Baricitinib (Olumiant)
Emergency Use Evaluation for COVID-19

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Background

- COVID-19 disease severity may be in due part to a dysregulated inflammatory response
- Regulation of immune response may improve clinical outcomes
- Baricitinib is a selective inhibitor of Janus kinase (JAK)
  - Reduces cellular activation and inflammation
  - Approved for the treatment of RA
  - EUA Nov 2020 for the treatment of COVID-19

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

Double-blind, randomized, placebo-controlled trial evaluating baricitinib plus remdesivir in hospitalized adults with COVID-19

Primary Outcome
Time to recovery

Secondary Outcomes
Clinical status at day 15
Mortality at 14- and 28-days
Adverse drug reactions

- May 8, 2020 – July 1, 2020
- Randomized 1:1 to receive remdesivir and baricitinib or remdesivir and placebo
- Patients assessed daily during hospitalization from day 1 through day 29
  - Eight-category ordinal scale used to assess clinical status
  - Other experimental treatments were prohibited

Kalil AC, et al. NEJM 2020; DOI: 10.1056/NEJMoa2031994.

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	All Patients (N = 1033)	Baricitinib+RDV (N = 515)	Placebo+RDV (N = 518)
Age			
Mean — yr	55.4±15.7	55.0±15.4	55.8±16.0
Distribution — no. (%)			
<40 yr	173 (16.7)	87 (16.9)	86 (16.6)
40–64 yr	555 (53.7)	281 (54.6)	274 (52.9)
≥65 yr	305 (29.5)	147 (28.5)	158 (30.5)
Sex — no. (%)			
Female	381 (36.9)	196 (38.1)	185 (35.7)
Male	652 (63.1)	319 (61.9)	333 (64.3)
Race — no. (%)†			
Asian	101 (9.8)	49 (9.5)	52 (10.0)
Black	156 (15.1)	77 (15.0)	79 (15.3)
White	496 (48.0)	251 (48.7)	245 (47.3)
Other or unknown	280 (27.1)	138 (26.8)	142 (27.4)
Disease severity — no. (%)			
Moderate	706 (68.3)	358 (69.5)	348 (67.2)
Severe	327 (31.7)	157 (30.5)	170 (32.8)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	142 (13.7)	70 (13.6)	72 (13.9)
5. Hospitalized, requiring supplemental oxygen	564 (54.6)	288 (55.9)	276 (53.3)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	216 (20.9)	103 (20.0)	113 (21.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	111 (10.7)	54 (10.5)	57 (11.0)

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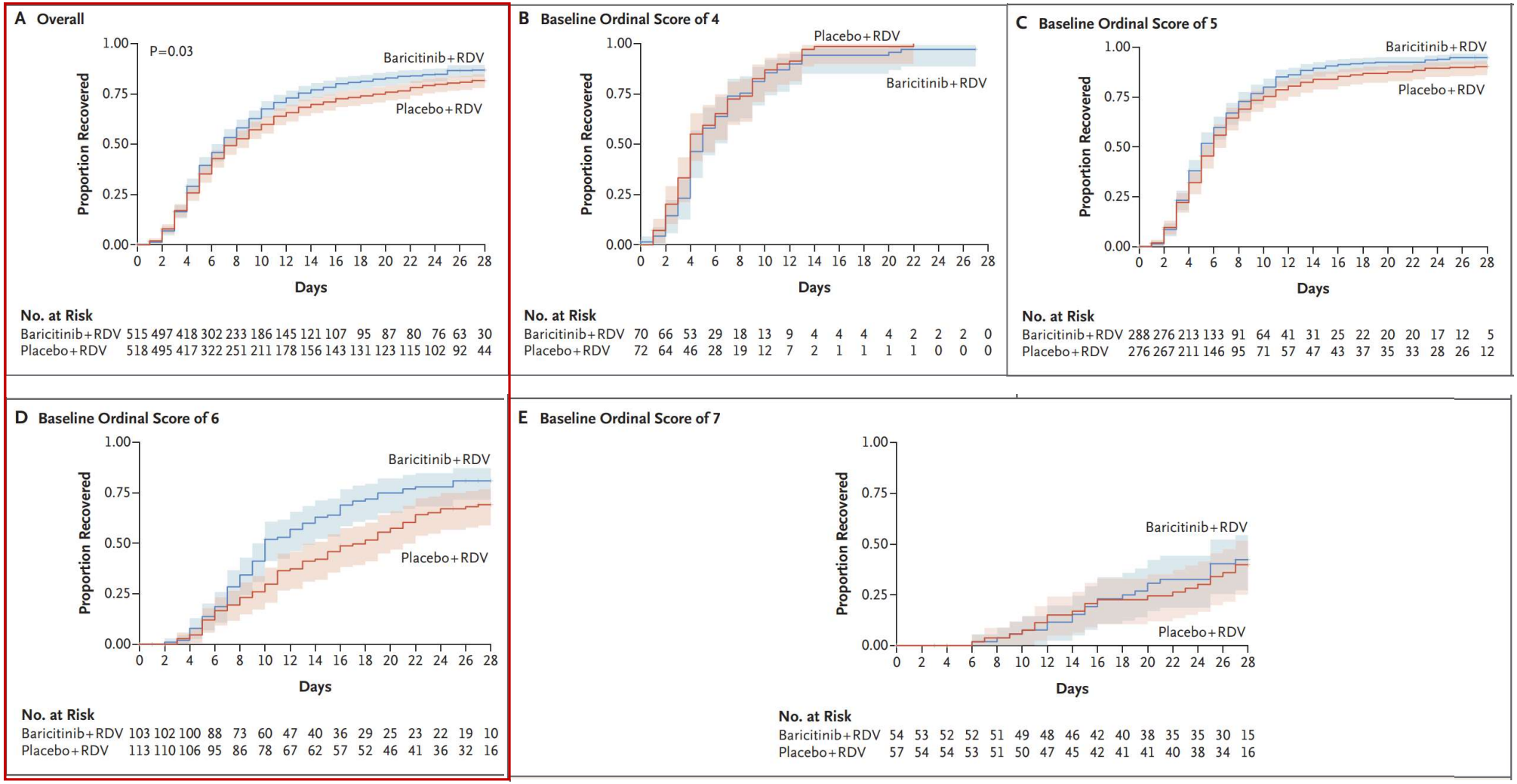

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Table 2. Outcomes Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population.*

Outcome	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Baricitinib (N=515)	Placebo (N=518)	Baricitinib (N=70)	Placebo (N=72)	Baricitinib (N=288)	Placebo (N=276)	Baricitinib (N=103)	Placebo (N=113)	Baricitinib (N=54)	Placebo (N=57)
Recovery										
No. of recoveries	433	406	67	69	262	243	82	73	22	21
Median time to recovery (95% CI) — days	7 (6–8)	8 (7–9)	5 (4–6)	4 (4–6)	5 (5–6)	6 (5–6)	10 (9–13)	18 (13–21)	NE (25–NE)	NE (26–NE)
Rate ratio (95% CI)†	1.16 (1.01–1.32 [P=0.03])		0.88 (0.63–1.23)		1.17 (0.98–1.39)		1.51 (1.10–2.08)		1.08 (0.59–1.97)	
Mortality over first 14 days‡										
Hazard ratio (95% CI) for data through day 14	0.54 (0.23–1.28)		NE		0.73 (0.16–3.26)		0.21 (0.02–1.80)		0.69 (0.19–2.44)	
No. of deaths by day 14	8	15	0	0	3	4	1	5	4	6
Kaplan–Meier estimate of mortality by day 14 — % (95% CI)	1.6 (0.8–3.2)	3.0 (1.8–5.0)	0 (NE–NE)	0 (NE–NE)	1.1 (0.4–3.4)	1.5 (0.6–3.9)	1.0 (0.1–6.7)	4.6 (2.0–10.8)	7.6 (2.9–19.1)	11.3 (5.3–23.5)
Mortality over entire trial period‡										
Hazard ratio (95% CI)	0.65 (0.39–1.09)		NE		0.40 (0.14–1.14)		0.55 (0.22–1.38)		1.00 (0.45–2.22)	
No. of deaths by day 28	24	37	0	0	5	12	7	13	12	12
Kaplan–Meier estimate of mortality by day 28 — % (95% CI)	5.1 (3.5–7.6)	7.8 (5.7–10.6)	0 (NE–NE)	0 (NE–NE)	1.9 (0.8–4.4)	4.7 (2.7–8.1)	7.5 (3.6–15.2)	12.9 (7.7–21.3)	23.1 (13.8–37.1)	22.6 (13.5–36.4)

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Table 3. Serious and Non-Serious Adverse Events Occurring in Any Preferred Term by Treatment Group		
Adverse Event	**Baricitinib + Remdesivir (n=507) n (%)**	**Placebo + Remdesivir (n=509) n (%)**
Serious Adverse Events (> 1%)		
Any serious event	81 (16)	107 (21)
Respiratory failure	26 (5.1)	37 (7.3)
Acute kidney injury	5 (1.0)	11 (2.2)
Septic shock	4 (0.8)	8 (1.6)
Pneumonia	2 (0.4)	8 (1.6)
Multiple organ dysfunction syndrome	1 (0.2)	6 (1.2)
Acute kidney injury	5 (1.0)	11 (2.2)
Acute respiratory distress syndrome	4 (0.8)	6 (1.2)
Non-Serious Adverse Events (> 5%)		
Any non-serious event	187 (36.9)	220 (43.2)
Anemia	24 (4.7)	31 (6.1)
Reduced glomerular filtration rate	49 (9.7)	42 (8.3)
Acute kidney injury	15 (3.0)	27 (5.3)
Hyperglycemia	25 (4.9)	40 (7.9)
Blood glucose increased	22 (4.3)	27 (5.3)
Lymphocyte count decreased	23 (4.5)	35 (6.9)
Hemoglobin decreased	30 (5.9)	30 (5.9)

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ORIGINAL ARTICLE

Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19

Conclusions

Baricitinib plus remdesivir was superior to remdesivir alone in reducing recovery time and accelerating improvement in patients with COVID-19, notably among those receiving high-flow oxygen or noninvasive ventilation

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Top Clinical Trials

Study Title	Interventions	Location	Status
Safety and efficacy of baricitinib for COVID-19	Baricitinib	United States	Not yet recruiting
A study of baricitinib in participants with COVID-19	Baricitinib vs placebo	United States	Recruiting
Baricitinib, placebo, and antiviral therapy for the treatment of patients with moderate and severe COVID-19	Baricitinib vs hydroxychloroquine vs placebo	United States	Recruiting
Baricitinib compared to standard therapy in patients with COVID-19	Baricitinib vs standard therapy	Italy	Not yet recruiting
Multi-arm therapeutic study in pre-ICU patients admitted with COVID-19 – repurposed drugs (TACTIC-R)	Ravulizumab vs baricitinib vs standard of care	United Kingdom	Recruiting
Clinical trial to evaluate efficacy of 3 types of treatment in patients with pneumonia by COVID-19	Imatinib vs baricitinib vs supportive treatment	Spain	Recruiting
Clinical-epidemiological characterization of COVID-19 disease in hospitalized older adults	Baricitinib vs anakinra	Spain	Recruiting
Adaptive COVID-19 treatment trial 2 (ACTT-2)	Remdesivir + baricitinib vs remdesivir + placebo	Multiple countries	Completed
Adaptive COVID-19 treatment trial 2 (ACTT-4)	Remdesivir + baricitinib vs Remdesivir + dexamethasone	Multiple countries	Recruiting

www.clinicaltrials.gov

Baricitinib
Emergency Use Authorization
Nov 19th, 2020

Permits use of baricitinib (with remdesivir), for the treatment of COVID-19 in:

- Hospitalized adults and pediatric patients 2 years of age or older AND
- Requiring supplemental oxygen, mechanical ventilation, or ECMO

Inpatient pharmacies must order directly from an authorized distributor of record. List available at:

www.lillytrade.com
www.baricitinibemergencyuse.com

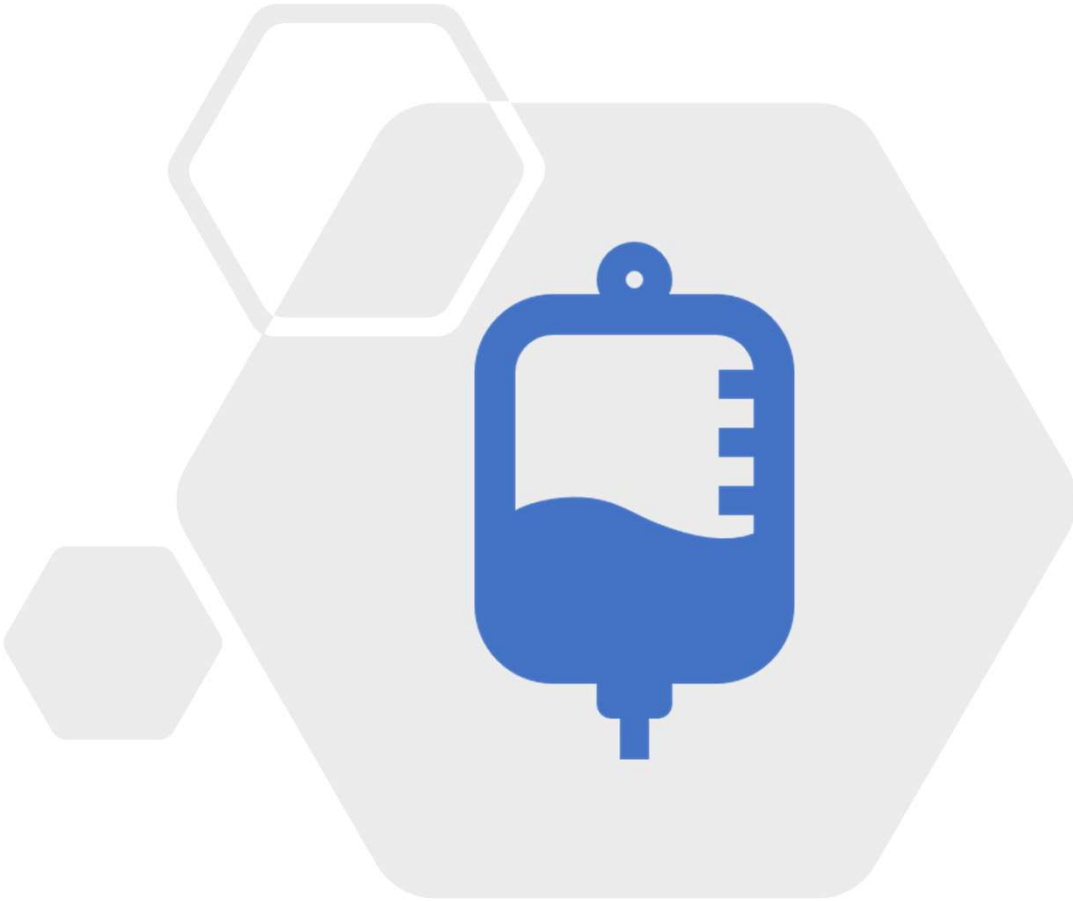
"Fact Sheet for Patients" must be completed prior to receiving baricitinib

All serious ADEs to baricitinib must be reported to FDA Medwatch within 7 days

US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Baricitinib
Available from: https://www.fda.gov/media/143823/download

Dose and Duration

- **Dose**
  - Adult and pediatric patients ≥ 9y
    - 4 mg PO once daily
  - Pediatric patients 2 years to < 9y
    - 2 mg PO once daily
- **Duration**
  - Total of 14 days or until hospital discharge, whichever comes first



US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Baricitinib. Nov 2020
Olumiant (baricitinib). Package Insert. Lilly; 2020.

Dose Adjustments

Laboratory Analyte	Laboratory Analyte Value	Recommendation
eGFR	≥ 60 mL/min/1.73 m^2	• Patients ≥ 9 years of age: 4 mg PO daily • Patients 2 to < 9 years of age: 2 mg PO daily
	20 to <60 mL/min/1.73 m^2	• Patients ≥ 9 years of age: 2 mg PO daily • Patients 2 to < 9 years of age: 1 mg PO daily
	15 to <30 mL/min/1.73 m^2	• Patients ≥ 9 years of age: 1 mg PO daily • Patients 2 to < 9 years of age: not recommended
	<15 mL/min/1.73 m^2	• Not recommended
Absolute Lymphocyte Count (ALC)	≥ 200 cells/µL	• No adjustment
	< 200 cells/µL	• Consider interruption until ALC is ≥ 200 cells/µL
Absolute Neutrophil Count (ANC)	≥ 500 cells/µL	• No adjustment
	< 500 cells/µL	• Consider interruption until ANC is ≥ 500 cells/µL
Aminotransferases	If increases in LFTs are observed and drug-induced liver injury (DILI) is suspected	• Interrupt treatment until the diagnosis of DILI is excluded

US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Baricitinib. Nov 2020
Olumiant (baricitinib). Package Insert. Lilly; 2020.

Administration

- For patients who are unable to swallow whole tablets:
  - Mix tablet(s) with ~15 mL of room temperature water and disperse
  - Alternative routes
    - Oral dispersion
    - Gastrostomy tube (G tube)
    - Nasogastric tube (NG tube)

Administration	Dispersion Volume	Container Rinse Volume
Oral dispersion	10 mL	10 mL
G tube	15 mL	15mL
NG tube	30 mL	15 mL

US FDA: Fact Sheet for Health Care Providers Emergency Use Authorization (EUA) of Baricitinib. Nov 2020
Olumiant (baricitinib). Package Insert. Lilly; 2020.

Side Effects

	Placebo n = 1070 (%)	Baricitinib 2 mg n=479 (%)	Baricitinib 4 mg n=997 (%)
Upper respiratory tract infections [a]	125 (11.7)	78 (16.3)	147 (14.7)
Nausea	17 (1.6)	13 (2.7)	28 (2.8)
Herpes simplex [b]	7 (0.7)	4 (0.8)	18 (1.8)
Herpes zoster	4 (0.4)	5 (1.0)	14 (1.4)

[a] Includes acute sinusitis, acute tonsillitis, chronic tonsillitis, epiglottitis, laryngitis, nasopharyngitis, oropharyngeal pain, pharyngotonsillitis, pharyngitis, rhinitis, sinobronchitis, sinusitis, tonsillitis, tracheitis, and upper respiratory tract infection

[b] Includes eczema herpeticum, genital herpes, herpes simplex, ophthalmic herpes simplex, and oral herpes

Olumiant (baricitinib). Package Insert. Lilly; 2020.

Black Box Warnings

Serious infections

Requiring hospitalization or death, including *M.tuberculosis*

Malignancies

Including lymphoma and other malignancies

Thrombosis

VTE prophylaxis recommended unless contraindicated

Olumiant (baricitinib). Package Insert. Lilly; 2020.

Other Warnings and Precautions

Hepatotoxicity

Increased incidence of LFT elevation; monitor indicated

Dyslipidemia

Dose-dependent increases in lipid parameters observed

GI perforations

Use with caution in patients at an increased risk

Olumiant (baricitinib). Package Insert. Lilly; 2020.

Drug Interactions

- Strong OAT2 inhibitors
  - Probenecid co-administration results in a 2-fold increase in baricitinib AUC
- Other JAK inhibitors or biologic DMARDs, or potent immunosuppressants
- Vaccines (live and inactivated)
  - Immunosuppressants may diminish the therapeutic effect of vaccines
  - Vaccinate at least 3 months after immunosuppressant discontinuation
- No clinically meaningful changes in the pharmacokinetics of CYP3A4 and Pgp substrates

Olumiant (baricitinib). Package Insert. Lilly; 2020.

Monitoring
(baseline and daily)

- Complete blood count with differential
- Basic metabolic panel
- Abdominal symptoms
- Signs and symptoms of infection

Olumiant (baricitinib). Package Insert. Lilly; 2020.

Pharmacokinetics

- Absorption
  - Bioavailability: 80%; C_{max} ~1 hour
- Distribution
  - Distributes well into tissues; V_d 76L; 50% protein bound
  - Substrate of Pgp, OAT3 and MATE2-K transporters
- Metabolism
  - About 6% of dose is metabolized, predominantly via CYP3A4
  - $t_{1/2}$ 12 hours
- Excretion
  - About 75% eliminated unchanged in the urine; 20% in feces

Olumiant (baricitinib). Package Insert. Lilly; 2020.

Cost

Drug	Cost per Day	Cost per Course
Dexamethasone	6 mg, PO = $1.31 6 mg, IV = $0.85	10 days, PO = $18 10 days, IV = $12
Remdesivir	200 mg (load) = $1,040 100 mg (maintenance) = $520	5 days = $3,120 10 days = $5,720
Baricitinib	4 mg = $293	14 days = $4,102

Supply and Storage

- How Supplied
  - Available as debossed, film-coated, immediate-release tablets
  - 1 mg; 2 mg
- Storage and Handling
  - Store at 20°C (68° to 77° F); excursions permitted to 15° to 30° (59° to 86° F)

Special Patient Populations

Limited Data

Pediatrics — Dosing & efficacy data

Pregnancy & Lactation — Maternal and fetal outcomes

Hepatic Impairment — PK/PD & ADRs

Renal Impairment — PK/PD & ADRs

Baricitinib EUA Requirements Summary

1. Treatment of suspected or confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO

2. Patient or parent/caregivers education ("Patient Fact Sheet") prior to receiving baricitinib. Providers must document in the EMR that the patients received the fact sheet, was informed of alternatives, and was informed that baricitinib is investigational

3. Patients must have an eGFR, aminotransferases, and CBC with differential determined prior to first administration

4. The provider is responsible for mandatory reporting of all medication errors and all serious adverse events within 7 calendar days from the onset of the event

5. The provider and/or the provider's designee are/is to provide mandatory responses to requests from FDA for information about adverse events or medication errors

6. Adverse events and medication errors must also be reported to Lilly and FDA MedWatch

Baricitinib Use at RGH

Evaluate for inclusion into ACTT-4 (remdesivir + baricitinib versus remdesivir + dexamethasone)

If patient does not meet criteria or does not want to participate, the following criteria must be met:

- Requiring high-flow O_2 or BiPAP/CPAP
- Receiving remdesivir
- No contraindications to receiving baricitinib
- Safety data assessing concomitant baricitinib and dexamethasone not available; not recommended

Infectious Diseases and Pulmonary support use (authorizing provider field in EHR profile)

Baricitinib 4 mg PO daily (or dosing equivalent) up to 14 days approved

Recommendations

Add baricitinib to formulary

Patient and authorizing provider restrictions apply

EUA Links

- Additional access information: www.baricitinibemergencyuse.com
- Lilly's authorized distributors: www.lillytrade.com