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Task Force on Repurposing of Drugs (TFORD) for COVID19

S&T Core Group on COVID19 constituted by PSA to GoI

Molecule Brief: Tocilizumab

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About this document: *This document summarizes information available on drug candidates for COVID19. One Molecule Brief document covers one candidate at a time.*	
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1. Summary Information on Tocilizumab

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Tocilizumab
Brand Name	Actemra
Category/ Type	Immuno-suppressant (Monoclonal Antibody)
Drug Bank ID/Link	DB06273 https://www.drugbank.ca/drugs/DB06273
Mode of Action	Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R), and has been shown to inhibit IL-6-mediated signaling through these receptors.
Therapeutic Target	Interleukin 6 (IL-6) receptor
Is action Host or Virus directed?	Host directed
Currently Approved for which Indication(s)	1. Adults with moderately to severely active rheumatoid arthritis (RA) after at least one other medicine called a disease modifying antirheumatic drug (DMARD) has been used and did not work well 2. Adults with giant cell arteritis (GCA) 3. Patients with active polyarticular juvenile idiopathic arthritis (PJIA) 2 years of age and older 4. Patients with active systemic juvenile idiopathic arthritis (SJIA) 2 years of age and older
Approved Dose	• Intravenous Infusion Injection: 80 mg/4 mL (20 mg/mL), 200 mg/10 mL (20 mg/mL), 400 mg/20 mL (20 mg/mL) in single-dose vials for further dilution prior to intravenous infusion. • Subcutaneous Injection : 162 mg/0.9 mL in a single-dose prefilled syringe
Route of Administration	Intravenous (IV) infusion
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	4 mg/kg IV q4Weeks initially; may increase to 8 mg/kg q4Weeks based on clinical response. Not to exceed 800 mg/dose q4weeks
Adverse events/Side effects reported at the current approved dose	Affects immune system. Lowers the ability of immune system to fight infections including tuberculosis (TB), and infections caused by bacteria, fungi, or viruses that can spread throughout the body.
Reported Drug-Drug Interactions	A total of 251 drugs are known to interact with tocilizumab. • 39 major drug interactions

	• 205 moderate drug interactions • 7 minor drug interactions *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125276s114lbl.pdf
Current TRL level of the Drug	Approved drug
Has the drug been repurposed for any other indication before?	No
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Cipla has signed distribution deal with Roche in India
International Manufacturer(s)	Hoffmann–La Roche (co-development with Chugai), Genetech
Price of the Drug in India	Rs. 40,000 Actemra 400mg Injection
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	1. Cytokine Release Syndrome (CRS)/Cytokine storm is a systemic inflammatory response characterized by a sharp increase in the level of a large number of pro-inflammatory cytokines. 2. Evidence indicates that CRS of varying degrees have occurred in severe patients with SARS and MERS. 3. The SARS-CoV-2 bind to alveolar epithelial cells, activating the innate immune system and adaptive immune system, resulting in the release of a large number of cytokines, including IL-6. This causes vascular permeability increase, a large number of fluid and blood cells coming into the alveoli, resulting in dyspnea and even respiratory failure. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7118634/ (For points 1-3) 4. Studies indicate that IL-6 is significantly up-regulated in patients with COVID-19, correlates with disease severity and viral load. The increase of baseline IL-6 level suggests that it may positively correlate with the severity of COVID-19 and could potentially be used as a disease biomarker. • http://medrxiv.org/content/10.1101/2020.03.01.20029769v2.full.pdf • https://www.medrxiv.org/content/10.1101/2020.02.29.20029520v1 • https://www.medrxiv.org/content/10.1101/2020.02.25.20025643v1
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	No in-vitro or in-vivo data available. Based on data mentioned in the “Rationale” section, it is thought an IL-6 inhibitor can be a potential therapeutic for COVID-19
Status of Clinical Trials	0 Completed + 2 Ongoing
Trial Details	See table below

Trial ID/Link	Type of Trial	Number of patients	Drug Combination/Dose/ Stage of Disease	Primary and Secondary Measures	Has data from the trial been published (Yes/No)
NCT04320615 (Roche)	Randomized	330	No combination Dose: Intravenous (IV) infusion of TCZ, dosed at 8 mg/kg, up to a maximum dose 800 mg Stage: severe COVID-19 pneumonia confirmed	Primary: Clinical Status Assessed Using a 7-Category Ordinal Scale Secondary: Time to Clinical Improvement, Ventilator free, organ failure, mortality rate, Covid viral load	No
NCT04317092	Open Label	400	No combination Dose: Two doses of Tocilizumab 8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours: Stage: Patients with COVID-19 pneumonia	Primary: One-month mortality rate Secondary: Interleukin-6 level, Lymphocyte count, Sequential Organ Failure Assessment, Days of hospitalization, time to independence from oxygen therapy in days	No

Key Data from Clinical Trials	1. Effective Treatment of Severe COVID-19 Patients with Tocilizumab 21 Chinese patients with severe diagnosed as severe or critical COVID-19 were given Tocilizumab in addition to routine therapy between February 5 and February 14, 2020. The changes of clinical manifestations, CT scan image, and laboratory examinations were retrospectively analyzed. Results: Within a few days, the fever returned to normal and all other symptoms improved remarkably. Fifteen of the 20 patients (75.0%) had lowered their oxygen intake and one patient need no oxygen therapy. 2. NCT04320615: Roche is not releasing too much data or news about the drug and its efficacy till it completes its Phase III trial (just about to start). Its Phase I and Phase II trials were extremely promising with almost 95% of patients recovered. Although data has not been published, they have received approvals for Phase III trials from US https://www.thailandmedical.news/news/breaking-covid-19-drug-research-tocilizumab-actemra-by-roche-emerging-as-the-best-drug-candidate-for-treating-covid-19-so-far-while-others-are-simply-
TRL Level for COVID19	**TRL-7/8 (Phase II, Phase III)**
IP Status	**Status/ Molecule** — **Tocilizumab** Pending applications — Not applicable Approved and Active applications — IN278603 Title: Improved Antibody Molecule Assignee: Chugai Seiyaku Kabushiki Kaisha Priority Date: 26/09/2008 Grant date: 27/12/2016 Expected expiry date: 19/03/2030 IN229692 Title: An Antibody-Containing Solution Formulation Assignee: Chugai Seiyaku Kabushiki Kaisha Priority Date: 14/02/2002 Grant date: 04/03/2009 Expected expiry date: 14/02/2023 IN278603 Title: Improved antibody molecule Assignee: Chugai Seiyaku Kabushiki Kaisha Priority Date: 26/09/2008 Grant date: 30/12/2016 Expected expiry date: 25/09/2029, subject to payment of

	Expired or Lapsed application IN286348 Title: Anti-IL-6 receptor antibody Assignee: Chugai Seiyaku Kabushiki Kaisha Priority Date: 26/09/2007 Grant date: 14/08/2017 Expected expiry date: 26/09/2028 Status: Patent ceased: Renewal Discontinued: 26/03/2019 6429/DELNP/2015 Title: Improved Antibody Molecule Assignee: Chugai Seiyaku Kabushiki Kaisha Priority Date: 26/09/2008 Publication date: 29/07/2016 Status: Abandoned section 21(1) 3898/CHENP/2008 Title: Antibody-Containing Solution Formulations Assignee: Chugai Seiyaku Kabushiki Kaisha Priority Date: 14/02/2002 Publication date: 13/03/2009 Status: No status update on Indian patent site
Other Key References	1. https://www.onclive.com/web-exclusives/tocilizumab-effectively-treats-covid19-in-patient-with-myeloma 2. https://www.thailandmedical.news/news/breaking-covid-19-drug-research-tocilizumab-actemra-by-roche-emerging-as-the-best-drug-candidate-for-treating-covid-19-so-far-while-others-are-simply- 3. https://www.pmlive.com/pharma_news/fda_approves_roches_actemra_covid-19_trial_1329887

2. Background information

About TFORD-COVID19
The Principal Scientific Advisor to the GoI, Dr K VijayRaghavan, has constituted a S&T Core Group on COVID19. Under the aegis of the S&T Core Group on COVID19, a Task Force has been constituted focused on Repurposing of Drugs for COVID19 (in short "TFORD-COVID19"). The Task Force is being coordinated by Dr V Premnath, Head, NCL Innovations at CSIR-NCL and Director, Venture Center and Dr Anurag Agarwal, Director, CSIR-IGIB. The Nerve Center for the Coordination is located be at Venture Center, Pune (located in the campus of CSIR-NCL).

Credits
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