Document prepared by Nerve Center of TFORD, Venture Center, Pune
Task Force on Repurposing of Drugs (TFORD) for COVID19
S&T Core Group on COVID19 constituted by PSA to GoI

Molecule Brief: Hydroxychloroquine

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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 Hydrochloroquine

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Hydroxychloroquine
Brand Name	Plaquenil
Category/ Type	Antimalarial
Drug Bank ID/Link	DB01611 https://www.drugbank.ca/drugs/DB01611
Mode of Action	HQ affects the function of lysozomes in humans as well as plasmodia. It accumulates in the lysosomes of the malaria parasite, raising the pH of the vacuole. This activity interferes with the parasite's ability to proteolyse hemoglobin, preventing the normal growth and replication of the parasite. HQ also accumulates in human organelles, raising their pH, which inhibits antigen processing, prevents the alpha and beta chains of the major histocompatibility complex (MHC) class II from dimerizing, inhibits antigen presentation of the cell, and reduces the inflammatory response.
Currently Approved for which Indication(s)	• Prophylaxis and Treatment of Uncomplicated Malaria • Rheumatoid Arthritis • Lupus Erythematosus
Approved Dose	400 to 600 mg daily
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	Total dose of 25 mg base per kg has been found to be safe
Adverse events/Side effects reported at the current approved dose	Retinal or visual field changes, known hypersensitivity, retinopathy, hair loss, photosensitivity, tinnitus, myopathy (long-term therapy)
Reported Drug-Drug Interactions	58 major drug interactions, 266 moderate drug interactions, 5 minor drug interactions
Link to Datasheet	https://www.medsafe.govt.nz/Profs/Datasheet/p/Plaquenilt ab.pdf

Current TRL level of the Drug	TRL9; Approved Drug
Has the drug been repurposed for any other indication before?	No
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	IPCA, Torrent, Cadila
International Manufacturer(s)	Sanofi
Information About the Candidate for COVID19	
Repurposing Claim	New Indication (COVID19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	• Pre-clinical evidence shows HQ has anti-viral activity against SARS-CoV-2 (see details below) • Chloroquine is also being tested for COVID-19. HQ clinical safety profile is better than that of Chloroquine (during long-term use) and allows higher daily dose and has fewer concerns about drug-drug interactions. https://www.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub Illustration of possible MoA: https://science.sciencemag.org/content/367/6485/1412
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID19	1. In vitro studies in SARS-CoV-2 infected Vero cells showed that HQ (EC50=0.72 µM) was more potent than Chloroquine (EC50=5.47µM) to inhibit SARS-CoV-2. https://www.ncbi.nlm.nih.gov/pubmed/32150618 2. HCQ inhibits SARS-CoV-2 infection in vitro in African green monkey kidney VeroE6 cells. The 50% cytotoxic concentration (CC50) value for HCQ was 249.50 µM. HCQ blocked the transport of SARS-CoV-2 from early endosomes (EEs) or endolysosomes (ELs), which appears to be a requirement to release the viral genome as in the case of SARS-CoV https://www.nature.com/articles/s41421-020-0156-0
Status of Clinical Trials	• Completed/Ongoing (See details below) • 1 of the 4 drugs which are being tested in a WHO global multi-centric trial SOLIDARITY ➢ https://www.sciencemag.org/news/2020/03/who-launches-global-megatrial-four-most-promising-coronavirus-treatments ➢ https://science.sciencemag.org/content/367/6485/1412
Number of Trials	1 Completed NCT04261517 in China (Phase II) + 17 Ongoing NCT04308668 NCT04315948, NCT04316377 NCT04318444 NCT04321616 NCT04303507 NCT04322123 NCT04321278 NCT04307693 NCT04315896 NCT04318015 NCT04323631 NCT04322396 NCT04303299 NCT04321993 NCT04304053 NCT04320277
Dose being tested for COVID-19?	• 400 mg per day for 5 days • Based on Physiologically-based pharmacokinetic simulation models (PBPK) results, a loading dose of 400 mg twice daily of HQ sulfate given orally, followed by a maintenance dose of 200 mg given twice daily for

	4 days is recommended for SARS-CoV-2 infection https://www.ncbi.nlm.nih.gov/pubmed/32150618
Countries where Clinical Trials are being/been done	US, Norway, France, Brazil, China, Korea
Key Data from Clinical Trials	1. French Study # 1- French Confirmed COVID-19 patients (26-Test/16 Control) were included in a single arm protocol from early March to March 16th, to receive 600mg of HQ as daily dose and their viral load in nasopharyngeal swabs was tested daily in a hospital setting (Open label non-randomized clinical trial) Key Results: • At day6 post-inclusion, 70% of HQ-treated patients were virologicaly cured comparing with 12.5% in the control group (p= 0.001). • Please note – this study had another Arm (HQ + Azithromycin) - At day6 post-inclusion, 100% of patients treated with HQ and Azithromycin combination were virologicaly cured comparing with 57.1% in patients treated with hydroxychloroquine only and 12.5% in the control group (p<0.001). https://www.sciencedirect.com/science/article/pii/S0924857920300996?via%3Dihub 2. Study in China with 30 COVID-19 patients given 400mg HQ/day for 5 days. Key Results: • Day 7 - COVID-19 nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group (*P*>0.05). • The median duration from hospitalization to virus nucleic acid negative conservation was 4 (1-9) days in HCQ group, which is comparable to that in the control group[2 (1-4) days, (U=83.5, *P*>0.05)]. • The median time for body temperature normalization in HCQ group was 1 (0-2) after hospitalization, which was also comparable to that in the control group 1 (0-3). • Radiological progression was shown on CT images in 5 cases (33.3%) of the HCQ group and 7 cases (46.7%) of the control group, and all patients showed improvement in follow-up examination. http://www.zjujournals.com/med/CN/10.3785/j.issn.1008-9292.2020.03.03 3. French Study # 2- Open label trial with 80 patients – HCQ+Azithromycin. Key Results: • A rapid fall of nasopharyngeal viral load tested by qPCR was noted, with 83% negative at Day7, and 93% at Day8. The number of contagious patients (with positive culture) early decreased after three days of treatment. After five days of treatment, two patients only were contagious. On Day8 post-treatment only one of these two patients was contagious and ceased to be contagious on Day9. The proportion of negative culture significantly decreased overtime. • 66/80 (81%) of patients showed favorable clinical outcome and were discharged. https://www.mediterranee-infection.com/wp-

	content/uploads/2020/03/COVID-IHU-2-1.pdf
TRL Level for COVID19	TRL > 7 (Ph II/ Ph III Clinical Trials)
IP Status	**Pending applications** • IN201821021981 **Title:** Process For Preparation Of Hydroxychloroquine And Intermediates Thereof **Assignee:** Cadila Health Care Ltd **Filing date:** 11/06/2018 • IN201621005522A **Title:** Anhydrous Crystalline Form Of S-(+) Hydroxychloroquine Sulfate And Process For Preparation Thereof **Assignee:** IPCA Laboratories **Filing date:** 17/02/2016 • 1454/MUM/2015 **Title:** HCQS for prophylaxis and treatment of statin induced diabetes **Assignee:** IPCA Laboratories **Filing date:** 07/04/2015 • 684/MUM/2013 **Title:** Treatment And Prophylaxis Of Kidney Diseases **Assignee:** IPCA Laboratories **Filing date:** 06/03/2013 • WO2019075229A1 **Title:** Hydroxychloroquine Sulfate Formulations And Methods For Preparation And Use Thereof **Assignee:** Res Triangle Inst **Filing date:** 11/10/2018 **Status:** Subject to national phase entry • WO2019200284A1 **Title:** Chloroquine-Based Materials For The Treatment Of Diseases **Assignee:** UNIV NEBRASKA **Filing date:** 12/04/2019 **Status:** Subject to national phase entry **Approved and Active applications** • IN280009 **Title:** Pharmaceutical Composition **Assignee:** IPCA Laboratories **Filing date:** 12/07/2011 **Grant date:** 07/02/2017 **Expected Expiry date:** 12/07/2031 • IN291470 **Title:** Pharmaceutical Composition **Assignee:** IPCA Laboratories **Filing date:** 12/10/2009 **Grant date: :** 08/01/2018 **Expected Expiry date:** 12/10/2029

		• IN206244 **Title:** A Process For The Preparation Of 7-Chloro-4-(5(-N-Ethyl-N-2-Hydroxyethylamine)-2-Pentyl] Aminoquinoline [Hydroxychloroquine] And Its Acid Addition Salts **Assignee:** IPCA Laboratories **Filing date:** 24/11/2003 **Grant date: :** 24/05/2007 **Expected Expiry date:** 24/11/2023
	Expired or Lapsed application	NA
Other Key References	1. WHO: Table of Therapeutics	

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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