

7th Invitation to Manufacturers of therapeutics against COVID-19 to submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Unit

To support national and global efforts to increase access to and affordability of products for treatment of COVID-19. WHO invites manufacturers of this pharmaceutical product to submit Expressions of Interest (EOI) for product evaluation.

ARTICLE 1. PROCEDURE FOR THIS INVITATION TO EOI

The current Invitation is published in accordance with the *Procedure for Prequalification of Pharmaceutical Products*, adopted in 2001 by the 37th WHO Expert Committee on Specifications for Pharmaceutical Preparations, and amended subsequently as part of the 45th report of the Committee, published as [No. 961 of the WHO Technical Report Series](#) in 2011.

Assessment of product(s) submitted under this Invitation will include evaluation of:

- product dossiers, which must include product data and information as specified in the guidelines for submission (see [Procedures & Fees](#))
- manufacturing sites, which must adhere to [good manufacturing practices](#) (GMP)
- clinical sites (if applicable), which must adhere to [good clinical practices](#) (GCP).

If evaluation demonstrates that a product and its corresponding manufacturing (and clinical) site(s) meet WHO recommended standards, it will be included in the list of medicinal products that are considered to be acceptable for procurement by UN organizations and others.

ARTICLE 2. MEDICINAL PRODUCTS INVITED

The aim of this Invitation is to increase the range of selected products and sources available in relation to management of the COVID-19 pandemic.

Dexamethasone

Dexamethasone, a corticosteroid, is included in the [WHO Model List of Essential Medicines, with clinical uses in multiple diseases and conditions](#), mainly as an anti-inflammatory agent. In COVID-19, a randomised controlled clinical trial (RECOVERY)¹ has shown that dexamethasone reduced deaths by one-third in ventilated patients and by one fifth in other patients receiving supplemental oxygen compared to usual care alone. There was no benefit among those patients who did not require respiratory support

IL-6 Inhibitors

Tocilizumab and sarilumab are monoclonal antibodies that inhibit the Interleukin-6 (IL-6) receptor. Interleukin-6 is a cytokine produced by macrophages that induces a pro-inflammatory response. It is often elevated in patients with COVID-19.

Tocilizumab and sarilumab have been shown to provide benefit in hospitalized patients with severe or critical COVID-19.^{2,3} (Data supporting tocilizumab is more robust than for sarilumab.) They should be administered with systemic corticosteroids. Tocilizumab and sarilumab are administered as single intravenous doses, typically over one hour.

Tocilizumab is dosed at 8 mg per kilogram of actual body weight, up to a maximum of 800 mg. Sarilumab may be dosed at 400 mg or 200 mg. Renal dose adjustment is not currently warranted for either drug.

Kinase Inhibitors

Janus Kinase Inhibitors

Baricitinib

Baricitinib is an oral Janus kinase (JAK) inhibitor, a targeted synthetic disease-modifying anti-rheumatic drug (tsDMARD). It has known anti-inflammatory effects on autoimmune diseases, and a postulated antiviral effect of blocking SARS-CoV-2 from entering and infecting lung cells. Studies with baricitinib have confirmed a reduction in mortality and need for invasive mechanical ventilation in patients with severe and critical COVID-19.^{4,5}

Neutralizing Antibodies

Casirivimab and imdevimab

Casirivimab and imdevimab are human immunoglobulin G-1 (IgG1) monoclonal antibodies produced by recombinant DNA technology. They bind to non-overlapping epitopes of the spike protein receptor-binding domain (RBD) of SARS-CoV-2, blocking viral entry into host cells.

Neutralizing antibodies directed at the RBD of the SARS-CoV-2 spike protein have demonstrated benefit as prophylactic and therapeutic agents for COVID-19. This has been seen in both non-hospitalized and hospitalized patients.^{6,7,8} Antibody therapy may more rapidly reduce viral load and minimize virus-induced lung and airway pathology.

Sotrovimab

Sotrovimab is an engineered human monoclonal antibody that neutralizes SARS-CoV-2, targeting a pan-sarbecovirus epitope. It has effector functions that may result in immune-mediated viral clearance. Sotrovimab has shown reduction in hospitalization in persons with mild to moderate disease who are at high risk for developing severe disease.⁹

Direct-Acting Antivirals

Molnupiravir

Molnupiravir is a prodrug that is metabolized in the human body to the ribonucleoside analogue N-hydroxycytidine (NHC). It is phosphorylated to form the active triphosphate (NHC-TP). This acts by a mechanism known as lethal mutagenesis, causing an accumulation of viral genome errors which result in inhibition of replication.

In clinical trials molnupiravir showed a reduction of hospitalization in patients with early Covid-19 at high risk for severe disease.

Nirmatrelvir and ritonavir

Nirmatrelvir is a protease inhibitor which acts on the intracellular 3CL protease of the SARS-CoV-2 virus to suppress viral replication. Ritonavir slows the metabolism of nirmatrelvir, allowing higher drug levels for more prolonged periods. In clinical studies, the combination of the two products taken orally reduced the risk of hospitalization or death in outpatients who began treatment within 5 days of symptoms of Covid-19.

Interested manufacturers are encouraged to submit documentation for recommended dosage forms as specified below:

Dexamethasone products¹:

1. Dexamethasone tablet, containing dexamethasone base 1.5mg, 2mg, 6mg
2. Dexamethasone oral solution, containing dexamethasone base 2mg/5ml or 10mg/5ml, as the base or sodium phosphate
3. Dexamethasone solution for injection, containing dexamethasone base 3.3mg/ml or 6.6mg/ml*, as the sodium phosphate (*equivalent to dexamethasone phosphate 4mg/ml or 8mg/ml, respectively)

¹ Other dexamethasone products with similar strengths as the ones listed may be considered. Please contact PQT.

Tocilizumab products

Tocilizumab IV 20 mg/mL for further dilution prior to intravenous infusion.

Sarilumab products

Sarilumab 200 mg/1.14 mL for further dilution prior to intravenous infusion.

Sarilumab 150 mg/1.14 mL for further dilution prior to intravenous infusion.

For details on specific requirements for tocilizumab and sarilumab products, see:

[Prequalification Procedure \(PQ\) for Therapeutics: product specific requirements for currently invited therapeutics.](#)

Baricitinib Products

Baricitinib 2 mg tablets

Neutralizing Antibody Products

Casirivimab + imdevimab (IV or subcutaneous)

Intravenous administration requires dilution in 0.9% Sodium Chloride Injection or 5% dextrose Injection

Co-packaged 6 mL single-use vials

Casirivimab 6 mL vial containing 300 mg of casirivimab per 2.5 mL (120 mg/mL). Imdevimab 6 mL vial containing 300 mg imdevimab per 2.5 mL (120 mg/mL).

Co-packaged 20 mL multi-dose vials

Casirivimab 20 mL multi-dose vial containing 1,332 mg of casirivimab per 11.1 mL (120 mg/mL). Imdevimab 20 mL multi-dose vial containing 1,332 mg imdevimab per 11.1 mL (120 mg/mL).

For details on specific requirements for casirivimab+imdevimab products, see: [Prequalification Procedure \(PQ\) for Therapeutics: product specific requirements for currently invited therapeutics.](#)

Sotrovimab solution for infusion, 500 mg/8 mL (62.5 mg/mL) single use vial

Direct-Acting Antiviral Products

Molnupiravir 200 mg capsules for oral administration

Nirmatrelvir 150 mg tablets (2) plus ritonavir 100 mg tablet (1), co-packaged for oral administration¹

Note, regarding general requirements for biotherapeutic products see: <https://extranet.who.int/pqweb/medicines/pilot-prequalification-biotherapeutic-products>

ARTICLE 3. HOW TO SUBMIT AN EXPRESSION OF INTEREST

In order to submit an expression of interest for product evaluation, the manufacturer must send the requested documentation, arranged according to the information provided on the WHO Prequalification Unit – Medicines Assessment Team (PQT/MED) [website](#) in the [Procedures and Fees](#) section.

ARTICLE 4. QUALITY ASSESSMENT PROCEDURE FOLLOWING SUBMISSION OF AN EXPRESSION OF INTEREST BY A MANUFACTURER

The quality assessment is undertaken to evaluate whether the pharmaceutical product being evaluated meets the requirements recommended by WHO, and is manufactured in compliance with good manufacturing practices (GMP).

The procedure established by WHO for quality assessment incorporates:

- general understanding of the production and quality control activities of the manufacturer;
- assessment of product data and information on safety, efficacy and quality submitted by the manufacturer, including product formulation, manufacture and test data and results;
- assessment of the manufacturing site's adherence to GMP, and its consistency in production and quality control of starting materials, with specific emphasis on active pharmaceutical ingredients, and finished product;
- assessment of clinical testing units or organizations (i.e. parties performing one or more clinical trials with the product) for compliance with good clinical practices and good laboratory practices, as appropriate;
- random sampling and testing of medicines supplied.

¹ For specific requirements please contact PQT/MED

Once WHO is satisfied that quality assessment has been completed for the manufacturer of the relevant starting materials, the finished pharmaceutical product, and the clinical testing units, and that the product meets WHO recommended standards, the product (as produced at the specified manufacturing site) is added to the [WHO List of Prequalified Medicinal Products](#).

ARTICLE 5. REFERENCES AND FURTHER INFORMATION

Dexamethasone

1. RECOVERY Trial, N Engl J Med 25 February 2021
<https://www.nejm.org/doi/full/10.1056/NEJMoa2021436>

Tocilizumab and Sarilumab

2. RECOVERY Trial, The Lancet 1 May 2021
<https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2900676-0>
3. REMAP-CAP Study, N Engl J Med 22 April 2021
<https://www.nejm.org/doi/full/10.1056/NEJMoa2100433>

Baricitinib

4. COV-BARRIER Study, Lancet Respir Med, 1 September 2021.
[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(21\)00331-3/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00331-3/fulltext).
5. ACTT-2 Study, N Engl J Med. 2021;384(9):795-807
<https://www.ncbi.nlm.nih.gov/pubmed/33306283>.

Casirivimab+imdevimab

6. REGN-COV2, a neutralizing antibody cocktail, in outpatients with Covid-19. N Engl J Med, 18 Dec 2020
<https://www.nejm.org/doi/pdf/10.1056/NEJMoa2035002?articleTools=true>
7. RECOVERY Trial: REGEN-COV for COVID-19, 16 June 2021
<https://www.medrxiv.org/content/10.1101/2021.06.15.21258542v1.full.pdf>
8. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19, N Engl J Med, 4 August 2021
<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8362593/pdf/NEJMoa2109682.pdf>

Sotrovimab

9. COMET-ICE Study, N Engl J Med 2021; 385:1941-1950
<https://www.nejm.org/doi/full/10.1056/NEJMoa2107934>