NHS
Cheshire and Merseyside

BARICITINIB tablets (Olumiant®) for COVID-19

The Cheshire and Merseyside Area Prescribing Group recommends the prescribing of BARICITINIB tablets (Olumiant®), by specialists only, for patients hospitalised due to COVID-19 (adults and children aged 2 years and over)

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Adopted from Template NHS Clinical Commissioning Policy: Baricitinib for patients hospitalised due to COVID-19 (adults and children aged 2 years and over) March 2023

Commissioning position

Baricitinib is recommended to be available as a treatment option through routine commissioning for adults and children (aged 2 years and over) hospitalised with COVID-19 in accordance with the criteria set out in this document. Baricitinib may be used in combination with corticosteroids and tocilizumab, or as an alternative when treatment with tocilizumab is not appropriate or is contraindicated. Use of baricitinib in the treatment of COVID-19 is off-label.

NICE guidance on therapeutics for people with COVID-19 [TA878], recommends tocilizumab within its marketing authorisation, as an option for treating COVID-19 in adults. Tocilizumab (RoActemra, Roche Products) is indicated 'for the treatment of coronavirus disease 2019 (COVID-19) in adults who are receiving systemic corticosteroids and require supplemental oxygen or mechanical ventilation'. The efficacy of tocilizumab has not been established in the treatment of COVID-19 patients who do not have elevated CRP levels. Baricitinib may be considered where patients with COVID-19 have lower CRP levels and fulfil the eligibility criteria set out in this document.

Evidence and policy summary

Baricitinib is an anti-inflammatory treatment licensed for use in moderate to severe rheumatoid arthritis, moderate to severe atopic dermatitis and severe alopecia areata and has been studied in patients who are hospitalised due to COVID-19. It is a selective and reversible Janus kinase (JAK) 1 and 2 inhibitor. JAK-inhibitors are thought to control high levels of cytokines and inflammation, seen in patients with severe SARS-CoV-2 infection (Walz et al 2020).

Results from the RECOVERY trial demonstrate that baricitinib reduces the risk of death when given to hospitalised patients with severe COVID-19. Between February and December 2021, 4,008 patients randomly allocated to usual care alone were compared with 4,148 patients who were randomly allocated to usual care plus baricitinib. Treatment with baricitinib significantly reduced deaths: 513 (12%) of the patients in the baricitinib group died within 28 days compared with 546 (14%) patients in the usual care group, a relative reduction of 13% (age-adjusted rate ratio 0.87, 95% confidence interval [CI] 0.77 to 0.98; p= 0.026). The benefit of baricitinib was consistent regardless of which other COVID-19 treatments the patients were also receiving, including corticosteroids, tocilizumab, or remdesivir (RECOVERY Collaborative Group, 2022).

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

The World Health Organization (WHO) updated its 'Therapeutics and COVID-19: Living guideline' on 16 September 2022 and the recommendations have been considered in the development of this policy. The WHO makes a strong recommendation for use of baricitinib in patients with severe COVID-19 illness, and in patients with critical COVID-19 illness. (WHO, September 2022).

Recent evidence continues to indicate efficacy of baricitinib in this patient cohort. Cherian et al, 2022 conducted a systematic review and meta-analysis which demonstrated improved 28-day mortality data in patients treated with baricitinib when compared to standard of care. Results from a systematic review and metanalysis (Tekantapeh et al, 2022) demonstrated that baricitinib in moderate to severe COVID-19 may reduce mortality (RR 0.84 (P = 0.001)) and improve time to recovery (RR 1.07 (P = 0.014)).

The COVINIB trial compared baricitinib plus standard care to alternate COVID-19 therapies or standard care alone in hospitalised patients with COVID-19 pneumonia. It was noted there was a trend towards the likelihood of discontinuing oxygen in the baricitinib arm. The Bari-SolidAct trial was stopped before reaching planned sample size (n=275 analysed versus n=1900 planned) due to external evidence indicating survival benefit of baricitinib in the trial population. Results published demonstrated mortality rate estimates at day 28 were consistent with the day 28 estimate of the RECOVERY trial.

Results from two further studies have demonstrated non-inferiority of baricitinib when compared to tocilizumab. Karamoutsakos et al (2022) demonstrated no significant difference between the baricitinib and tocilizumab arms in the change in the WHO scale at day 10. Baricitinib was non-inferior to tocilizumab for the primary outcome of mechanical ventilation or death by day 28 and was non-inferior in time to hospital discharge within 28 days. Furthermore, Albuquerque et al, 2022 conducted a systematic review and meta-analysis on the effect of baricitinib on mortality among patients hospitalised for COVID-19 treatment with corticosteroids. Twenty-seven RCTs with 13,549 patients were included that directly compared tocilizumab, baricitinib, or sarilumab to the standard of care or placebo. The average odds ratio for mortality was 0.78 (95% CrI: 0.56, 1.03) for baricitinib. Compared to tocilizumab, there were ≤94% probability of noninferiority with baricitinib.

Implementation

Eligibility criteria

Patients must meet all the eligibility criteria and none of the exclusion criteria. Patients hospitalised due to COVID-19 are eligible[1] to be considered for **baricitinib** if the following criteria are met:

- COVID-19 infection is confirmed by microbiological testing or where a multi-disciplinary team has a high level of confidence that the clinical and/or radiological features suggest that COVID-19 is the most likely diagnosis;

  AND

- Viral pneumonia syndrome[2] is present;

  AND

[1] The decision to initiate treatment with baricitinib should be made by the receiving consultant, with support from multi-disciplinary colleagues in cases of uncertainty.

[2] Viral pneumonia syndrome. In general, viral pneumonia (as per the RECOVERY protocol) should be suspected when a patient presents with:

- typical symptoms (e.g., influenza-like illness with fever and muscle pain, or respiratory illness with cough and shortness of breath); AND
- compatible chest X-ray findings (consolidation or ground-glass shadowing); AND
- alternative causes have been considered unlikely or excluded (e.g., heart failure, bacterial pneumonia).

- Aged 2 years and over;[3]

  AND

- Receiving supplemental oxygen or respiratory support[4] for the treatment of COVID-19;

  AND

- Receiving dexamethasone or an equivalent corticosteroid[5] unless contraindicated.

Please note that baricitinib can be used either a) in combination with tocilizumab; or b) alone when tocilizumab treatment is not appropriate or contraindicated.

Exclusion criteria and cautions

Baricitinib should not be administered in the following circumstances:

- Known hypersensitivity to baricitinib;
- eGFR <15 mL/min/1.73m^2 [If the individual being treated is <9 years, this exclusion criteria should be eGFR <30 mL/min/1.73m^2];[6]
- Receiving dialysis or haemofiltration;[6]
- Absolute neutrophil count (ANC) less than 0.5 x 10^9 cells/L;[6]
- Active tuberculosis;
- Pregnancy or breastfeeding.

Please refer to the Summary of Product Characteristics (SmPC) for baricitinib (*in Northern Ireland, refer to the EMA SmPC for baricitinib*) for special warnings and precautions for use, although some may not be relevant for use in the acute setting, as the licensed indications address long- term use for chronic conditions.

Pregnancy and women of childbearing potential

Baricitinib should not be used during pregnancy.

The SmPC for baricitinib currently states that: *"The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity which can affect early embryonic development. There are no adequate data from the use of baricitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Baricitinib was teratogenic in rats and rabbits.*

Animal studies indicate that baricitinib may have an adverse effect on bone development in utero at higher doses.

Olumiant [baricitinib]*is contraindicated during pregnancy (see section 4.3). Women of childbearing potential have to use effective contraception during and for at least 1 week after treatment. If a patient*

[3] Baricitinib can be considered in children (age 2 to 17 years inclusive) with severe COVID-19, guided by clinical judgement and multi-disciplinary team assessment. Although the RECOVERY trial included this age group, it should be noted that this cohort was too small to reach statistical significance, the SmPC is only for adults and there are limited data on both clinical effectiveness and safety in children. Use in all ages is off-label.

[4] Defined as: high-flow nasal oxygen, continuous positive airway pressure (CPAP) or non-invasive ventilation, or invasive mechanical ventilation.

[5] Patients are expected to be on a corticosteroid as the current standard of care, except where there is a strong contraindication against its use.

[6] Please note that the drug criterion used here in this policy is taken directly from the RECOVERY trial, and the same criterion differs in the SmPC. The key reason for the difference is that the SmPC is written for long-term use in a low-risk condition, whereas this policy is for a short course in a high-risk condition in an acute clinical context (where the balance of benefits and risks is different). Please see the SmPC for further information. Clinical judgement should be exercised as appropriate. Additionally, although the SmPC lists an absolute lymphocyte count (ALC) of <0.5 x 109 cells/L as an exclusionary criterion for licensed indications, this was not used in the RECOVERY trial.

becomes pregnant while taking baricitinib the parents should be informed of the potential risk to the foetus."

For women who are breast-feeding, the SmPC for baricitinib states: *"It is unknown whether baricitinib/metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of baricitinib in milk (see section 5.3).*

A risk to newborns/infants cannot be excluded and Olumiant [baricitinib] *should not be used during breast-feeding. A decision must be made whether to discontinue breast-feeding or to discontinue Olumiant* [baricitinib] *therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman."*

Dose and administration

The recommended dose of baricitinib is 4mg once daily for 10 days (or until discharge if sooner)[7]. The dose should be halved to 2mg once daily in the following circumstances:

- Age 2 to <9 years with eGFR ≥60 mL/min/1.73m^2;[6]
- Age ≥9 years with eGFR 30 to <60 mL/min/1.73m^2;[6]
- Co-administration of an Organic Anion Transporter 3 (OAT3) inhibitor with a strong inhibition potential, such as probenecid.

The dose should be reduced further to 2mg on alternate days in the following circumstances:

- Age 2 to <9 years with eGFR 30 to <60 mL/min/1.73m^2;[6]
- Age ≥9 years with eGFR 15 to <30 mL/min/1.73m^2.[6]

Baricitinib should be taken with or without food and may be taken at any time.

Individuals who are being considered for treatment under this policy, who are already taking baricitinib for a licenced indication at the dose of 4mg per day, should not receive additional baricitinib doses. However, if such individuals are already taking baricitinib at a dose of 2mg per day, the dose may be increased for the recommended treatment interval as described in this policy provided all eligibility criteria are met and provided the increased dose is deemed clinically appropriate (which includes the patient not being within the dose reduction categories described).

Combination treatment

Baricitinib may be administered in combination with tocilizumab (as well as corticosteroids, unless contraindicated) according to clinical judgement in patients with severe or critical COVID-19.

If treatment with tocilizumab is not appropriate or contraindicated, baricitinib treatment may still be considered as an alternative.

Co-administration

There is no interaction expected between baricitinib with the other currently routinely available COVID-19 treatments. For up-to-date information please visit the University of Liverpool COVID-19 Drug Interactions website (https://www.covid19-druginteractions.org/checker).

Please refer to the NICE Therapeutics MTA for people with COVID-19, the NICE COVID-19 rapid guideline, and the WHO clinical management of COVID-19 living guideline setting out available COVID-19 treatments for further information.

[7] There are limited safety data on the use of baricitinib in people with severe acute or chronic renal impairment. Prescribers should use clinical judgement and exercise caution with regards to dosing in those with unstable renal function in the context of acute kidney injury.

Safety reporting

It is vital that any serious suspected adverse reactions are reported directly to the MHRA via the new dedicated COVID-19 Yellow Card reporting site at: https://coronavirus- yellowcard.mhra.gov.uk/.

Treatment with baricitinib can lower the ability of the immune system to fight infections. This could increase the risk of getting a new infection or make any infection the patient contracts worse. All handovers of clinical care (including between hospitals if patients are transferred, between levels of care and clinical teams within hospitals, and between hospitals and primary care) must explicitly mention that baricitinib has been given, ideally using SNOMED codes, and the date of administration. Clinicians must ensure the GP is aware the patient has received baricitinib and should provide information to the patient to such effect.

Marketing authorisation

Baricitinib has a marketing authorisation for:

- Oral use in adults with moderate to severe active rheumatoid arthritis.
- Oral use in adults with moderate to severe atopic dermatitis.
- Oral use in adults with adults with alopecia areata

The use of baricitinib in COVID-19 is off label.

Governance

Off-label use of medication

Any provider organisation treating patients admitted due to COVID-19 with baricitinib, as an off- label product, will be required to assure itself that the internal governance arrangements have been completed before the medicine is prescribed. These arrangements may be through the health board/hospital/trust's drugs and therapeutics committee, or equivalent.

Data collection requirement

Submission of Blueteq forms for COVID-19 treatments will be required when implemented across Cheshire and Merseyside.

Equality statement

Promoting equality and addressing health inequalities are at the heart of the NHS values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010 or equivalent equality legislation) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Definitions

COVID-19	Refers to the disease caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus

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