Emergency Use Authorization (EUA) for baricitinib, FOR THE UNAPPROVED USE OF AN APPROVED PRODUCT
Center for Drug Evaluation and Research (CDER) Review

I. Issue Summary

The FDA granted authorization on November 19, 2020 for the emergency use of baricitinib (EUA 92), in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). On July 28, 2021, the EUA was revised to no longer require that baricitinib be used in combination with remdesivir for the treatment of COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, noninvasive or
invasive mechanical ventilation, or ECMO. The current EUA amendment requests that the Agency authorize use of a baricitinib 4 mg tablet for treatment of COVID-19.

Under the EUA (EUA 92) a dose of baricitinib 4 mg once daily is recommended for adults and pediatric patients 9 years of age and older with estimated glomerular filtration rate ≥60 mL/min/1.73m². Currently under the EUA the 1-mg and 2-mg tablet strengths are authorized. The 4 mg once-daily dose of baricitinib is achieved using 2 x 2 mg tablets. The Sponsor (Eli Lilly and Company) has seen a significant increase in orders of the baricitinib 2-mg tablets in the US leading to a potential drug shortage and is therefore requesting the FDA to authorize the 4 mg tablet.

Baricitinib is approved for the treatment of rheumatoid arthritis (RA) under NDA 207924 and the approved dosage forms are 1 mg and 2 mg tablets. The 1 mg tablet was added post-approval to comply with a post-marketing requirement. The original NDA 207924 proposed the 2 mg and 4 mg tablets as once-daily doses for moderate to severe rheumatoid arthritis (RA) and the Office of Pharmaceutical Quality (OPQ) review team evaluated both the 2 and 4 mg tablets chemistry, manufacturing and controls (CMC) information and recommended approval of both strengths under NDA 207924 with 24 months of shelf life, from a quality perspective. However, the clinical division only approved the 2 mg tablet for once-daily dosing for the RA indication in the initial approval. Subsequently, the 1 mg strength tablet was approved via Supplement-1 for dose adjustment in RA patients with moderate renal impairment or patients taking strong OAT3 inhibitors.

OPQ has evaluated the CMC changes that have been submitted to the NDA since the original approval and changes associated with the unapproved 4 mg tablet strength. The CMC team has determined that the changes do not impact the original recommendation from a quality perspective (under NDA 207924). OPQ concluded, and the Division of Rheumatology and Transplant Medicine (DRTM) agrees, to recommend authorization of the 4 mg tablets to help mitigate the potential shortage of the 2 mg tablets of baricitinib. Additionally, the CMC team concluded that the alternate administration instructions are reasonable (refer to the CMC memorandum dated 13-OCT-2021 for full details).

II. Clinical Pharmacology

This EUA amendment requests that the Agency authorize the use of a 4 mg tablet for treatment of COVID-19 in addition to the use of 1 mg and 2 mg tablets. Baricitinib has linear PK. The original NDA 207924 evaluated both the 2 mg and 4 mg tablets as once-daily regimen for moderate to severe rheumatoid arthritis (RA). However, as the approved dosing regimen was 2 mg once-daily for the RA indication in the initial approval, only the 2 mg tablet was
approved. Although the 4 mg dose of baricitinib has not been approved under NDA 207924 for RA, it is approved outside of the US.

In the original NDA 207924, the commercial 4 mg tablets were evaluated in multiple Phase 2 studies as well as Phase 3 studies. Food effect for 4 mg tablet was evaluated in Study JAGO. A low-fat meal only slightly decreased (approximately 15%) the systemic exposure with 90% CIs for the ratios of geometric LS means were all completely contained within the limits of 0.8 to 1.25 and did not affect the rate of baricitinib absorption. This food effect assessment showed that baricitinib 4 mg tablets, as with 2 mg tablets, can be administered in either the fed or the fasted state. As such, clinical pharmacology recommends authorization of the 4 mg tablets to help mitigate the potential shortage of the 2 mg tablets of baricitinib.

III. Summary of Revision to EUA Fact Sheets

The proposed revisions to the EUA healthcare provider fact sheet include updates to include the 4 mg tablet and are shown below (additions are shown in underline, deletions shown by strikethrough). The revision to the healthcare provider fact sheet do not alter the analysis of benefit and risks that underlies the authorization of EUA 92.

Revisions to health care provider fact sheet include the following changes to the Alternate Administration and How Supplied Sections:
How Supplied/Storage and Handling

How Supplied
Baricitinib for oral administration is available as debossed, film-coated, immediate-release tablets. Each tablet contains a recessed area on each face of the tablet surface.

Under this EUA, baricitinib is supplied in 30 count bottles as follows:

- OLUMIANT (baricitinib) tablet 1 mg (NDC 0002-4732-30)
- OLUMIANT (baricitinib) tablet 2 mg (NDC 0002-4182-30), and
- baricitinib tablet 4 mg (NDC 0002-6885-30)
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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