Application for Inclusion of Baricitinib to the World Health Organization's Model Lists of Essential Medicines and Essential Medicines for Children

1 Summary statement of the proposal for inclusion

Cumulative cases of Covid-19 are over 642 million, with 6.6 million global deaths.[1] Vaccination is having a substantial impact on hospitalizations and death in a number of high-income countries, but limitations in global access to COVID-19 vaccines mean that many populations remain vulnerable. There remains a need for more effective treatments for COVID-19.

WHO guidance makes a strong recommendation for the use of baricitinib for patients with severe or critical Covid-19 disease.[2] This is based on high certainty of a reduction in mortality of 20 per 1000 people, and an adverse event profile within clinical trials which does not differ from patients who did not receive baricitinib. The evidence for benefit derives from prospective meta-analysis which is the basis of all of the WHO Therapeutics and COVID-19 Living Guidelines; these are summarised here.

The application relates to both the Model List of Essential Medicines and the Essential Medicines for Children.

2 Relevant WHO technical department and focal point

Janet Diaz, Clinical Management Unit, Country Readiness Strengthening, HQ.

3 Name of organisation(s) consulted and/or supporting the application

The WHO Guideline Development Group for Covid-19 therapeutics has developed and published recommendations on the use of this medicine.[2]

4 International names for medicine within this application

4.1 International non-proprietary name (INN)

baricitinib

4.2 Anatomical Therapeutic Chemical code (ATC)

L04AA37

5 Dose

The recommended dose for Covid-19 is 4 mg daily orally in adults.[3]

For patients with creatinine clearance between 30 and 60 mL/min, the manufacturer's recommended dose is 2mg once daily. Baricitinib is not recommended for use in patients with creatinine clearance <30 mL/min.[3]

No dose adjustment is required in patients with mild or moderate hepatic impairment. Baricitinib is not recommended for use in patients with severe hepatic impairment.[3]

The US FDA has an Emergency Use Authorisation for baricitinib in children.[4] The recommended dosage for patients 9 years of age and older is 4 mg once daily, and for patients ages 2 years through less than 9 years of age is 2 mg once daily.

6 Whether listing is requested as an individual medicine or as representative of a pharmacological class

This application is for listing as an individual medicine.

7 Treatment details

7.1 Requirements for diagnosis

The medication should ideally be administered within five days of symptom onset. Diagnostic possibilities include rapid diagnostic tests (RDT) and polymerase chain reaction (PCR), both of which are supplied by multiple manufacturers. There is no stated preference for diagnostic approach within the guidance, although it is noted that:

> *…availability and use of appropriate SARS-CoV-2 diagnostic tests is needed to improve access to drugs, especially those targeting the early phase of disease. The appropriate use of rapid diagnostic tests such as antigen-detection assays can improve early diagnosis in the community and in primary health care settings. Health care systems must, however, gain expertise in choosing and implementing rapid tests, choosing those most applicable to their settings.*

7.2 Requirements for treatment and monitoring

There is no stipulated monitoring regimen for use in Covid-19.

8 Mechanism of action

Type I and type II cytokine receptors are a family of receptors employed by over 50 interleukins, interferons, colony stimulating factors, and hormones.[5] The intracellular signalling triggered by these receptors is mediated by Janus kinases (JAKs), a small family of kinases including JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Type I cytokines include IL-2, IFN-γ, IL-12, and TNFβ, and type II cytokines include IL-4, IL-5, IL-6, IL-10, and IL-13.

JAK inhibitors are a class of drugs which inhibit intracellular signalling through multifactorial effects on cytokine signalling. As a consequence, they interfere with many cellular responses, including antiviral responses, angiotensin-converting enzyme 2 (ACE2) expression, T cell function and differentiation, and macrophage activation.[5]

Baricitinib, ruxolitinib, and tofacitinib are three of at least nine JAK inhibitors. These three drugs are all generally considered to be non-specific JAK inhibitors, but differences in the specificity and potency for different JAKs are evident. Baricitinib has been described as a JAK1/JAK2 inhibitor, ruxolitinib as JAK1/JAK2 > TYK2, and tofacitinib as JAK3/JAK1 > JAK2/TYK2; other differences have also been previously described.[6,7]

Studies evaluating JAK inhibitors for the treatment of COVID-19 have been conducted at doses that are as high or higher than those approved for other indications, such as rheumatoid arthritis, myelofibrosis, and ulcerative colitis. Therefore, plausibility is contingent upon the role of cytokine signalling in COVID-19, and not on whether the pharmacokinetics at the studied dose is sufficient to inhibit the target proteins. There are notable differences in the approved doses, schedules, pharmacokinetics, contraindications, and indications of these drugs for other indications. Collectively, these differences limit the confidence to consider a class-wide recommendation with currently available data.

9 Review of benefits (summary of evidence of comparative effectiveness)

9.1 Evidence from WHO living guidelines and systematic review: strong recommendation for use

Recommendations concerning baricitinib for patients with severe and critical COVID-19 were updated on 16 September 2022 as the twelfth version of the WHO living guideline. It follows the availability of two RCTs within a network analysis, with the following PICO:

Population	Patients with non-severe, severe or critical illness with confirmed COVID-19
Intervention	Bariticinib + usual care

Comparator	Usual care
Outcomes	See outcome prioritization
Potential Subgroups of Interest	Children vs adults vs. older people Illness stage at time of starting treatment Serostatus
Co-intervention at baseline	Corticosteroids, IL-6 RB

The evidence summary on baricitinib was informed by four trials with 10815 participants with Covid-19 included in the meta-analysis.[8-11] This showed an odds ratio for mortality of 0.83 (95%CI 0.74 – 0.93) amongst patients receiving baricitinib compared with those who did not. This represents 20 fewer deaths per 1000 people (95%CI 8 fewer to 30 fewer).

Figure 1 – Graphical evidence summary of the benefit of baricitinib for severe or critical Covid-19[2]

Additionally, as part of the network analysis, a subgroup examination based on patients already receiving IL-blockers confirmed that there was an independent mortality benefit of treatment with baricitinib (OR 0.79, 95%CI 0.63-0.97) based on 2659 patients from a single study.[8] This represents 24 fewer deaths per 1000 people.

The interpretations forming the recommendation[2] are given below:

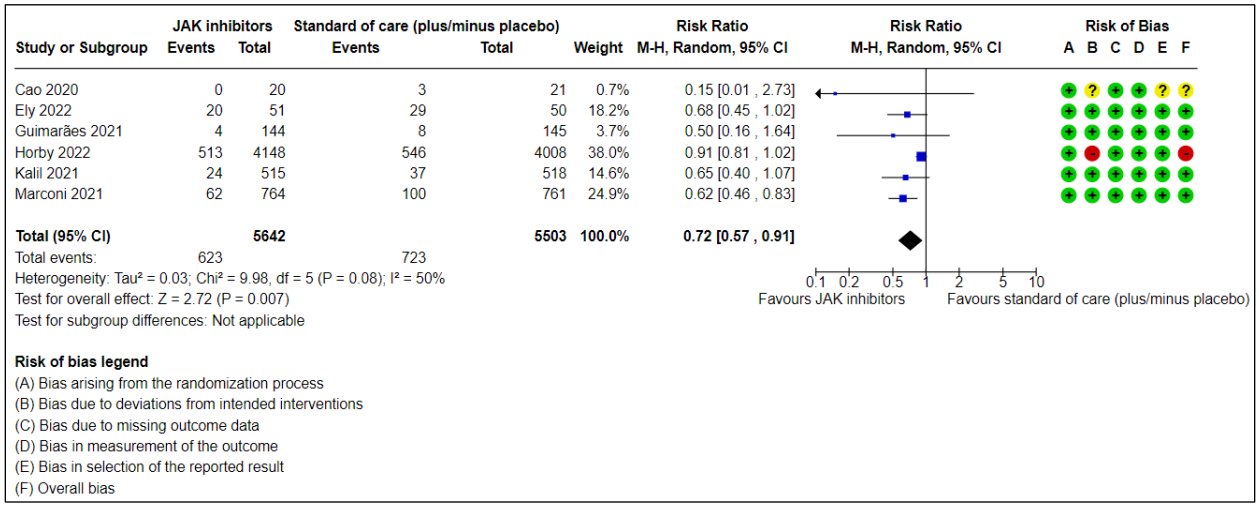
> *In patients with severe or critical illness, baricitinib reduces mortality and probably reduces duration of mechanical ventilation and hospital length of stay. It probably results in little or no increase in serious adverse events.*
>
> *Subgroup analyses were undertaken for JAK inhibitors as a class (rather than on individual drugs) and revealed no evidence of a subgroup effect on relative risk in younger (< 70 years) versus older patients; those with critical versus severe COVID-19; those receiving and not receiving corticosteroids at baseline; and those receiving and not receiving remdesivir or IL-6 blockers at baseline.*

Certainty of evidence was rated as: high for decreased mortality (although the panel acknowledged that the relatively short follow-up period close to 28 days is possibly insufficient to capture all relevant events); moderate for reduction in hospital length of stay, mechanical ventilation and serious adverse events, all rated down for serious imprecision; and low for time to clinical stability, rated down for very serious imprecision.

9.2 Other evidence

A separate meta-analysis by the Cochrane group in June 2022 examined efficacy of baricitinib, concluding that systemic JAK inhibitors probably decrease all-cause mortality at up to day 28 (95 of 1000 participants in the intervention group versus 131 of 1000 participants in the control group; risk ratio (RR) 0.72, 95% confidence interval (CI) 0.57 to 0.91; 6 studies, 11,145 participants; moderate-certainty evidence, see Figure 2.[12]

Figure 2 – Cochrane review findings for the effect of Janus kinase inhibitors on 28-day all-cause mortality for treatment of Covid-19[12]



10 Review of harms and toxicity (summary of evidence of safety)

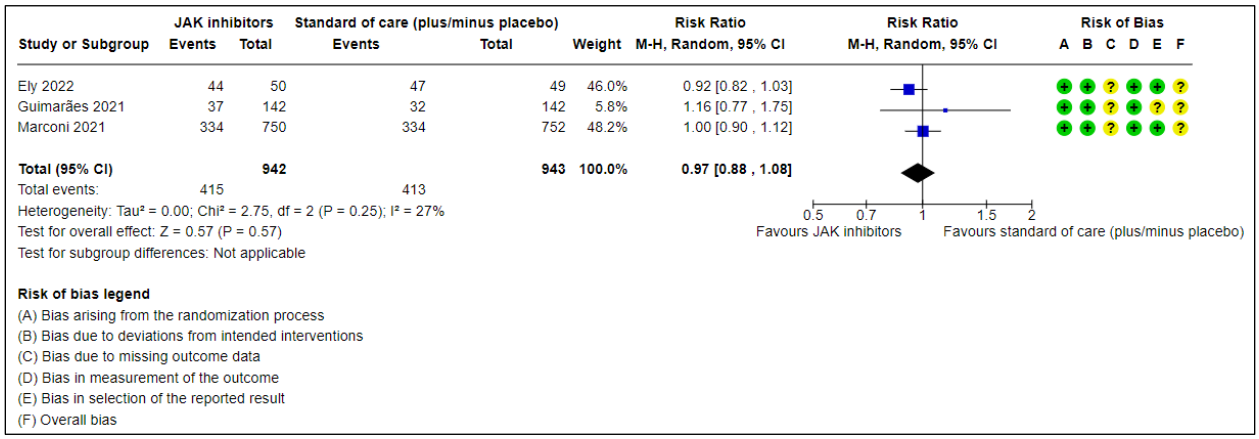
The WHO living guidelines (v12) commented on the available evidence with respect to Covid-19.[2] They noted that risks of immunosuppression exist, particularly where multiple immunosuppressants are concurrently used (such as baricitinib with corticosteroids and IL-6 blockers). The GDG noted in particular that, in addition to known risks (see below):

> *the risk of serious infections (bacterial and fungal) may vary considerably in different parts of the world according to the background prevalence of infections (such as tuberculosis). This may not be so important given the short course of baricitinib used for treatment of COVID-19, but evidence is limited given the limited geographic spread of the included trials and short follow-up periods.*

The Cochrane review estimated that 441 per 1000 participants experienced any adverse events without Janus kinase inhibitors, noting that there was little or no difference in the rate of adverse events of any grade (estimated 427 per 1000 participants (95% CI 388 to 476 per 1000)) compared to placebo (RR 0.97, 95% CI 0.88 to 1.08; I^2 = 27%; 3 studies, 1885 participants; moderate-certainty evidence), see Figure 3.[12] For serious adverse events, baseline rates (without systemic JAK inhibitors), occurred in 202 per 1000 participants. There was a decrease in risk for serious adverse events in the JAK inhibitor treated patients (estimated 160 per 1000 participants (95% CI 138 to 186 per 1000)) compared to placebo (RR 0.79, 95% CI 0.68 to 0.92; I^2 = 0%; 4 studies, 2901 participants; moderate-certainty evidence).[12] Less evidence was

available on secondary infection (and was downgraded due to indirectness and missing outcome data). However, the group concluded that JAK inhibitors may make little or no difference in the rate of secondary infection (estimated 111 per 1000 participants (95% CI 100 to 123 per 1000)) compared to standard of care (RR 0.98, 95% CI 0.89 to 1.09; I^2 = 0%; 4 studies, 10,041 participants; low-certainty evidence).

Figure 3 – Cochrane review findings for any adverse effects of Janus kinase inhibitors when use in the treatment of Covid-19[12]



Adverse reactions with baricitinib are listed in the SmPC:[3]

- Very common (≥ 1/10): upper respiratory tract infections, hypercholesterolaemia
- Common (≥1/100 to <1/10): herpes zoster, herpes simplex, gastroenteritis, urinary tract infections, pneumonia, folliculitis, thrombocytosis, headache, nausea, abdominal pain, alanine transaminase increased to ≥ 3 x ULN, rash, acne, creatine phosphokinase increased > 5 x ULN
- Uncommon (≥1/1,000 to <1/100): neutropenia, swelling of the face, urticaria, hypertriglyceridaemia, deep vein thrombosis, diverticulitis, aspartate transaminase increased to ≥ 3 x ULN, weight increase.

By frequency for any indication, the most common adverse events for baricitinib are increased LDL cholesterol (26.0 %), upper respiratory tract infections (16.9 %), headache (5.2 %), herpes simplex (3.2 %), and urinary tract infections (2.9 %). Serious pneumonia and serious herpes zoster occurred uncommonly in patients with rheumatoid arthritis. It should be noted that this represents data from use in chronic conditions in patient populations and for durations which are not representative of the use when indicated for Covid-19.

An US FDA review of a large, randomized safety clinical trial in people with rheumatoid arthritis compared tofacitinib [a drug in the same class as baricitinib] to tumor necrosis factor inhibitors over 4 years and found that tofacitinib was associated with additional serious adverse events, including heart attack or stroke, cancer, blood clots, and death.[13] However, data from randomized trials evaluating the safety of short-term use of baricitinib in patients with Covid-19 have not revealed significant safety signals, including thrombosis.[8-10,14]

10.1 Interactions

Dose reductions are warranted in patients taking strong organic anion transporter 3 (OAT3) inhibitors (e.g. probenecid).

10.2 Use in specific populations

None of the included COVID-19 RCTs enrolled children, and therefore the applicability to children remains uncertain. The US FDA has an emergency use authorisation for children age ≥2 to 18 years who require supplemental oxygen, or forms of non-invasive or mechanical ventilation.[4]

Uncertainty also remains with regard to administration of baricitinib to pregnant or lactating women. The FDA notes that: "*As small-molecule drugs, JAK inhibitors are likely to pass through the placenta; therefore, fetal risk cannot be ruled out*. *Decisions regarding the administration of JAK inhibitors must include shared decision-making between pregnant individuals and their health care providers, and potential maternal benefit and fetal risks should be considered. In the decision-making process, factors to be considered include maternal COVID-19 severity, comorbidities, and gestational age."*[15] This concerns and suggestions were reflected in similar wording by the WHO GDG.

11 Summary of available data on comparative cost and cost-effectiveness of the medicine

There is currently no formal cost-effectiveness analysis as part of the WHO guideline, although the GDG noted:

> *Compared with some other candidate treatments for COVID-19, baricitinib is expensive. The recommendation does not take account of cost-effectiveness. Access to these drugs is challenging in many parts of the world, and, without concerted effort, is likely to remain so, especially in resource-poor areas. It is therefore possible that this*

> *strong recommendation could exacerbate health inequity. The GDG was also sensitive to the fact that allowing the combined use of the JAK inhibitor baricitinib and IL-6 receptor blockers would likely further reduce the availability of these medications. The GDG strongly reinforces the need to improve drug availability, particularly in resource-constrained areas.*

Please see below for changes in market availability which are likely to increase affordability.

12 Summary of regulatory status and market availability

Currently, this medicine is provided commercially by Eli Lilly, which has been granted patents in over 50 countries. Baricitinib is not listed in the Medicines Patent Pool scheme, and is not being currently procured through the ACT Accelerator programme. Non-peer reviewed work from Harvard University estimate the cost of generic baricitinib to be US$2 per treatment course, compared with the list price from Eli Lilly of $1,109.92.[16]

13 Availability of pharmacopoeia standards

Baricitinib is listed in the British National Formulary and by the European Medicines Agency for non-Covid-19 conditions (rheumatological disease).[17]

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