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: Lopinavir + Ritonavir

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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 Lopinavir + Ritonavir

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Lopinavir+Ritonavir
Brand Name	Kaletra (Abbott)
Category/ Type	Antiviral
Mode of Action	Lopinavir is an anti-retroviral protease inhibitor. Lopinavir is marketed and administered exclusively in combination with Ritonavir. This combination is necessary due to Lopinavir's poor oral bioavailability and extensive biotransformation. Ritonavir is a potent inhibitor of the enzymes responsible for Lopinavir metabolism, and its co-administration "boosts" Lopinavir exposure and improves antiviral activity. MoA in HIV: Lopinavir is an inhibitor of the HIV-1 protease enzyme. Its design is based on the "peptidomimetic" principle, wherein the molecule contains a hydroxyethylene scaffold which mimics the normal peptide linkage (cleaved by HIV protease) but which itself cannot be cleaved. By preventing HIV-1 protease activity, and thus the proteolysis of the Gag polyprotein, lopinavir results in the production of immature, non-infectious viral particles.
Currently Approved for which Indication(s)	HIV infection
Approved Dose	5 ml solution (400mg Lopinavir/100mg Ritonavir), twice a day
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	Data Not available
Adverse events/Side effects reported at the current approved dose	Diarrhoea, abdominal pain, asthenia, headache, dyspepsia, vomiting, myalgia, bronchitis, hypertension, palpitation, thrombophlebitis, vasculitis, nausea, loss of appetite, numbness of the hands and feet

Reported Drug-Drug Interactions	36 Contraindicated 151 Serious - Use Alternative 437 Monitor Closely 37 Minor
Link to Datasheet	https://reference.medscape.com/drug/kaletra-lopinavir-ritonavir-342629#4
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)	Lupin, Hetero, Aurobindo, Emcure, SunPharma, Cipla (Licenses under UN medicine pool) https://medicinespatentpool.org/licence-post/lopinavir-ritonavir-lpvr/
International Manufacturer(s)	Abbvie
Information About the Candidate for COVID19	
Repurposing Claim	New Indication (COVID19) + New Dose (to be confirmed)
Rationale for Repurposing for COVID19/MoA?	• Lopinavir improved outcomes in SARS and MERS patients. • Pre-clinical evidence showing activity against other SARS and MERS viruses. SARS-CoV-2 shares 79.5% sequence identity with SARS (2002 epidemic) https://onlinelibrary.wiley.com/doi/full/10.1002/jmv.25729 http://archcid.com/articles/13823.html Illustration of possible MoA: https://science.sciencemag.org/content/367/6485/1412
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	Data not available
Status of Clinical Trials	• Ongoing/Completed (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 + 12 Ongoing 1. NCT04307693 2. NCT04321174 (+HQ) 3. NCT02845843 (+IFNb) 4. NCT04261907 5. NCT04252885 (+Arbidol) 6. NCT04276688 (+Ribavirin and IFN-beta) 7. NCT04255017 8. NCT04295551 9. NCT04315948 10. NCT04314817 11. NCT04321993 12. NCT04303299 : Various Combination of Protease Inhibitors, Oseltamivir, Favipiravir, and Hydroxychloroquine
Dose being tested for COVID-19?	500mg, 1-2 times/day, 2 weeks

Countries where Clinical Trials are being/been done	China, US, Korea
Key Data from Clinical Trials	Randomized, controlled, open-label trial with 199 patients. Key Results: • Treatment with lopinavir–ritonavir was not associated with a difference from SOC in the time to clinical improvement (hazard ratio for clinical improvement, 1.24; 95% confidence interval [CI], 0.90 to 1.72). • Mortality at 28 days was similar in the lopinavir–ritonavir group and the standard-care group (19.2% vs. 25.0%; difference, −5.8 percentage points; 95% CI, −17.3 to 5.7). • The percentages of patients with detectable viral RNA at various time points were similar. • In a modified intention-to-treat analysis, lopinavir–ritonavir led to a median time to clinical improvement that was shorter by 1 day than that observed with standard care (hazard ratio, 1.39; 95% CI, 1.00 to 1.91). • Gastrointestinal adverse events were more common in the lopinavir–ritonavir group, but serious adverse events were more common in the standard-care group. • Lopinavir–ritonavir treatment was stopped early in 13 patients (13.8%) because of adverse events. https://www.nejm.org/doi/full/10.1056/NEJMoa2001282
TRL Level for COVID19	TRL > 7 (Ph II/ Ph III Clinical Trials)
IP Status	**Pending applications** • WO2019224779 **Title:** Lopinavir And Ritonavir For The Treatment Of Cervix Disorders **Assignee**: Douglas Pharmaceuticals Limited **Prioirty date**: 24/05/2018 **Status**: Time limit to enter in India will expire on: 24/12/2020 **Approved and Active applications** NA **Expired or Lapsed or abandoned application** • 6733/DELNP/2007 **Title:** A solid pharmaceutical dosage formulation **Assignee:** Abbott Lab **Priority date:** 23/03/2005 **Status:** Abandoned (U/S 21(1)) • 351/MUMNP/2009 **Title:** Antiretroviral Solid Oral Composition **Assignee:** Cipla Ltd **Priority date**: 10/08/2010 **Status**: Abandoned U/s 21 (1) • 496/MUM/2008 **Title:** Novel Process For Manufacture Of Lopinavir & Ritonavir Tablets **Assignee:** Macleods Pharmaceuticals Limited **Priority date**: 10/08/2010 **Status**: Application has been ceased

	• 665/CHE/2011 **Title:** Amorphous Form Of Lopinavir And Ritonavir Mixture **Assignee:** Hetero Research Foundation **Priority date**: 07/03/2011 **Status**: Abandoned • 2828/CHE/2011 **Title:** Amorphous Mixture Of Lopinavir And Ritonavir Co-Precipitated On Copovidone **Assignee:** Hetero Research Foundation **Filing date:** 18/08/2011 **Status:** Abandoned section 9(1) • 2627/MUM/2011 **Title:** Solid Antiretroviral Composition For Oral Delivery **Assignee:** Vavia Pradeep Ratilal **Filing date:** 16/09/2011 **Status:** Abandoned section 21(1) • 3410/DEL/2011 **Title:** A process for the preparation of solid dispersion of lopinavir and ritonavir **Assignee:** Ranbaxy Laboratories Limited **Filing date:** 28/11/2011 **Status:** Abandoned 9(1) • IN/PCT/2001/01312/MUM **Title:** Improved Pharmaceutical Formulations **Assignee:** Abbott Laboratories **Priority date:** 04/06/1999 **Status:** Abandoned section U/S 21(1) • 339/MUMNP/2006 **Title:** Solid Pharmaceutical Dosage Form **Assignee:** Abbott Laboratories **Priority date:** 28/03/2003 **Status:** Rejected by controller on 30/12/2010 • 726/MUMNP/2009 (divisional) **Title:** Solid Pharmaceutical Dosage Form **Assignee:** Abbott Laboratories **Priority date:** 28/03/2003 **Status:** Abandoned section U/S 21(1) • 2474/DELNP/2009 (divisional) **Title:** Solid Pharmaceutical Dosage Form **Assignee:** Abbott Laboratories **Priority date:** 28/03/2003

	Request for examination	**Status:** Application rejected • 1269/MUM/2006 **Title:** An Antiretroviral Composition Of Lopinavir And Ritonavir **Assignee:** Cipla Ltd **Priority date:** 28/03/2003 **Status:** No data and status available online on Indian Patent office website. • 201741046596 **Title:** Capsule Compositions Comprising Lopinavir And Ritonavir **Assignee:** Hetero Research Foundation **Filing date:** 26/12/2017 **Status:** Request for examination not yet filed • 513/MUMNP/2014 **Title:** Compositions Of Lopinavir And Ritonavir **Assignee:** The University Of Liverpool **Priority date:** 09/09/2011 **Status:** Under Examination
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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