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)	September 10, 2021
Receipt Date(s)	September 10, 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, 2 mg, 1 mg
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 ventilation or ECMO

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, non-invasive or invasive mechanical ventilation, or ECMO. The current EUA amendment requests that the Agency authorize splitting of the unscored 2 mg tablet in half and administering half the tablet once daily if the 1 mg tablet is unavailable. The request is due to a potential shortage of the 1 mg tablets. The 1 mg once-daily dose is for adult and pediatric patients 9 years of age and older

with severe renal impairment and for pediatric patients aged 2 to less than 9 years of age with moderate renal impairment.

The sponsor (Eli Lilly) indicates that the annual US demand for baricitinib is (b) (4) 2 mg tablets and (b) (4) 1 mg tablets for the rheumatoid arthritis indication. Thus far in 2021, an additional (b) (4) 2 mg tablets were produced for COVID-19 treatment. However, the sponsor has seen an increase in orders for baricitinib 30 count 2 mg bottles since the beginning of August 2021 from an average of (b) (4) per month to (b) (4) in the month of August. The sponsor has also seen an increase in shipments for the 1 mg 30 count bottles to wholesalers from a baseline of (b) (4) bottles per month to (b) (4) in August 2021. (b) (4) .

The sponsor evaluated (b) (4) options to derive 1 mg doses from the 2 mg tablets which are in greater supply, but which are not scored for splitting: 1) splitting using a tablet splitter; (b) (4) Of these options, the sponsor recommends the use of a tablet splitter that has a razor blade, to obtain 1 mg doses from the 2 mg tablets.

The sponsor's proposal of splitting the 2 -mg tablet in half with a tablet splitter along the longest diameter of the tablet and administering half the tablet once daily if the 1 -mg tablet is unavailable, was reviewed by Office of Pharmaceutical Quality (OPQ) and Office of Clinical Pharmacology. Based on the reviews of OPQ, Clinical Pharmacology, and clinical teams, it is not expected that minor differences in split tablet size would have significant impact on the clinical efficacy or safety of baricitinib for the treatment of COVID-19. OPQ and Clinical Pharmacology concluded, and the Division of Rheumatology and Transplant Medicine (DRTM) agrees, that the proposal to split the 2 mg tablet in half is a reasonable approach to mitigate the anticipated temporary shortage related to availability of the 1 mg tablet. Based on the reviews of OPQ and Clinical Pharmacology teams, it is not expected that minor differences in split tablet size would have significant impact on the clinical efficacy.

The EUA authorization will be revised to allow tablet splitting of the 2 mg tablet only in cases where the 1 mg tablet is not available for patients requiring the 1 mg dose. The EUA fact sheet will also be updated to specify how the tablet can be split, care in storing the second dose and visual inspection of the tablet parts.

II. CMC

EUA 92 from Eli Lilly is authorized for the treatment of hospitalized COVID-19 patients. The treatment utilizes Olumiant (baricitinib) tablets of both 1 and 2 mg strengths, approved under NDA 207924. The sponsor submitted an EUA amendment requesting that hospitals be allowed to split the unscored 2 mg tablets with a tablet splitter with a razor blade along the longest diameter. The reason for the request is that there is an anticipated shortage of the 1 mg tablet

strength, which is used to treat patients with renal impairment, as per the approved dose adjustments of NDA 207924. The sponsor provided data for the weights and drug assay of split 2 mg tablets in support of the proposal. The CMC team have reviewed these data and summarized the results for the clinical and clinical pharmacology teams to evaluate whether or not the splitting of the unscored tablets will provide doses with sufficient comparability to that provided by the 1 mg tablets that are likely to be in shortage in the near future. A summary of conclusions and recommendations is provided below (refer to the CMC memorandum dated 22-SEP-2021 for full details).

III. Clinical Pharmacology

In this amendment, the sponsor is seeking authorization of splitting the 2 mg tablet in half with a tablet splitter and administering half the tablet once daily if the 1 mg tablet is unavailable. This request is to mitigate a potential drug shortage of the 1 mg baricitinib tablets as a result of significant increase in orders since the EUA for baricitinib was issued on November 19, 2020. The 1 mg baricitinib tablet is used for adult and pediatric patients 9 years of age and older with severe renal impairment (15 to <30 mL/min/1.73 m2) and pediatric patients aged 2 to less than 9 years with moderate renal impairment (30 to <60 mL/min/1.73 m2), whose recommended dose is 1 mg once daily.

In addition to the proposal of splitting the 2 mg tablet in half, (b) (4) alternative options were submitted in this amendment: (b) (4)

The alternative option of (b) (4)

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As such, from a clinical pharmacology perspective, the alternative option (b) (4) is not an optimal option to mitigate the potential drug shortage of the 1 mg tablet.

The sponsor's proposal of "splitting the 2 mg tablet in half with a tablet splitter and administering half the tablet once daily if the 1 mg tablet is unavailable" was

reviewed by OPQ. OPQ concluded that the proposal is reasonable with the following comments pertaining to clinical pharmacology:

"Only 5 of the assay values of the portions of the 16 split tablets, if used as 1 mg doses, would be within specification per the approved assay acceptance criterion for Olumiant (1 and 2 mg), which is (b) (4) % LC (NDA 207924). Recall that the replicate 8a tablet was determined visually to be unequally split. Depending on whether or not the replicate 8a portion assays are included or excluded from the results, the estimated dose variability would be 67-127% or 80-120% of 1 mg, respectively. The CMC team defers to the clinical and/or clinical pharmacology teams to decide which estimated level(s) of dosing variability is (are) acceptable for renally impaired hospitalized patients. If it is decided that split portions that are determined visually to be unequal are to be discarded, the footnote c of Table 1 of the EUA factsheet would need to be revised accordingly."

As described in the summary, the split portions if visually determined to be unequal could lead to dosing variability (e.g., 67-127%), which is likely to result in further variation in exposure. As such, we agree with OPQ that the split portions that are determined visually to be unequal should be discarded and the footnote c of Table 1 of the EUA healthcare provider fact sheet will be revised accordingly.

IV. Summary of Revisions to EUA Fact Sheets

Proposed changes to the EUA healthcare provider fact sheet include the addition of a footnote [c] to Table 1 shown below. For clarification, dosage adjustments when coadministered with other medications (strong OAT3 inhibitors) were also added to Table 1. These dosage adjustments were previously described under Drug Interactions. The revised Table 1 is shown below. The revision to the healthcare provider fact sheet do not alter the analysis of benefits and risks that underlies the authorization of EUA 92.

Table 1: Dosage Adjustments

Dosage Adjustments for Patients with Abnormal Laboratory Values[a, b]		
Laboratory Analyte	**Laboratory Analyte Value**	**Recommendation**
eGFR	≥60 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 4 mg once daily • Pediatric patients 2 years to less than 9 years of age: 2 mg once daily
	30 to <60 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 2 mg once daily • Pediatric patients 2 years to less than 9 years of age: 1 mg[c] once daily
	15 to <30 mL/min/1.73 m^2	• Adults and pediatric patients 9 years of age and older: 1 mg[c] once daily • Pediatric patients 2 years to less than 9 years of age: Not recommended
	<15 mL/min/1.73 m^2	Not recommended
Absolute Lymphocyte Count (ALC)	≥200 cells/µL	Maintain dose
	<200 cells/µL	Consider interruption until ALC is ≥200 cells/µL
Absolute Neutrophil Count (ANC)	≥500 cells/µL	Maintain dose
	<500 cells/µL	Consider interruption until ANC is ≥500 cells/µL
Aminotransferases	If increases in ALT or AST are observed and drug-induced liver injury (DILI) is suspected	Interrupt baricitinib until the diagnosis of DILI is excluded
Dosage Adjustments when Coadministered with Other Medications		
Concomitant Medication		**Recommendation**
Strong OAT3 Inhibitors (e.g., probenecid)		• If the recommended baricitinib dose is 4 mg once daily, reduce dose to 2 mg once daily. • If the recommended baricitinib dose is 2 mg once daily, reduce dose to 1 mg[c] once daily. • If the recommended baricitinib dose is 1 mg once daily, consider discontinuing probenecid.

[a] Abbreviations: ALC = absolute lymphocyte count, ALT = alanine transaminase, ANC = absolute neutrophil count, AST = aspartate transaminase, DILI = drug induced liver injury, eGFR = estimated glomerular filtration rate.

[b] If a laboratory abnormality is likely due to the underlying disease state, consider the risks and benefits of continuing baricitinib at the same or a reduced dose.

[c] Only if a 1 mg tablet is not available, a 2 mg tablet can be split using a tablet splitter that has a razor blade to administer half a 2 mg tablet once daily. The tablet should be split along the longest diameter. If the portions of the tablet are determined to be visually unequal they should be discarded. Take care in storing the second tablet half to avoid breakage prior to next dose.

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