS was not significantly different for baricitinib monotherapy compared with MTX monotherapy at 24 weeks.

The cross-discipline team leader concluded that the studies provide evidence of efficacy of baricitinib for reducing signs and symptoms of RA based on the proportion of patients experiencing an ACR20 response and improvement in physical function as measured by the HAQ-DI, and efficacy of baricitinib 4 mg on structural damage progression.

5 Risk Assessment & Safe-Use Conditions

3464 patients received baricitinib in the Phase 1, 2, and 3 RA studies (the ALL BARI RA safety set). The primary safety analysis set is comprised of six placebo-controlled studies (three Phase 2 studies and studies JADV, JADW, and JADX) and includes 1070 patients in the placebo arms and 997 patients in the baricitinib 4 mg arms (study JADZ was not included in the primary analysis set because there was no placebo arm). An additional safety analysis set (BARI 2mg/4mg) evaluated 1476 patients who received baricitinib 4mg or 2mg in the placebo-controlled studies mentioned above.

5.1 Serious Adverse Events

In the Phase 2 and 3 RA studies (n=3411 patients), there were 22 deaths reported. During the placebo- and active-controlled portions of the Phase 2/3 studies (up to rescue or switch to baricitinib), there were 7 deaths in the combined placebo, MTX monotherapy and adalimumab arms (n=1610 patients) compared with 13 deaths in patients who received baricitinib. Two deaths that occurred during screening in Studies JADC (Phase 2) and JADV were both due to myocardial infarction and were not considered related to study procedures. The causes of death in patients treated with baricitinib included respiratory failure, pneumonia, abdominal infection, bleeding ulcer/circulatory failure, hemorrhagic stroke, thrombotic stroke, lung cancer, pancreatic cancer, myocardial infarction, pulmonary thromboembolism, presumed cardiorespiratory arrest, presumed myocardial infarction, and natural causes. The clinical reviewer considered the overall number of deaths to be low and that there did not appear to be unexpected mortality for a population of patients with RA.

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\(^1\) Maynard J. Cross-Discipline Team Leader Review for Olumiant (baricitinib), NDA 207924, January 5, 2017.

\(^k\) FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.

\(^l\) Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

\(^m\) FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.

\(^n\) Nair R., Clinical Reviewer, Olumiant (baricitinib), NDA 207924, email communication, January 5, 2017.
In the primary safety analysis set, the proportion of patients who had a serious adverse event (SAE) up to Week 16 was slightly higher in the baricitinib 4mg group (3.9% [39/997]) compared with the placebo group (3.7% [40/1070]). In the BARI 2mg/4mg safety set, the proportion of patients in the treatment group who experienced an SAE (3.7% [54/1476]) through Week 16 was essentially the same as the placebo group. Table 1 below lists the SAEs occurring in at least 2 patients in either the placebo group or baricitinib 2mg/4mg group by MedDRA preferred term up to Week 16.

Table 1. Serious Adverse Events Up to Week 16 and n≥2 in the BARI 4mg/2mg safety set

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>Placebo [n=1070] n</th>
<th>Baricitinib 4mg/2mg [n=1476] n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>Coronary artery disease</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Eye</td>
<td>Cataract</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td>Pneumonia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Infections</td>
<td>Herpes zoster</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Infections</td>
<td>Cellulitis</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td>Urinary tract infection</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Infections</td>
<td>Bronchitis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Injury</td>
<td>Fall</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hyperglycemia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Rheumatoid arthritis</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Back pain</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
<td>Renal failure</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Vascular</td>
<td>Hypertension</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

5.2 Serious Infections

In the primary analysis set, the proportion of patients with treatment-emergent infections was higher in the baricitinib 4mg group (29.7%) than in the placebo group (23.4%) up to Week 16. The proportion of serious infections was similar between the baricitinib group (1.1% [11/997]) and the placebo group (1.2% [13/1070]). In the BARI 2mg/4mg safety set, the proportion of patients with serious infections was the same (1.1% [16/1476]) as in the 4mg analysis set. Serious infections associated with baricitinib included herpes zoster, epiglottitis, viral gastroenteritis, helicobacter gastritis, upper or lower respiratory tract infection, pneumonia, urinary tract infection, viral infection, vulval abscess, bronchitis, gastroenteritis, and intervertebral discitis. In the ALL BARI RA safety set, the three most frequently reported serious infection preferred terms were pneumonia (n=22), herpes zoster (n=20), and urinary tract infection (n=15).

Herpes zoster

Administration of baricitinib was associated with an increased risk of herpes zoster compared to placebo. In the primary analysis set, there were 18 patients in the baricitinib group with treatment-emergent herpes zoster (3 serious cases) compared with 4 patients (1 serious case) in the placebo group. With the exception of one severe case in the treatment group, all cases were mild to moderate in severity. In the BARI RA safety set, there were 141 cases of treatment-emergent herpes zoster; 21 of these cases were serious and 9 were considered severe. Three treatment-emergent cases were multidermatomal and two cases involved facial palsy.
**Tuberculosis**

In the ALL BARI RA safety set, 7 treatment-emergent adverse events (3 serious) of tuberculosis occurred in patients receiving baricitinib 4mg either during or after the randomized, controlled period. One case involved disseminated pulmonary tuberculosis. The other six cases included pulmonary tuberculosis and extrapulmonary tuberculosis that involved the lymph nodes; the mediastinum; vertebrae; and the psoas muscle compartment.

**Other potential opportunistic infections**

Five cases of esophageal candidiasis (none serious) and 3 serious cases of pneumocystis pneumonia were reported in association with baricitinib treatment in the ALL BARI RA safety set.

### 5.3 Potential Major Adverse Cardiovascular Events

In the Phase 3 placebo-controlled studies up to Week 16, a total of 48 (3.7%) of 1294 baricitinib-treated patients had at least 1 potential major adverse cardiovascular event (MACE) or other cardiovascular event compared with 10 (1.1%) of 892 patients in the placebo group. However, elevations in creatine phosphokinase accounted for the majority of events associated with baricitinib and were reported in 43 of the 48 patients in the baricitinib group and 4 of 10 patients in the placebo group. There was 1 myocardial infarction in each group; 1 ischemic stroke in the baricitinib group vs. 0 in the placebo group; and 3 coronary revascularizations in the baricitinib group compared with 1 in the placebo group. There was also 1 report of ventricular tachycardia in the placebo group but no ventricular arrhythmias in the baricitinib group.

In the placebo- or active-controlled Phase 3 studies (including long-term extension study JADY), positively adjudicated MACE occurred in 16 patients treated with baricitinib compared with 2 patients in the placebo group, 2 patients treated with MTX monotherapy, and 1 patient treated with adalimumab. The most common type of MACE was myocardial infarction, which accounted for 8 of the 13 MACE in patients treated with baricitinib 4 mg. The clinical reviewer noted that while more cardiovascular events occurred in the baricitinib group, greater exposure to baricitinib was probably the reason for this finding, and that the overall incidence rate of MACE in all baricitinib RA studies was low.

### 5.4 Malignancies

Malignancies were observed in the clinical studies. In the Phase 2 and 3 RA studies (n=3411 patients) there were a total of 34 (1.0%) serious treatment-emergent malignancies associated with baricitinib identified by the MedDRA neoplasms SOC. There were 3 cases of invasive ductal breast carcinoma and 2 cases each of basal cell carcinoma, breast cancer, clear cell renal cell carcinoma, malignant lung neoplasm, and uterine leiomyoma. All other malignancies were reported only one time. In the primary safety analysis set, the overall incidence rate of malignancy was 0.5 events per 100 patient years in the baricitinib 2mg/4mg group compared with 0 in the placebo group during the first 16 weeks. The cross-discipline team leader review noted that given the number of events observed, there is limited ability to rule out increases in risk based on currently available data.

### 5.5 Gastrointestinal Perforations
In the Phase 2 and 3 RA studies, there were 7 treatment-emergent adverse events in 6 patients. Three of the adverse events were serious, including one case of diverticular perforation and peritonitis, and a second case of a perforated appendix. The other non-serious adverse events included abdominal abscess, abdominal wall abscess, anal abscess, and rectal abscess.

5.6  **Transaminase Elevations**

A comparison of the baricitinib 4mg group and the placebo group through 24 weeks of treatment found a higher proportion of patients in the baricitinib group (221/902 [24.5%]) with at least one abnormal high ALT level compared with placebo (134/932 [14.4%]). A slightly higher proportion of patients in the baricitinib group (1.5%) also experienced at least one ALT value ≥3x the upper limit of normal (ULN) compared with the placebo group (1.3%) in patients whose ALT was normal at baseline. Two patients who received baricitinib experienced an ALT value 10x the ULN. No patient in the baricitinib group developed a total bilirubin level greater than or equal to 2x the ULN.

In the ALL BARI RA safety set, 1.9% of patients in the baricitinib group with a normal baseline value experienced an ALT elevation ≥3x the ULN, and 1 patient developed a total bilirubin ≥2x the ULN. No cases meeting Hy’s Law criteria were identified in patients receiving baricitinib.

5.7  **Other Laboratory Abnormalities**

In the primary safety dataset, treatment-emergent abnormal low neutrophil counts occurred in 2.7% of patients treated with placebo and 8.3% of patients treated with baricitinib 4 mg up to Week 16. There were no neutrophil counts below 500 cells/mm³ observed in any treatment group. Additionally, lymphocyte counts less than the lower limit of normal were associated with infection in patients treated with baricitinib in the clinical studies. Treatment with baricitinib was also associated with decreases in hemoglobin.

Baricitinib was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol. In the primary safety dataset, treatment-emergent hyperlipidemia adverse events were reported in 6.9% of patients treated with baricitinib compared with 3.5% of patients who received placebo up to Week 16. None of the adverse events resulted in serious outcomes.

6  **Expected Postmarket Use**

We expect the prescribing community for baricitinib to be similar to that for the other Janus kinase inhibitor indicated for RA. In the FDAAA Section 915 New Molecular Entity (NME) Postmarket Safety Summary for tofacitinib NDA 203214, dated December 4, 2014, a review of prescription claims data found that rheumatologists comprised approximately 80% of tofacitinib prescribers, followed by primary care physicians, and to a small extent, other specialties. Baricitinib is likely to be prescribed by a similar provider profile. As an orally administered drug, baricitinib will primarily be self-administered by patients in the outpatient setting as a chronic therapy.
7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application, but the submission includes a risk management plan that proposes routine risk minimization measures through the use of the labeling and routine pharmacovigilance. Lilly is also proposing the use of a Medication Guide as part of the labeling.

7.1 OTHER PROPOSED RISK MANAGEMENT ACTIVITIES

The applicant's risk management plan proposes observational postmarketing safety studies to further investigate the incidence and profile of serious infections and hepatic effects; fetal malformation; MACE; malignancies; and the safety profile in the very elderly.

Reviewer’s comment: We note that these other activities proposed by the applicant are outside of the scope of a REMS program and defer to the appropriate review divisions for review, as needed.

8 Discussion of Need for a REMS

The cross-discipline team leader recommends approval of baricitinib based on the data in the submission, the seriousness of RA, and an adequately favorable benefit/risk profile.

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disorder of unknown etiology that primarily involves synovial joints. If uncontrolled, the disease can lead to joint destruction due to erosion of cartilage and bone, causing deformities and significant disability. In patients with severe joint disease, non-articular organs can become involved, including the skin, eye, lung, heart, kidney, and other organ systems, which is associated with increased disease severity, morbidity, and premature mortality.

Four randomized, double-blind, trials demonstrate effectiveness of baricitinib for the treatment of rheumatoid arthritis. Studies JADX and JADW, which evaluated patients with insufficient response to treatment with conventional DMARDs and TNF inhibitors, showed statistically significant effects of baricitinib 4mg and 2mg therapy compared to placebo based on the ACR20 response. Study JADV evaluated patients with insufficient response to MTX to treatment with baricitinib 4mg, adalimumab 40 mg SC every other week or placebo as add-on therapies to MTX. Statistically significant improvements in the ACR20 response were observed for the baricitinib group compared to both placebo and adalimumab. Study JADZ evaluated treatment with baricitinib 4mg, baricitinib 4mg plus MTX, or MTX alone. Baricitinib alone or administered concurrently with MTX showed significantly improved ACR20 response rates compared to MTX monotherapy.

The serious risks associated with baricitinib include serious infections (including opportunistic infections such as tuberculosis, candidiasis, and pneumocystis) and malignancies. The proposed prescribing information, at this time, includes a Boxed Warning for these risks. Additional serious adverse reactions include gastrointestinal perforations and laboratory abnormalities, including decreased blood counts, elevated liver enzymes, and hyperlipidemia. These risks as well as respective monitoring recommendations will be found in the warnings and precautions section of the label. Elevations in creatine phosphokinase will be described in the adverse reactions section.

Baricitinib is a Janus kinase inhibitor similar to tofacitinib. The proposed indication statement for baricitinib is the treatment of adults with moderately to severely active rheumatoid arthritis who have had
an inadequate response or intolerance to methotrexate; this proposed indication is the same as the approved indication for tofacitinib. Tofacitinib was approved with a REMS in November 2012 to address the risk of serious infections, malignancies, lymphoproliferative disorders, increased cholesterol, and low blood cell counts, by informing healthcare prescribers and pharmacists about these risks. The REMS was released in February 2016 after the Agency determined the communication plan was no longer necessary because it had been completed and the most recent REMS assessment demonstrated the communication plan had met its goals. Therefore, based on the data available, the prescribing community is expected to be familiar with the risks associated with baricitinib, which do not pose unique REMS considerations compared with the risks associated with tofacitinib. At this time, this reviewer is not recommending a REMS for the management of the risks of baricitinib therapy.

9 Conclusion & Recommendations

Based on the available data, a REMS is not necessary to ensure the benefits of baricitinib outweigh the risks. In general, healthcare providers who treat moderate to severe rheumatoid arthritis are already familiar with the risks and need for patient monitoring associated with Janus kinase inhibitors as well as other DMARDs that have been approved for the treatment of rheumatoid arthritis.

Should DPARP have any concerns or questions or if new safety information becomes available, please send a consult to DRISK.

10 Materials Reviewed

The following is a list of materials informing this review:

1 Venables PJW and Maini RM. Clinical manifestations of rheumatoid arthritis. In:UpToDate, O’Dell JR, Romain PL (Eds), Waltham, MA 2016.

2 Matteson EL and Davis JM. Overview of the systemic and nonarticular manifestations of rheumatoid arthritis. In:UpToDate, Maini RN, Romain PL (Eds), Waltham, MA 2016.

3 Gabriel SE and Crowson CS. Epidemiology of, risk factors for, and possible causes of rheumatoid arthritis. In:UpToDate, Maini RN, Romain PL (Eds), Waltham, MA 2016.

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/s/

ROBERT G PRATT
01/06/2017

JAMIE C WILKINS PARKER
01/06/2017

Reference ID: 4037982