USE OF BARICITINIB FOR COVID-19 IN HOSPITALISED ADULTS DRUG GUIDELINE

Baricitinib (Olumiant®) is registered for use in Australia for the treatment of moderate-severe rheumatoid arthritis and moderate-severe atopic dermatitis but not for the treatment of COVID-19.[1] *The National COVID-19 Clinical Evidence Taskforce (NCCET)(current as at 29/09/21) gives a conditional recommendation for use of baricitinib as an immunomodulator for adults hospitalised with COVID-19 who require supplemental oxygen and/or non-invasive ventilation.*[2] *(Certainty of evidence for outcomes: moderate for all-cause mortality; and, low for invasive ventilation or ECMO). This conditional recommendation is largely based on the results of the ACTT-2 trial*[3] *and the COV-BARRIER trial*[8] *suggesting that baricitinib probably reduces the risk of death. Use in pregnant or breastfeeding women or children and adolescents is NOT recommended outside randomised trials.*[2]

This guideline requires endorsement by your local Drug and Therapeutics Committee (DTC) prior to implementation.

Supply of baricitinib for registered indications and clinical trials takes precedence over supply for off-label use outside of clinical trials.

This guideline aims to provide supportive information for clinicians if they decide to prescribe baricitinib for off-label use in hospitalised patients with COVID-19 when patients are not eligible for a clinical trial or when a clinical trial is not available.[10]
This guideline should be used in conjunction with the Baricitinib resources available here:

- *Individual Patient Use (IPU) Application Form,*
- *Outcomes Reporting Form,*
- *Patient Consent Form and*
- *Patient Information Leaflet.*

For further information regarding consent see the NSW Health Consent to Medical and Healthcare Treatment Manual, particularly Section 4.

Off-label use of baricitinib is not recommended in the Hospital in the Home setting or in community-based patients with COVID-19.

Drug Class: Janus Kinase (JAK) 1 and 2 inhibitor, disease modifying anti-rheumatic drug (DMARD), immunomodulator.[1]

Authorised Prescribers:

- Immunologists,
- Infectious disease physicians,
- Respiratory physicians,
- Intensivists,

Other physicians in accordance with local governance regulations e.g. emergency physicians.

Indication for applying this guidance[2]:

In accordance with relevant DTC approval, off-label baricitinib may be considered for patients with a current diagnosis of COVID-19:

- who require supplemental oxygen, high-flow oxygen and/or non-invasive ventilation including those who may be intolerant of steroid therapy.

Contraindications and Precautions[1,2,4-7]:

- **Hypersensitivity:** Contraindicated in patients with known hypersensitivity to baricitinib or any of the excipients in the product.
- **Thrombosis:** Baricitinib may increase the risk of venous thromboembolism (VTE). Thrombosis including pulmonary embolism, deep vein thrombosis and arterial thrombosis have been observed. Use with caution in individuals with an increased risk of thrombosis.
- **Haematological toxicity:**
  - Baricitinib may cause leucopenia, lymphopenia, neutropenia and anaemia. Cytopenias are generally reversible with treatment interruption. Do not commence if haemoglobin <80 g/L, lymphocyte[7] count <0.2 x 10^9/L or neutrophil[7] count <0.5 x 10^9/L. (Baricitinib use may still be considered if the patient is haemolysing).
- **Infection:**
  - Baricitinib is contraindicated in patients with serious active infections (other than COVID-19).
  - Baricitinib is associated with an increased risk of serious infections including bacterial, viral, fungal and opportunistic infections. There is an increased risk of infection when baricitinib is used with other immunosuppressive agents (see section on drug interactions).
  - Patients should be monitored for signs and symptoms of infection during and after treatment with baricitinib.
  - Tuberculosis has been reported in patients receiving baricitinib. Patients should be evaluated for latent tuberculosis.

  N.B. Baseline testing for viral hepatitis, tuberculosis, strongyloides and HIV should be undertaken. Baricitinib treatment should NOT be delayed pending results of baseline tests.
- **Renal**: Baricitinib is not recommended for patients on dialysis or patients with acute kidney injury or eGFR<30mL/minute/1.73m^2.[1,8] However baricitinib has been used in patients with eGFR 15-30mL/minute/1.73m^2.[8,9] See ***dose*** section for further information.
- **Hepatic**: Baricitinib has not been studied in patients with severe hepatic impairment. It should only be used in patients with severe hepatic impairment if the potential benefit outweighs the potential risk of harm. See also monitoring section below.
- **Gastrointestinal (GI):**
  - GI perforations have been reported. Use with caution in patients at risk of GI perforation. Evaluate new onset abdominal symptoms.
- **Pregnancy and breastfeeding**: Avoid use. Baricitinib is a pregnancy Category D medication. A pregnancy test must be conducted in any COVID-19 positive woman of childbearing age in whom this therapy is being considered. (For treatment of pregnant and breastfeeding women with COVID-19, see National COVID-19 Clinical Evidence Taskforce guidelines.)
- **Immunisations:**
  - Live vaccines should not be given concomitantly.

Drug Interactions[1,9,11-13]:

Potential drug interactions have not been investigated in patients with COVID-19.

Considerations:

- Baricitinib exposure is increased when baricitinib is used with strong OAT3 inhibitors e.g. probenecid and gemfibrozil.
- Additive immunosuppressive risk when used with other immunomodulatory agents e.g. methotrexate, corticosteroids*, tocilizumab, adalimumab, rituximab and anakinra. Use of monoclonal antibodies targeting cytokines (e.g. TNF-alpha, interleukin-1, interleukin-6) or T-cells within the last 4 weeks and monoclonal antibodies targeting B-cells within the last 3 months are contraindicated.
  Given the potential for significant harm and no evidence of benefit for concurrent or sequential use of immunomodulatory therapy (with the exception of concurrent dexamethasone use), further/sequential immunomodulatory therapy is not recommended in a patient who continues to deteriorate while on baricitinib therapy, outside a clinical trial.
  *Note: 6 mg dexamethasone (or equivalent corticosteroid) is standard of care treatment in COVID-19 patients in whom baricitinib is conditionally recommended.
- Clozapine: increased risk of agranulocytosis.
- Live vaccines should be avoided just prior to and during treatment with baricitinib. Specialist input should be obtained regarding timing of future vaccinations. Information is likely to evolve, see Australian Immunisation Handbook for further information or contact the NSW Immunisation Specialist Service (NSWISS) Advice Line (1800 679 477).

A variety of resources are available to check specific drug combinations, e.g. Liverpool COVID-19 Drug Interactions tool and Micromedex drug interaction tool (CIAP link). Contact the local pharmacy department or medicines information service for tailored advice.

Presentation and Storage[1]:

Available as:

- 2 mg film-coated tablets
- 4 mg film-coated tablets.

Store below 30°C in original package.

Dose[1,8,9]:

The recommended dose is:
4 mg orally ONCE DAILY for up to 14 days or until hospital discharge, whichever comes first.

Dose adjustments

- Renal impairment:
  - Halve dose to 2 mg orally ONCE DAILY when eGFR = 30 - 60 mL/min/1.73m^2.
  - Reduce dose to 1 mg orally ONCE DAILY when eGFR = 15 - 30 mL/min/1.73m^2.[9]
- Patients taking strong OAT3 inhibitors, such as probenecid or gemfibrozil:
  - Halve the dose

Preparation and Administration[1,9,14,15]:

- Can be given without regard to food.
- Do not crush or break the tablet** (see ***handling*** section below).
- For patients who are unable to swallow whole tablets, place tablet(s) to achieve desired dose in a suitable container with room temperature water (see Table 1) and disperse by gentle swirling until an even suspension is formed. Tablet may take 5 minutes to completely disperse.[15]
- Dispersed tablets are stable in water for up to 4 hours; however, the solution should be administered immediately whenever possible. The container should be rinsed with additional room temperature water (see Table 1) and these contents also administered.

Table 1: Dispersion instructions for 2 mg and 4 mg baricitinib tablet(s)[15]

Administration via	Dispersion volume of water	Container rinse volume
Oral dispersion	5 - 10 mL	At least 5 mL
Gastrostomy tube	15 mL	At least 15 mL
Nasogastric tube~	30 mL	At least 15 mL

~ To avoid clogging of small diameter tubes (smaller than 12 Fr), the syringe can be held horizontally and shaken several times during administration.

Please note: if no formulation is available that matches the dose (e.g. 1 mg or 2 mg doses), consider the following options depending on local logistics and handling requirements (see below):

1. Give double the dose every second day e.g. 2 mg once daily is given as 4 mg every second day.
   This alternate day dosing option is based on the RECOVERY trial protocol[16] Eli Lilly was unable to provide any information or recommendations for baricitinib dose regimens outside those described in the Product Information for Olumiant®.
2. Cut the 4 mg tablet in HALF **in a laminar flow hood,** if available, to obtain 2 mg dose**.** Contact your local Pharmacy Department.

If the dose cannot be easily obtained e.g. 1 mg dose from 2 mg tablets, use alternative therapy.

Handling[9,14,15,17,18]

- **Intact** baricitinib tablets can be handled with standard precautions for handling of oral medications.
- Occupational exposure to **non-intact** tablets (i.e. dispersed, **crushed or **broken) may be harmful by posing a reproductive hazard. Staff who are actively trying to conceive or who are pregnant or breast-feeding should not prepare or handle a dispersed dose.
- For all other staff, use standard Personal Protective Equipment (PPE) (or refer to local guidelines) if preparation or administration of a dispersed tablet is required.

Monitoring Requirements[4,9]:

- Baseline FBC (with differential)
- LFTs
- EUCs
- Monitor for adverse effects (see below section) – including FBC and LFTs.
  Interrupt treatment if:
  - Neutrophil count <0.5 x 10^9 cells/L,
  - Lymphocyte count <0.2 x 10^9 cells/L,
  - Haemoglobin <80 g/L.
  - Increases in ALT or AST are observed and drug-induced liver injury is suspected

Adverse Effects[¥4]:

It may be difficult to distinguish between adverse effects of baricitinib and signs and symptoms of COVID-19. As the proposed use is off-label, it is important to document and report all (from possible to confirmed) adverse effects experienced by the patient during treatment to inform its safety profile and future use.

- **Common (>1%):**
  Infections (including serious and opportunistic), hypercholesterolaemia, thrombocytosis (not associated with thrombotic events), nausea (especially in first 2 weeks), abdominal pain, headache, increased creatine kinase.
- **Infrequent (0.1–1%):**
  Thrombosis, neutropenia, lymphopenia, anaemia, acne, vomiting, hypertriglyceridaemia, increased liver enzymes.

¥ Refer to Product Information for complete list of possible adverse effects.

Reporting:

Access via the IPU pathway will enable appropriate medicines governance and ensure the collection and analysis of patient outcomes and systematic monitoring of medicines use. The prescribing clinician is responsible for reporting medication errors and adverse events occurring as a result of baricitinib treatment:

- Adverse events related to medicines should be reported to the TGA and via the hospital ims+ or Riskman system.
- Approval of off-label baricitinib IPU requires reporting of clinical outcomes. Prescribing declarations or IPU applications and outcome reporting should occur as per local governance processes. A NSW TAG-developed drug registry using an online IPU application and outcome reporting processes has been developed. See https://www.nswtag.org.au/covid-19-medicines-resources/. Contact your local DTC or pharmacist for further information.

Summary of amendments/updates made in version 1.2 11 October 2021:

- Introductory section (page 1): updated NCCET guideline latest version date; updated citation to COV-BARRIER trial article which is no longer a pre-print.
- Contraindications & Precautions section (page 2): updated lymphocyte count and neutrophil count cut-offs to FDA Emergency Use Authorization of baricitinib for COVID-19 specifically; added screening for strongyloides, HIV and pregnancy.
- Preparation & Administration section (page 4): minor additions to align with the baricitinib monograph in the SHPA Australian Don't Rush to Crush Handbook, Fourth Edition.
- Monitoring requirements section (page 4): updated lymphocyte count and neutrophil count cut offs as well as note regarding drug induced liver injury to the FDA Emergency Use Authorization of baricitinib for COVID-19 specifically.

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