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: Tofacitinib

Ref: TFORD/MB/021	**Date:** 18 June 2020
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 Tofacitinib

Information About the Candidate for Approved Indication(s)

Common Name of Drug	Tofacitinib
Brand Name	Xeljanz
Category/ Type	Immunomodulator
Drug Bank ID/Link	DB08895 (DB08183) https://www.drugbank.ca/drugs/DB08895
Mode of Action	Tofacitinib works by inhibiting the JAK-STAT signaling pathway, hence disrupting the activation of downstream signaling molecules and proinflammatory mediators. https://www.drugbank.ca/drugs/DB08895
Therapeutic Target	Tyrosine-protein kinase JAK1, Tyrosine-protein kinase JAK2, Tyrosine-protein kinase JAK3, Non-receptor tyrosine-protein kinase TYK2 https://www.drugbank.ca/drugs/DB08895
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	Rheumatoid Arthritis, Psoriatic Arthritis, Ulcerative Colitis
Approved Dose	• Rheumatoid Arthritis- 5 mg twice daily/11 mg once daily • Psoriatic Arthritis- 5 mg twice daily/11 mg once daily • Ulcerative Colitis-10 mg twice daily for at least 8 weeks; then 5 or 10 mg twice daily. Discontinue after 16 weeks of 10 mg twice daily, if adequate therapeutic benefit is not achieved https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	5 mg and 10 mg https://arthritis-research.biomedcentral.com/articles/10.1186/s13075-019-1866-2

Adverse events/Side effects reported at the current approved dose	Nasopharyngitis, elevated cholesterol levels, headache, upper respiratory tract infection, increased blood creatine phosphokinase, rash, diarrhea, and herpes zoster. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf
Reported Drug-Drug Interactions	• Strong CP3A4 Inhibitors (e.g., ketoconazole)- Increased exposure to tofacitinib • Moderate CYP3A4 Inhibitors Coadministered with Strong CYP2C19 Inhibitors (e.g., fluconazole)- Increased exposure to tofacitinib • Strong CYP3A4 Inducers (e.g., rifampin)- Decreased exposure to tofacitinib and may result in loss of or reduced clinical response • Immunosuppressive Drugs (e.g., azathioprine, tacrolimus, cyclosporine)- Risk of added immunosuppression https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/203214s018lbl.pdf
Current TRL level of the Drug	TRL-9; Approved Drug
Has the drug been repurposed for any other indication befoe?	No. But has been tested in the following conditions: • Refractory Dermatomyositis (NCT03002649) • Early Diffuse Cutaneous Systemic Sclerosis (NCT03274076) • Depression (NCT04141904) • Active Ankylosing Spondylitis (AS) (NCT03502616) • Prevent Ventilator-induced Diaphragm Dysfunction (NCT03681275) • Down Syndrome (NCT04246372) • Inflammatory Eye Disease (NCT03580343)
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Pfizer
International Manufacturer(s)	**Pfizer** https://www.pharmacompass.com/pharma-services/api-manufacturing-services/shouyuan-chemical https://www.pharmacompass.com/pharma-services/api-manufacturing-services/shandong-haohong-biotechnology-coltd
Cost of the Drug in India	Rs. 23,000 (60 Tablets pack)

Information About the Candidate for Approved Indication(s)

Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	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. Evidence indicate that cytokine storm is observed in COVID-19 patients (as in SARS and MERS patients) and is responsible for the occurrence of ARDS multiorgan failure, and eventually death. Many cytokines implicated in COVID-19-associated CRS signal via the JAK-STAT pathway including IL-2, IL-6, IL-7, IL-10, G-CSF, GM-CSF, and IFN-γ. Since JAK3 is limited to cytokines using the common γ chain family, Tofacitinib can effectively block IL-2, IL-7, and IL-6. https://www.thelancet.com/action/showPdf?pii=S2213-2600%2820%2930216-2 https://www.sciencedirect.com/science/article/pii/S1359610120300927 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7144601/pdf/main.pdf

	https://pubmed.ncbi.nlm.nih.gov/31986264/ https://pubmed.ncbi.nlm.nih.gov/32360286/ https://www.karger.com/Article/FullText/508247
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	Data not available
Status of Clinical Trials	1 Ongoing Trial
Trial Details	See the 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 ?
NCT04332042	Prospective cohort study	50	Tofacitinib Dose: 10mg twice a day administered within 24h from hospital admission for 14 days Stage: Patients With Early Onset SARS-CoV2 Interstitial Pneumonia	Primary: Need of mechanical ventilation [Time Frame: day 14] Secondary: Need of admission in intensive care unit [Time Frame: day 14] Death [Time Frame: day 28] Rate of adverse events [Time Frame: day 28]	No

Key Data from Clinical Trials	Data not available
TRL Level for COVID19	TRL > 7 (Phase II Trial)
Other Key References	• https://pubchem.ncbi.nlm.nih.gov/compound/Tofacitinib#section=ClinicalTrials-gov • https://europepmc.org/article/med/29139090

IP Status

Status/ Molecule	Tofacitinib
Pending applications	737/MUMNP/2011 Title: A method for resolving enantiomers of a compound of the formula (III) Assignee: Pfizer Products Inc Priority date: 31/05/2001 Publication date: 25/01/2013 Status: Under Examination 3684/MUM/2012 Title: Process for preparation of Tofacitinib and intermediates thereof Assignee: Glenmark Generics Limited Filing date: 28/12/2012 Publication date: 04/07/2014 Status: Under Examination 8222/DELNP/2015 Title: Tofacitinib oral sustained release dosage forms Assignee: Pfizer Inc

	Priority date: 16/03/2013 Publication date: 31/08/2016 Status: Under Examination 460/KOLNP/2015 Title: New synthetic route for the preparation of 3 amino piperidine compounds Assignee: Lek Pharmaceuticals Priority date: 25/07/2012 Publication date: 18/12/2015 Status: Under Examination 1996/KOLNP/2015 Title: Preparation of 3 amino piperidine compounds via nitro tetrahydropyridine precursors Assignee: Lek Pharmaceuticals Priority date: 30/11/2012 Publication date: 19/02/2016 Status: Under Examination 201621007953 Title: Resinates of Tofacitinib for taste masking Assignee: Unichem Laboratories Filing date: 08/03/2016 Publication date: 18/10/2019 Status: Awaiting Examination 201621007954 Title: Resinates of Tofacitinib for taste masking Assignee: Unichem Laboratories Filing date: 08/03/2016 Publication date: 17/11/2017 Status: Awaiting Examination 201844023522 Title: Improved process for the preparation of chiral 3-amino-piperidins, useful intermediates for the preparation of Tofacitinib Assignee: Fabbrica Italiana Sintetici S.P.A. Priority date: 29/06/2017 Publication date: 04/01/2019 Status: Under Examination
Approved and Active applications	241773 Title: Pyrrolo[2,3-D] pyrimidine compounds Assignee: Pfizer Products Inc. Filing date: 23/11/2000 Grant Date: 24/07/2010 Expected expiry date: 23/11/2020 218212 Title: Crystalline 3-{(3R,4R)-4-Methyl-3-[Methyl-[7H-Pyrrolo[2,3- D]Pyrimidin-4-Yl)-Amino]-Piperidin-L-Yl}-3-oxo-propinitrile mono citrate salt and its method of preparation Assignee: Pfizer Products Inc. Priority date: 06/12/2001 Grant date: 23/05/2008 Expected expiry date: 25/11/2022 328338 Title: Novel Tofacitinib addition salts and process for the preparation thereof Assignee: Phalanx Labs Pvt Limited Filing date: 31/12/2015 Grant date: 27/12/2019 Expected expiry date: 31/12/2035
Expired or Lapsed application or examination request not filed	7857/DELNP/2013 Title: Crystalline and non crystalline forms of Tofacitinib and a pharmaceutical composition comprising Tofacitinib and a penetration enhancer Assignee: Pfizer Inc Priority date: 08/04/2011 Publication date: 19/12/2014 Status: Application is abandoned 4330/CHE/2013 Title: Tofacitinib Citrate Process And Polymorphs Assignee: Dr. Reddys Laboratories Limited Filing date: 24/09/2013 Publication date: 28/08/2015

	Status: Application has been withdrawn 991/MUMNP/2003 Title: Chiral Salt Resolution Assignee: Pfizer Products Inc Priority date: 31/05/2001 Publication date: 16/03/2007 Status: Refused 8419/CHENP/2014 Title: Anti Tofacitinib antibodies and uses thereof for drug monitoring Assignee: Pfizer Inc Priority date: 28/06/2012 Publication date: 01/07/2016 Status: Application has been abandoned 5946/DELNP/2015 Title: Process For The Preparation Of Tofacitinib And Intermediates Thereof Assignee: Ranbaxy Lab Ltd Priority date: 17/12/2012 Publication date: 19/02/2016 Status: Application has been abandoned 2842/MUM/2015 Title: Tofacitinib orally disintegrating tablets Assignee: Unichem Laboratories Filing date: 27/07/2015 Publication date: 07/04/2017 Status: Application has been withdrawn 201617044915 Title: Oral pharmaceutical composition of Tofacitinib Assignee: Sun Pharmaceuticals Priority date: 23/06/2014 Publication date: 21/04/2017 Status: Application has been withdrawn

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
Editor: Dr Priya Nagaraj; Contributors: Dr Priya Nagaraj, Dr Vidula Walimbe, Dr Smita Kale, Dr Kirtee Wani, Dr Tejas Shah, Dr Mugdha Lele, Mr Navnath Kadam, Dr Manisha Premnath, Dr Premnath V; Information also contributed by Dr Gopakumar Nair, GNAS and GnanLex.

About Advisory Group
The Nerve Center at TFORD-COVID19 has constituted an inter-disciplinary Advisory Group. This Advisory Group reviews the information compiled by the Nerve Center, provides suggestions on data, information sources, organization of data etc. while also providing inputs to refine the analysis and create a structured information base to support decision-making. The Advisory Group also provides expert input and opinions on certain selected points where experience-based inputs are needed. The members of the Advisory Group for each Discussion Paper are listed at https://nclinnovations.org/covid19/teams/ .

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