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

Identifying Information

Application Type (EUA or Pre-EUA) If EUA, designate whether pre-event or intra-event EUA request.	EUA
EUA Application Number(s)	92
Sponsor (entity requesting EUA or pre-EUA consideration), point of contact, address, phone number, fax number, email address	Eli Lilly and Company Lilly Corporate Center Indianapolis IN 46285 Attention: Jillian Fuhs, JD, PharmD Advisor, Global Regulatory Affairs-North America (b) (6) jillian_fuhs@lilly.com
Submission Date(s)	October 4, 2021
Receipt Date(s)	October 4, 2021
OND Division / Office	Division of Rheumatology and Transplant Medicine (DRTM)/Office of Immunology and Inflammation (OII)
Established Name/Other names used during development	Baricitinib
Dosage Forms/Strengths	Tablet, 4mg
Therapeutic Class	Janus kinase inhibitor
Intended Use or Need for EUA	Treatment of coronavirus disease 2019 (COVID-19)
Intended Population(s)	Hospitalized adult and pediatric patients 2 years and older with COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical

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 $\geq$60 mL/min/1.73m^2. 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 summitted 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:

Preparation for Alternate Administration

- *Oral administration of dispersed tablets in water:*
  For patients who are unable to swallow whole tablets, 1-mg, ~~and/or~~ 2-mg, or 4-mg baricitinib tablet(s), or any combination of tablets necessary to achieve the desired dose up to 4-mg may be placed in a container with approximately 10 mL (5 mL minimum) of room temperature water, dispersed by gently swirling the tablet(s) and immediately taken orally. The container should be rinsed with an additional 10 mL (5 mL minimum) of room temperature water and the entire contents swallowed by the patient (see Table 2).

- *Administration via gastrostomy feeding tube:*
  For patients with a gastrostomy feeding tube, 1-mg, ~~and/or~~ 2-mg, or 4-mg baricitinib tablet(s), or any combination of tablets necessary to achieve the desired dose up to 4-mg may be placed in a container with approximately 15 mL (10 mL minimum) of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw entire contents from the container into an appropriate syringe and immediately administer through the gastric feeding tube. Rinse container with approximately 15 mL (10 mL minimum) of room temperature water, withdraw the contents into the syringe, and administer through the tube (see Table 2).

- *Administration via nasogastric feeding tube:*
  For patients with an enteral feeding tube, 1-mg, ~~and/or~~ 2-mg, or 4-mg baricitinib tablet(s), or a combination of tablets necessary to achieve the desired dose up to 4-mg may be placed into a container with approximately 30 mL of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw the entire contents from the container into an appropriate syringe and immediately administer through the enteral feeding tube. To avoid clogging of small diameter tubes (smaller than 12 Fr), the syringe can be held horizontally and shaken during administration. Rinse container with a sufficient amount (minimum of 15 mL) of room temperature water, withdraw the contents into the syringe, and administer through the tube (see Table 2).

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)

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