Baricitinib Receives Emergency Use Authorization from the FDA for the Treatment of Hospitalized Patients with COVID-19

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- ACTT-2 data serve as basis for EUA, the second COVID-19 authorization for a Lilly treatment

- Authorization enables use of baricitinib in combination with remdesivir in hospitalized patients needing oxygen

INDIANAPOLIS, Nov. 19, 2020 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) and Incyte (NASDAQ: INCY) announced today that the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization (EUA) for the distribution and emergency use of baricitinib to be used in combination with remdesivir in hospitalized adult and pediatric patients two years of age or older with suspected or laboratory confirmed COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

"Since the start of the COVID-19 pandemic, Lilly has been committed to finding potential treatments to help people around the world who've been impacted by this virus," said David A. Ricks, Lilly chairman and CEO. "Today's FDA action for baricitinib marks the second Lilly therapy to be granted an EUA, in addition to the recent neutralizing antibody EUA for high-risk non-hospitalized patients, increasing the number of treatment options for COVID-19 patients at different stages of the disease. This is an important milestone for hospitalized patients on oxygen, as baricitinib may help speed their recovery."

The FDA grants emergency use authorization to provide availability of a medicine that may help diagnose, treat or prevent a life-threatening disease when no adequate and approved alternatives are available. This use of baricitinib is authorized only for the duration of the declaration that circumstances exist justifying the authorization of the emergency use, unless the authorization is terminated or revoked sooner. The authorization is temporary and does not replace the formal review and approval process. In the U.S., baricitinib has not been approved by the FDA to treat COVID-19, and the efficacy, safety and optimal duration of treatment of baricitinib for COVID-19 has not been established. This is the first combination regimen authorized by FDA. Evaluation of baricitinib's efficacy and safety as a treatment for COVID-19 is ongoing in clinical trials.

Scientific evidence supporting this EUA:
The EUA is based on data from the Adaptive COVID-19 Treatment Trial (ACTT-2), a randomized double-blind, placebo-controlled study to evaluate the efficacy and safety of baricitinib in combination with remdesivir versus placebo with remdesivir in hospitalized patients with or without oxygen requirements conducted by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). All patients received standard supportive care by the trial site hospital. The recommended dose for this EUA is baricitinib 4-mg once daily for 14 days or until hospital discharge.

Summary of Key Efficacy and Safety Findings

- Patients treated with baricitinib in combination with remdesivir had a significant reduction in median time to recovery from 8 to 7 days (12.5% improvement) compared to remdesivir [hazard ratio: 1.15; 95% CI 1.00, 1.31; p=0.047].
- Patients treated with baricitinib in combination with remdesivir were more likely to have a better clinical status at Day 15 compared to patients treated with remdesivir [odds ratio: 1.26; 95% CI 1.01, 1.57; p=0.044].
- The proportion of patients who progressed to ventilation (non-invasive or invasive) or died by Day 29 was lower in baricitinib in combination with remdesivir (23%) compared to remdesivir (28%) [odds ratio: 0.74; 95% CI 0.56, 0.99; p=0.039].
- The proportion of patients who died by Day 29 was 4.7% for baricitinib in combination with remdesivir vs. 7.1% for remdesivir, a relative reduction of 35% [Kaplan Meier estimated difference in Day 29 probability of mortality: -2.6% (95% CI -5.8%, 0.5%)].
- Adverse events and serious adverse events were reported in 41% and 15% of patients treated with baricitinib in combination with remdesivir, respectively, vs. 48% and 20% in patients treated with remdesivir. Infections and venous thromboembolism (VTE) occurred in 6% and 4% of patients treated with baricitinib in combination with remdesivir, respectively, vs. 10% and 3% of patients treated with remdesivir. No new safety signals were identified for baricitinib-treated patients.

"The results of ACTT-2 provide physicians and the medical community much-needed insights and randomized placebo-controlled evidence supporting the use of baricitinib in combination with remdesivir for the treatment of hospitalized patients with COVID-19; also importantly, the progression to ventilation or death was significantly reduced with the baricitinib-remdesivir combination," said Andre Kalil, M.D., professor at the University of Nebraska Medical Center and a principal investigator of the ACTT studies. "Few treatment options have received an EUA to treat COVID-19 so the authorization of baricitinib is an important step that will give healthcare providers another clinical tool to help patients with advanced disease."

NIAID and the study investigators expect to have the full analysis published in a peer-reviewed manuscript soon.

Baricitinib, an oral JAK inhibitor discovered by Incyte and licensed to Lilly, is approved and commercially available as OLUMIANT in the U.S. and more than 70 countries as a treatment for adults with moderate to severe rheumatoid arthritis (RA) and was recently approved in the European Union for the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy.

"As a company, we have worked quickly and collaboratively to determine the potential utility of our medicines as treatments for COVID-19 and its related complications," said Hervé Hoppenot, Incyte CEO. "We are pleased that the FDA has authorized the use of baricitinib in combination with remdesivir for COVID-19, and look forward to the opportunity to make more therapies available to patients around the world affected by the global pandemic."

Access to baricitinib

Under the EUA, inpatient pharmacies in the U.S. may order OLUMIANT (baricitinib) 1-mg and 2-mg tablets through Lilly authorized specialty distributors. A current list of Lilly's authorized distributors of record for the EUA is available at lillytrade.com. More details about these efforts are available here or by contacting Lilly's 24-hour support line at 1-855-LillyC19 (1-855-545-5921).

Lilly is working with hospitals, healthcare professionals and governments to facilitate patient access to baricitinib and continues to explore the medicine's potential use in COVID-19 with other regulatory agencies outside the U.S. With respect to supply, Lilly remains confident in being able to meet the needs of patients under the EUA in the U.S., as well as for existing approved indications around the world.

Important information about baricitinib for COVID-19

This EUA permits the emergency use of baricitinib, in combination with remdesivir, for treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO. Although there is limited safety data, no new safety issues have been identified. Physicians should avoid the use of baricitinib in patients with known active tuberculosis and consider if the potential benefits outweigh the potential risks in patients with active serious infections other than COVID-19 or chronic/recurrent infections. Prophylaxis for VTE is recommended unless contraindicated. If clinical features of deep vein thrombosis/pulmonary embolism occur, patients should be evaluated promptly and treated appropriately. Evaluate renal, hematologic and hepatic laboratory values at baseline and thereafter, and monitor closely when treating patients with abnormal baseline and post-baseline laboratory values. Avoid use of live vaccines with baricitinib. If a serious hypersensitivity occurs, discontinue baricitinib while evaluating the potential causes of the reaction. Serious venous thrombosis, including pulmonary embolism, and serious infections have been observed in COVID-19 patients treated with baricitinib.

For more information about the authorized use of baricitinib in COVID-19 and mandatory requirements of the EUA, please see the FDA Letter of Authorization, Fact Sheet for Healthcare Providers and Fact Sheet for Patients, Parents and Caregivers (English) (Spanish). For media resources, including product images and fact sheets, please click here.

There are other ongoing trials with baricitinib in COVID-19 hospitalized patients. In June 2020, Lilly initiated a Phase 3 randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of baricitinib versus background therapy in hospitalized adults with COVID-19. The study includes a diverse patient population from Latin America, the U.S., Europe and Asia. Further information about this Phase 3 trial and other investigator-initiated trials can be accessed here or www.lillytrialguide.com.

Indication and Usage for OLUMIANT (baricitinib) tablets (in the United States) for RA patients

OLUMIANT® (baricitinib) 2-mg is indicated for the treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies. Limitation of Use: Not recommended for use in combination with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), or with potent immunosuppressants such as azathioprine and cyclosporine.

IMPORTANT SAFETY INFORMATION FOR OLUMIANT (baricitinib) TABLETS

WARNING: SERIOUS INFECTIONS, MALIGNANCY, AND THROMBOSIS

SERIOUS INFECTIONS: **Patients treated with Olumiant are at risk for developing serious infections that may lead to hospitalization or death. Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids. If a serious infection develops, interrupt Olumiant until the infection is controlled. Reported infections include:**

- **Active tuberculosis (TB), which may present with pulmonary or extrapulmonary disease. Test patients for latent TB before initiating Olumiant and during therapy. If positive, start treatment for latent infection prior to Olumiant use.**
- **Invasive fungal infections, including candidiasis and pneumocystosis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.**
- **Bacterial, viral, and other infections due to opportunistic pathogens.**

Carefully consider the risks and benefits of Olumiant prior to initiating therapy in patients with chronic or recurrent infection.

Closely monitor patients for the development of signs and symptoms of infection during and after treatment with Olumiant including the possible development of TB in patients who tested negative for latent TB infection prior to initiating therapy.

MALIGNANCIES: **Lymphoma and other malignancies have been observed in patients treated with Olumiant.**

THROMBOSIS: **Thrombosis, including deep venous thrombosis (DVT) and pulmonary embolism (PE), has been observed at an increased incidence in patients treated with Olumiant compared to placebo. In addition, there were cases of arterial thrombosis. Many of these adverse events were serious and some resulted in death. Patients with symptoms of thrombosis should be promptly evaluated.**

WARNINGS AND PRECAUTIONS

SERIOUS INFECTIONS: The most common serious infections reported with Olumiant included pneumonia, herpes zoster and urinary tract infection. Among opportunistic infections, tuberculosis, multidermatomal herpes zoster, esophageal candidiasis, pneumocystosis, acute histoplasmosis, cryptococcosis, cytomegalovirus and BK virus were reported with Olumiant. Some patients have presented with disseminated rather than local disease and were often taking concomitant immunosuppressants such as methotrexate or corticosteroids. Avoid Olumiant in patients with an active, serious infection, including localized infections. Consider the risks and benefits of treatment prior to initiating Olumiant in patients:

- with chronic or recurrent infection
- who have been exposed to TB
- with a history of a serious or an opportunistic infection
- who have resided or traveled in areas of endemic tuberculosis or endemic mycoses; or
- with underlying conditions that may predispose them to infection.

Closely monitor patients for infections during and after Olumiant treatment. Interrupt Olumiant if a patient develops a serious infection, an opportunistic infection, or sepsis. Do not resume Olumiant until the infection is controlled.

Tuberculosis – Before initiating Olumiant evaluate and test patients for latent or active infection and treat patients with latent TB with standard antimycobacterial therapy. Olumiant should not be given to patients with active TB. Consider anti-TB therapy prior to initiating Olumiant in patients with a history of latent or active TB in whom an adequate course of treatment cannot be confirmed, and for patients with a negative test for latent TB but who have risk factors for TB infection. Monitor patients for TB during Olumiant treatment.

Viral Reactivation – Viral reactivation, including cases of herpes virus reactivation (e.g., herpes zoster), were reported in clinical studies with Olumiant. If a patient develops herpes zoster, interrupt Olumiant treatment until the episode resolves.

The impact of Olumiant on chronic viral hepatitis reactivation is unknown. Screen for viral hepatitis in accordance with clinical guidelines before initiating Olumiant.

MALIGNANCY AND LYMPHOPROLIFERATIVE DISORDERS: Malignancies were observed in Olumiant clinical studies. Consider the risks and benefits of Olumiant prior to initiating therapy in patients with a known malignancy other than a successfully treated non-melanoma skin cancer (NMSC) or when considering continuing Olumiant in patients who develop a malignancy. NMSCs were reported in patients treated with Olumiant. Periodic skin examination is recommended for patients who are at increased risk for skin cancer.

THROMBOSIS: Thrombosis, including DVT and PE, has been observed at an increased incidence in Olumiant-treated patients compared to placebo. In addition, arterial thrombosis events in the extremities have been reported in clinical studies with Olumiant. Many of these adverse events were serious and some resulted in death. There was no clear relationship between platelet count elevations and thrombotic events. Use Olumiant with caution in patients who may be at increased risk of thrombosis. If clinical features of DVT/PE or arterial thrombosis occur, evaluate patients promptly and treat appropriately.

GASTROINTESTINAL PERFORATIONS: Gastrointestinal perforations have been reported in Olumiant clinical studies, although the role of JAK inhibition in these events is not known. Use Olumiant with caution in patients who may be at increased risk for gastrointestinal perforation (e.g., patients with a history of diverticulitis). Promptly evaluate patients who present with new onset abdominal symptoms for early identification of gastrointestinal perforation.

LABORATORY ABNORMALITIES:

Neutropenia – Olumiant treatment was associated with an increased incidence of neutropenia (absolute neutrophil count [ANC] <1000 cells/mm^3) compared to placebo. Avoid initiation or interrupt Olumiant treatment in patients with an ANC <1000 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Lymphopenia – Absolute lymphocyte count (ALC) <500 cells/mm^3 were reported in Olumiant clinical trials. Lymphocyte counts less than the lower limit of normal were associated with infection in patients treated with Olumiant, but not placebo. Avoid initiation or interrupt Olumiant treatment in patients with an ALC <500 cells/mm^3. Evaluate at baseline and thereafter according to routine patient management.

Anemia – Decreases in hemoglobin levels to <8 g/dL were reported in Olumiant clinical trials. Avoid initiation or interrupt Olumiant treatment in patients with hemoglobin <8 g/dL. Evaluate at baseline and thereafter according to routine patient management.

Liver Enzyme Elevations – Olumiant treatment was associated with increased incidence of liver enzyme elevation compared to placebo. Increases of ALT ≥5x upper limit of normal (ULN) and increases of AST ≥10x ULN were observed in patients in Olumiant clinical trials.

Evaluate at baseline and thereafter according to routine patient management. Promptly investigate the cause of liver enzyme elevation to identify potential cases of drug-induced liver injury. If increases in ALT or AST are observed and drug-induced liver injury is suspected, interrupt Olumiant until this diagnosis is excluded.

Lipid Elevations – Treatment with Olumiant was associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol. Assess lipid parameters approximately 12 weeks following Olumiant initiation. Manage patients according to clinical guidelines for the management of hyperlipidemia.

VACCINATIONS: Avoid use of live vaccines with Olumiant. Update immunizations in agreement with current immunization guidelines prior to initiating Olumiant therapy.

HYPERSENSITIVITY: Reactions such as angioedema, urticaria, and rash that may reflect drug sensitivity have been observed in patients receiving Olumiant, including serious reactions. If a serious hypersensitivity reaction occurs, promptly discontinue Olumiant while evaluating the potential causes of the reaction.

ADVERSE REACTIONS
Most common adverse reactions include: upper respiratory tract infections (16.3%, 11.7%), nausea (2.7%, 1.6%), herpes simplex (0.8%, 0.7%) and herpes zoster (1.0%, 0.4%) for Olumiant 2 mg and placebo, respectively.

USE IN SPECIFIC POPULATIONS

PREGNANCY AND LACTATION: No information is available to support the use of Olumiant in pregnancy or lactation. Advise women not to

breastfeed during treatment with Olumiant.

HEPATIC AND RENAL IMPAIRMENT: Olumiant is not recommended in patients with severe hepatic impairment or in patients with severe renal impairment.

Please click to access full Prescribing Information, including Boxed Warning about Serious Infections, Malignancies, and Thrombosis, and Medication Guide.

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About Lilly's COVID-19 Efforts
Lilly is bringing the full force of its scientific and medical expertise to attack the coronavirus pandemic around the world. Existing Lilly medicines are now being studied to understand their potential in treating complications of COVID-19, and the company is collaborating with two partner companies to discover novel antibody treatments for COVID-19. Lilly is testing both single antibody therapy as well as combinations of antibodies as potential therapeutics for COVID-19. Click here for resources related to Lilly's COVID-19 efforts.

About OLUMIANT®
OLUMIANT is a once-daily, oral JAK inhibitor approved in the U.S. for the treatment of adults with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more TNF inhibitor therapies, and approved outside of the U.S. for patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more DMARDs.[1] Olumiant is also approved in the European Union for the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy. There are four known JAK enzymes: JAK1, JAK2, JAK3 and TYK2. JAK-dependent cytokines have been implicated in the pathogenesis of a number of inflammatory and autoimmune diseases.[2] OLUMIANT has greater inhibitory potency at JAK1, JAK2 and TYK2 relative to JAK3; however, the relevance of inhibition of specific JAK enzymes to therapeutic effectiveness is not currently known.[1]

In December 2009, Lilly and Incyte announced an exclusive worldwide license and collaboration agreement for the development and commercialization of baricitinib and certain follow-on compounds for patients with inflammatory and autoimmune diseases.

About Eli Lilly and Company
Lilly is a global health care leader that unites caring with discovery to create medicines that make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at lilly.com and lilly.com/newsroom.

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About Incyte
Incyte is a Wilmington, Delaware-based, global biopharmaceutical company focused on finding solutions for serious unmet medical needs through the discovery, development and commercialization of proprietary therapeutics. For additional information on Incyte, please visit Incyte.com and follow @Incyte.

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about OLUMIANT (baricitinib) as a potential treatment for patients with COVID-19 and as a treatment for patients with rheumatoid arthritis, and about the supply of OLUMIANT, and reflects Lilly's and Incyte's current beliefs. This press release also contains forward-looking statements about Lilly's neutralizing antibodies as potential treatments for patients with or at risk of infection from COVID-19 and reflects Lilly current beliefs. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that OLUMIANT or Lilly's neutralizing antibody treatments will prove to be safe and effective treatments for patients with COVID-19, that OLUMIANT or Lilly's neutralizing antibody treatments will receive additional regulatory approvals or authorizations, that OLUMIANT will continue to be commercially successful, or that we can provide an adequate supply of OLUMIANT or Lilly's neutralizing antibody treatments in all circumstances. For further discussion of these and other risks and uncertainties, see Lilly's and Incyte's most recent respective Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly and Incyte undertake no duty to update forward-looking statements to reflect events after the date of this release.

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[1] Olumiant Prescribing Information, 2020.
[2] Walker JG and Smith MD. J Rheumatol. 2005;32;1650-1653.

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