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: Darunavir

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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 Darunavir

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Darunavir
Brand Name	Prezista (Darunavir + Ritonavir)
Category/ Type	Antiretroviral
Drug Bank ID/Link	DB01264 https://www.drugbank.ca/drugs/DB01264
Mode of Action	Protease inhibitor. Darunavir prevents HIV replication through binding to the enzyme HIV-1 protease, inhibiting its dimerization and catalytic activity. In particular, it inhibits the cleavage of HIV encoded Gag-Pol proteins.
Therapeutic Target	3CLpro
Is action Host or Virus directed?	Virus
Currently Approved for which Indication(s)	HIV infection (Approved only to be used along with other retrovirals)
Approved Dose	75, 150, 600, 800-mg tablets, 100-mg/mL oral suspension
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	LD50 information for Darunavir is not readily available in the literature. One-time doses of up to 3,200 mg of Darunavir in an oral solution and up to 1,600 mg of the tablet formulation of Darunavir with ritonavir have been given volunteers without significant symptoms.
Adverse events/Side effects reported at the current approved dose	Diarrhea, nausea, rash, headache, abdominal pain and vomiting
Reported Drug-Drug Interactions	Must be co-administered with ritonavir (PREZISTA/ritonavir) and with other antiretroviral agents Contraindicated (28) Serious - Use Alternative (98) Monitor Closely (283) Minor (43) *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021976s021lbl.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 (Generic Versions)
Indian Manufacturer(s)	Granules India, Aspen Biopharma Labs, Aurobindo Pharma, Cadila Healthcare, Cipla, Hangzhou Longshine Bio-Tech, Hetero Drugs, Laurus Labs, Mylan, Lupin, MSN Laboratories
International Manufacturer(s)	Janssen Pharmaceutica, Belgium; Mylan, Nanjing Clasien Pharmaceutical & Chemical
Price of the Drug in India	Rs. 4500/- for 60 tablets
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	Molecular docking and simulation studies show binding for Darunavir to SARS-CoV-2 (3CLpro).
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	1. Results from a molecular docking study shows high binding affinity for Darunavir with SARS-CoV-2 (3CLpro): -10.24 kJ/mol (binding energy) https://chemrxiv.org/articles/Insight_Derived_from_Molecular_Docking_and_Molecular_Dynamics_Simulations_into_the_Binding_Interactions_Between_HIV-1_Protease_Inhibitors_and_SARS-CoV-2_3CLpro/11932995/1 2. Results from a computational docking study identifies Darunavir as a high affinity candidate for SARS-CoV-2 https://www.preprints.org/manuscript/202003.0125/v1 3. In-vitro antiviral activity of DRV against SARS-CoV-2 was assessed. DRV showed no activity against SARS-CoV-2 at clinically relevant concentrations (EC50 >100μM). https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus 4. As outlined in a statement by the manufacturer Janssen, an initial report of Darunavir activity against SARS-CoV-2 in a laboratory dish involved a dose far higher than is achieved in the body. The company also reports that the drug does not bind well to SARS-CoV-2 protease. https://www.janssen.com/lack-evidence-support-use-darunavir-based-treatments-sars-cov-2
Status of Clinical Trials	3 trials ongoing
Trial Details	See table below

Trial ID/Link	Type of Trial	No. of patients	Drug Combination/Dose/ Stage of Disease	Primary and Secondary Measures	Has data from the trial been published? (Yes/No)
NCT04303299	Prospective, Open label, Randomized	80	Group 1: Oseltamivir + Chloroquine: Oseltamivir Dose: 300mg per day plus Hydroxychloroquine 800 mg per day Stage- Mild COVID-19 Group 2: Darunavir + Ritonavir + Oseltamivir Dose: 400 mg every 8 hours Ritonavir 200 mg (or 2.5 mg/kg) per day plus plus Oseltamivir 300mg (or 4-6 mg/kg) per day plus	Primary: SARS-CoV-2 eradication time. Secondary: Number of patient with Death, patient with Recovery adjusted by initial severity in each arm, days with ventilator dependent adjusted by initial severity in each arm, patient developed Acute Respiratory Distress Syndrome After treatment	No

			Hydroxychloroquine 400mg per day Stage - Mild COVID19 Group 3: Lopinavir + Ritonavir + Oseltamivir Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day Stage - Mild COVID-19 Group 4: Lopinavir and Ritonavir Oseltamivir moderate to severe COVID19 Lopinavir 800 mg (or 10 mg/kg) per day and Ritonavir 200 mg (or 2.5 mg/kg) per day plus Oseltamivir 300 mg (or 4-6 mg /kg) per day Stage - Moderate to critically ill		
NCT04252274	Randomized, Open label	30	Darunavir and Cobicistat	Primary: virological clearance rate of throat swabs, sputum, or lower respiratory tract secretions at day 7	No

Key Data from Clinical Trials	No published data available. Results from a single center, open label, randomized, and controlled trial conducted at Shanghai Public Health Clinical Center (SPHCC) of Darunavir and Cobistat (DRV/c) in treating laboratory-confirmed 30 COVID-19 patients showed that DRV/c was not effective. https://www.jnj.com/lack-of-evidence-to-support-darunavir-based-hiv-treatments-for-coronavirus
TRL Level for COVID19	TRL > 7 (Ph III Trials)
IP Status	Status/ Molecule **Darunavir** Pending applications 1875/MUMNP/2012 Title: Darunavir Polymorph And Process For Preparation Thereof Assignee: Cipla Limited Priority date: 05/01/2010 Publication date:04/07/2014 Status: Hearing notice issued on 02/02/2020 201917019679 Title: A simplified procedure for the preparation of Darunavir Assignee: Janssen Sciences Ireland Unlimited Company Priority date: 17/11/2016 Publication date: 09/08/2019 199/CHE/2012 Title: An Improved Process For Preparing Darunavir Assignee: Aurobindo Pharma Ltd Priority date: 18/01/2012 Publication date:29/11/2013 Status: Response to office action 04/02/2020 1875/MUMNP/2012 Title: Darunavir Polymorph And Process For Preparation Thereof Assignee: Cipla Ltd Priority date: 05/01/2010 Publication date: 04/07/2014 Status: Hearing notice 24/01/2020

	Expired or Lapsed 3598/DELNP/2004

	application or status not known	Title: Pseudopolymorphic Forms Of A HIV Protease Inhibitor Assignee: Tibotec Pharmaceuticals Ltd. Priority date: 16/05/2002 Publication date: 04/01/2008 Status: No update on Indian patent site 4069/CHENP/2012 Title: Polymorphs Of Darunavir Assignee: Hetero Research Foundation Priority date: 16/12/2009 Status: No update on Indian patent site 7790/DELNP/2010 Title: Polymorphs Of Darunavir Assignee: Mapi Pharma HK Limited Priority date: 16/09/2009 Publication date:24/02/2012 Status: Abandoned section 21(1) 2226/DELNP/2011 Title: Process For The Preparation Of Darunavir And Darunavir Intermediates Assignee: Mapi Pharma Hk Limited Priority date: 01/07/2010 Publication date: 31/08/2016 Status: No update on Indian patent site 2538/MUM/2007 Title: Anti-Retroviral Combination Assignee: Cipla Limited Filing date: 24/12/2007 Publication date: 16/07/2010 Status: No update on Indian patent site 4206/CHE/2011 Title: Novel Crystalline Darunavir And Process For Its Preparation Assignee: Mylan Laboratories Ltd Filing date: 05/12/2011 Publication date:14/06/2013 Status: Abandoned section 21(1) 2314/CHE/2012 Title: Novel Solvates Of Darunavir Assignee: Aurobindo Pharma Ltd Filing date: 11/06/2012 Publication date: 22/03/2013 Status: No update on Indian patent site 2314/CHE/2012 Title: Process For The Preparation Of Darunavir Assignee: Amneal Pharmaceuticals Company Filing date: 05/06/2015 Publication date: 20/04/2018 Status: No update on Indian patent site 1303/KOL/2009 Title: A novel process for preparation of Darunavir Assignee: Lupin Ltd Filing date: 30/10/2009 Publication date: 28/06/2006 Status: No update on Indian patent site 2226/DELNP/2011 Title: Process For The Preparation Of Darunavir And Darunavir Intermediates Assignee: Mapi Pharma Ltd. Priority date: 01/07/2010 Publication date: 31/08/2016 Status: No update on Indian patent site 2548/CHE/2009 Title: Processes For Preparation Of Amorphous Darunavir Assignee: Matrix Laboratories Ltd Filing date: 22/10/2009 Publication date:16/03/2012 Status: Abandoned section 21(1) 114/MUMNP/2014

Title: Darunavir Formulations
Assignee: Janssen R&D
Priority date: 04/07/2011
Publication date:21/11/2014
Status: Abandoned section 21(1)

201641025234
Title: A Novel Process For The Preparation Of Hiv Protease Inhibitor And Intermediates Thereof
Assignee: Granules India Limited
Filing date: 22/07/2016
Publication date: 26/01/2018
Status: No update on Indian patent site

3106/CHE/2009
Title: Novel Crystalline Form Of Darunavir And Process For Its Preparation
Assignee: Matrix Laboratories Ltd
Filing date: 16/12/2009
Publication date: 09/03/2012
Status: No update on Indian patent site

115/MUMNP/2014
Title: Darunavir Combination Formulations
Assignee: Janssen R&D, Gilead Science
Priority date: 07/07/2011
Publication date:21/11/2014
Status: Abandoned section 21(1)

1225/MUM/2011
Title: Improved Process For Preparation Of Carbamic Acid
Assignee: Sandoz
Filing date: 15/04/2011
Publication date: 30/11/2012
Status: No update on Indian patent site

2958/MUM/2014
Title: A Novel Process To Prepare Intermediates Of Hiv-Protease Inhibitors Thereof
Assignee: ZCL Chemicals Ltd.
Filing date: 16/09/2014
Publication date: 03/10/2014
Status: Abandoned section 21(1)

1994/MUM/2012
Title: Pharmaceutical Composition Of Darunavir
Assignee: Cipla Ltd
Filing date: 10/07/2012
Publication date: 07/02/2014
Status: No update on Indian patent site

1224/MUM/2011
Title: Improved Process For Preparation Of Carbamic Acid
Assignee: Sandoz
Filing date: 15/04/2011
Publication date: 30/11/2012
Status: No update on Indian patent site

82/DEL/2012
Title: A New Process For The Synthesis Of HIV Protease Inhibitors
Assignee: Council Of Scientific & Industrial Research
Filing date: 10/01/2012
Publication date: 01/05/2015
Status: Abandoned section 21(1)

1226/MUM/2011
Title: Improved Process For Preparation Of Carbamic Acid, N-[(1s, 2r)-3-[[(4-Aminophenyl) Sulfonyl] (2-Methylpropyl) Amino]-2-Hydroxy-1-(Phenylmethyl) Propyl]-, (3r, 3as, 6ar)-Hexahydrofuro [2, 3-B] Furan-3-Yl Ester And Novel Intermediate Use In The Preparation Thereof
Assignee: Sandoz
Filing date: 15/04/2011
Publication date: 30/11/2012
Status: No update on Indian patent site

1227/MUM/2011

Title: Improved Process For Preparation Of Carbamic Acid, N-[(1s, 2r)-3-[[(4-Aminophenyl) Sulfonyl](2-Methylpropyl) Amino]-2-Hydroxy-1-(Phenylmethyl) Propyl]-, (3r, 3as, 6ar)-Hexahydrofuro [2, 3-B] Furan-3-Yl Ester And Novel Intermediate Use In The Preparation Thereof
Assignee: Sandoz
Filing date: 15/04/2011
Publication date: 30/11/2012
Status: No update on Indian patent site

3027/MUM/2014
Title: Crystalline Form Of Darunavir And Process For Preparing Thereof
Assignee: Cadila Healthcare Ltd
Filing date: 22/09/2014
Publication date: 01/04/2016
Status: No update on Indian patent site

1647/DELNP/2004
Title: Combination of cytochome p450 dependent protease inhibitors
Assignee: Tibotec Pharmaceuticals Ltd.
Priority Date: 12/12/2002
Publication Date: 30/11/2007
Legal Status: Patent application withdrawn on 14/05/2013

2221/DELNP/2008 (Divisional PCT national phase application of parent application 1647/DELNP/2008)
Title: Combination of cytochome p450 dependent protease inhibitors
Assignee: Tibotec Pharmaceuticals
Priority Date: 12/12/2001
Publication Date: 25/04/2008
Legal Status: Application appears to be abandoned

5301/DELNP/2006
Title: Methods for the preparation of (3R,3AS, 6AR) hexahydro-furo [2,3-B] furan-3-ol
Assignee: Tibotec Pharmaceuticals Ltd
Priority Date: 31/03/2004
Publication Date: 03/08/2007
Legal Status: Patent application has been refused u/s 25 (1)

2122/DELNP/2006
Title: Process For The Preparation Of (3r, 3as, 6ar) Hexahydrofuro [2,3-B] Furan-3-Yl (1s,2r)-3-[[(4- Aminophenyl) Sulfonyl] (Isobutyl) Amino] -Benzyl-2- Hydroxypropylcarbamate
Assignee: Janssen Sciences Ireland UC
Priority Date: 23/12/2003
Publication Date: 13/07/2007
Status: Patent application has been refused u/s 15

5324/DELNP/2009
Title: Modulators of pharmacokinetic properties of therapeutics
Patent Applicant: Gilead Sciences, Inc
Priority Date: 23/02/2007
Publication Date: 23/04/2010
Status: Patent application appears to be abandoned for not submitting reply to examination report on 15/04/2017 u/s 21(1)

7100/DELNP/2014
Title: Combination therapy comprising tenofovir alafenamide hemifumarate and cobicistat for use in the treatment of viral infections
Assignee: Gilead Sciences Inc.
Priority Date: 03/02/2012
Publication Date: 31/08/2016
Legal Status: Application deemed to be abandoned u/s 21(1) on 21/09/2019

201641026995
Title: A high drug loaded tablet composition for treating HIV
Assignee: Hetero Research Foundation
Filing Date: 08/08/2016
Publication Date: 09/02/2018
Status: Application deemed to be withdrawn

201641026996

	Title: A multi-class anti-retroviral composition Assignee: Hetero Research Foundation Filing Date: 08/08/2016 Publication Date: 09/02/2018 Status: Patent application appears to be withdrawn 201641026997 Title: Anti-retroviral compositions Assignee: Hetero Research Foundation Filing Date: 08/08/2016 Publication Date: 09/02/2018 Status: Patent application withdrawn
`Other Key References	None

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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