Coronavirus disease (COVID-19) pandemic
Product specific requirements for currently invited combination of casirivimab and imdevimab

Casirivimab and imdevimab are two fully human neutralising monoclonal antibodies against SARS-CoV-2 spike protein. These two antibodies bind specifically to the receptor binding domain (RBD) of the spike (S) glycoprotein of SARS-CoV-2, blocking viral entry into host cells. Casirivimab and imdevimab are both potent neutralizing antibodies that block the interaction between the S protein and its canonical receptor angiotensin-converting enzyme 2 (ACE2). Casirivimab and imdevimab are intended to be utilized as a combination treatment and should not be used individually as monotherapies. A combination of antibodies that bind to non-overlapping epitopes may minimize the likelihood of loss of antiviral activity due to naturally circulating viral variants or development of escape mutants under drug pressure.

The combination of casirivimab and imdevimab is approved by SRAs as prophylaxis and treatment of acute Covid-19 infection.

The WHO Guideline Development Group is supporting the use of casirivimab and imdevimab based on results of studies in the public domain showing clinical benefit in prophylaxis and treatment of Covid-19. Based on the GDG opinion of positive benefit/risk in COVID-19, the WHO Prequalification Unit has developed a prequalification procedure for the combination of casirivimab and imdevimab, following either of two pathways:

1) abridged assessment of the combinantion of casirivimab and imdevimab, or their corresponding similar biotherapeutic products (SBPs), which have been approved by SRAs and marketed in the country of registration (hereinafter referred to as “Abridged Assessment”); or
2) full assessment of SBPs for the combination of casirivimab and imdevimab that have been registered by non-SRAs (based on a reference biotherapeutic product (RBP) approved by a SRA) (hereinafter referred to as “Full Assessment”)

This document addresses technical, communication, policy and other aspects as applicable to the specific medicines invited under the current prequalification (PQ) procedure as detailed below[1]. Based on experience gained during the PQ process, WHO reserves the right to revise the prequalification procedure.

[1] Please also refer to the applicable principles detailed in the “WHO Procedure for Prequalification of BTPs or their corresponding SBPs” (https://extranet.who.int/pqweb/sites/default/files/documents/01_Prequalification_procedure_General_0.pdf)

1) Abridged assessment of the combination of casirivimab and imdevimab, or their corresponding similar biotherapeutic products (SBPs), which have been approved by SRAs and marketed in the country of registration (hereinafter referred to as "Abridged Assessment")[2];

- Applicants must request a pre-submission meeting (PSM) to discuss their product. If the product is deemed eligible for submission according to the published EOI process, the following documents are required:
- A covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct
- A copy of the marketing authorization, or equivalent thereof, issued by the reference SRA demonstrating that the product is registered or licensed in accordance with the reference SRA's requirements. If applicable, a copy of the latest renewal of the marketing authorization should also be provided.
- If available, a copy of the current WHO-type certificate of a pharmaceutical product issued and fully completed, including answers to each question, by the reference SRA.
- A list of the SRA-approved manufacturer(s) of the drug substance (DS) and drug product (DP), including manufacturers of intermediates, primary packaging sites and DS and DP release-testing sites for both the DS and DP, with the physical address of the manufacturing site(s) (and unit if applicable).
- A declaration that the product offered for PQ is, and will be after PQ, identical in all aspects - including but not limited to composition/formulation, manufacturing, specifications, packaging and DS manufacturer(s) - to the SRA approved product.
- Clinical data supporting the use of the product in the management of Covid-19 infection, when available.
- There is no need to submit any quality/GMP documentation.
- The WHO prequalification-specific addendum to the RMP as detailed on the PQ BTP web page (https://www.who.int/medicines/regulation/RMP_AddStructureDec2019-2.pdf?ua=1P).
- Safety specification, pharmacovigilance plan, risk management plan (RMP) and post-marketing safety reports. It is expected that all available information at the time of submission specifically related to the SARS-CoV2 indication is discussed/addressed in each section of the SRA-approved RMP, specifically:

[2] For further guidance please refer to the applicable principles and documentation detailed in the "WHO Guidelines on submission of documentation for abridged assessment" (https://extranet.who.int/pqweb/sites/default/files/documents/03_Pilot_PQ_anticancer_AbridgedPathway_Feb2020.pdf)

- Populations not studied in clinical trials, exposure of special populations included or not in clinical development programs (considered as missing information)
- Identified and potential risks specific to SARS-CoV2 infected patients including characterization of the risk in groups with potential higher risk, e.g. immunocompromised patients, patients with comorbidities. Discussion of preventability and its potential impact on the benefit/risk
- Missing information (e.g. elderly, paediatric) specific in SARS-CoV2 infected patients and potential impact on benefit/risk
- Description of on-going/planned additional pharmacovigilance activities such as non-clinical, clinical or epidemiological studies (interventional or non-interventional), and the reason they are needed. Description of the type of study (e.g. long-term follow-up extensions of ongoing clinical trial(s), further effort to evaluate the missing data). Information on the study population should be part of the study description. Clear milestones and due dates should be provided (e.g. submission of final study report by 31/01/2022). Description (e.g. study type, study population, milestones and due date) of on-going/planned post-authorization efficacy studies (PAES) and the reason they are needed.
- Risk minimization measures, including additional measures and evaluation of the effectiveness of risk minimization activities.

2) Full assessment of SBPs for the combination of casirivimab and imdevimab that have been registered by non-SRAs (based on a reference biotherapeutic product (RBP) approved by an SRA) (hereinafter referred to as "Full Assessment")[3]

- Applicants must request a pre-submission meeting (PSM) to discuss their product. If the product is deemed eligible for submission according to the PQ process, the following apply:
- A covering letter, expressing interest in participating in the WHO prequalification procedure and confirming that the information submitted in the product dossier is complete and correct
- The data for an SBP should follow the structure of the CTD format containing the required quality, GMP, non-clinical and clinical information for the applicable sections. In addition, such applications should fulfil the specific requirements detailed in the ICH M4 guideline.

[3] For further guidance please refer to the applicable principles and documentation detailed in the "WHO Guidelines on submission of documentation for full assessment" (https://extranet.who.int/pqweb/sites/default/files/documents/02_Pilot_PQ_anticancer_fullPathway_20Feb2020.pdf)

- Head-to-head comparison of a biotherapeutic product with a SRA-licensed reference biotherapeutic product (RBP) with the goal of establishing similarity of quality, safety and efficacy.
- Safety specification, pharmacovigilance plan, risk management plan (RMP) and post-marketing safety reports. It is expected that all available information at the time of submission specifically related to SARS-CoV2 indication is discussed/addressed in the RMP and specifically:
    - Populations not studied in clinical trials, exposure of special populations included or not in clinical development programs (considered as missing information)
    - Identified and potential risks specific to SARS-CoV2 infected patients including characterization of the risk in groups with potential higher risk, e.g. immunocompromised patients, patients with comorbidities. Discussion of preventability and its potential impact on the benefit/risk
    - Missing information (e.g. elderly, paediatric) specific in SARS-CoV2 infected patients and potential impact on benefit/risk
    - Description of on-going/planned additional pharmacovigilance activities such as non-clinical, clinical or epidemiological studies (interventional or non-interventional), and the reason they are needed. Description of the type of study (e.g. long-term follow-up extensions of ongoing clinical trial(s), further effort to evaluate the missing data). Information on the study population should be part of the study description. Clear milestones and due dates should be provided (e.g. submission of final study report by 31/01/2022). Description (e.g. study type, study population, milestones and due date) of on-going/planned Post-authorization Efficacy Studies (PAES) and the reason they are needed.
    - Risk minimization measures, including additional measures and evaluation of the effectiveness of risk minimization activities.