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: Ruxolitinib

Ref: TFORD/MB/013	**Date:** 12 April 2020
About this document: *This document summarizes information available on drug candidates for COVID19. One Molecule Brief document covers one candidate at a time.*	
Circulation restrictions: *Non-confidential. Open Access. If you use this information in any other document or communication, please credit is as "Molecule Brief: Ruxolitinib, Task Force on Repurposing of Drugs for COVID19, India, April 2020".*	

1. Summary Information on Ruxolitinib

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Ruxolitinib
Brand Name	Jakafi
Category/ Type	Antiinflammatory, Immunomodulatory
Drug Bank ID/Link	DB08877 https://www.drugbank.ca/drugs/DB08877
Mode of Action	Janus-associated kinase inhibitor. Ruxolitinib is an inhibitor of JAK 1/2 which is responsable for multiple cellular signals including the proinflammatory IL-6. Ruxolitinib works as and immunomodulator decreasing the cytotoxic T lymphocytes and increasing the Treg cells.
Therapeutic Target	JAK1/2
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	Myelofibrosis, Polycythemia Vera, Acute Graft Versus Host Disease
Approved Dose	20 mg orally twice daily
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	≤20 mg twice daily
Adverse events/Side effects reported at the current approved dose	Anemia, Thrombocytopenia, Neutropenia, Infections and Edema
Reported Drug-Drug Interactions	• Fluconazole: Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily except in patients with acute GVHD. • Strong CYP3A4 inhibitors. • Strong CYP3A4 inducers. *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202192s017lbl.pdf
Current TRL level of the Drug	TRL 9; approved drug
Has the drug been repurposed	No

for any other indication before?	
Is the Drug being sold in India?	Yes (Generic version)
Indian Manufacturer(s)	MSN Laboratories
International Manufacturer(s)	Incyte, Novartis, Chongqing Huapont Pharmaceutical
Price of the Drug in India	49,000/- for 60 tablets
Information about the candidate for COVID19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	COVID-19 infections can result in a type of severe immune overreaction called cytokine storm leading to life threatening respiratory complications. It is speculated that anti-inflammatory/immune-modulatory drugs like Ruxolitinib can be effective under these circumstances. A news article states that Incyte, Novartis are planning a Phase 3 Trial for Ruxolitinib in" certain types" of COVID-19 patients. https://www.drugtopics.com/clinical-news/incyte-novartis-plan-phase-3-trial-ruxolitinib-covid-19
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	A Lancet study using computational methods identified JAK inhibitors as potential therapeutics for COVID-19. Based on the analysis, authors say" Our analysis of the closely related JAK inhibitors Ruxolitinib and Fedratinib illustrates that the predicted unbound plasma exposure required to inhibit the enzymes needed for clathrin-mediated endocytosis greatly exceeds the currently tolerated exposures used therapeutically. These drugs are, therefore, unlikely to reduce viral infectivity at tolerated doses, although they might reduce the host inflammatory response through JAK inhibition." https://www.thelancet.com/action/showPdf?pii=S1473-3099%2820%2930132-8
Status of Clinical Trials	0 completed + 5 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)
NCT04334044	Open Label	20	No combination Dose: 10mg BID Stage: Since the beginning of dyspnea or increment of work of breathing with pneumonia changes in chest CT-scan	Primary: Recovery of Pneumonia Secondary: Response of C-reactive protein, Ferritin, D-dimer; Rate of ICU admission, mechanical ventilation, toxicity; Overall Survival	No
NCT04338958	Non-randomized open phase II trial	200	No combination Dose: 2 x 10mg Ruxolitinib with defined response adapted dose escalation up to 2 x 20mg for a duration of 7 days Stage: Data not available	Primary: overall response rate in reversal of hyperinflammation Secondary: efficacy of ruxolitinib + standard-of-care	No
NCT04331665	A Single Arm Open-label	64	No combination Dose: 10 mg, twice a day, for 14 days,	Primary: Proportion of patients with COVID-19 pneumonia who become critically ill	No

			followed by 5 mg, twice a day, for 2 days and 5 mg, once daily, for 1 day. Stage: Data not available	Secondary: All cause mortality rate, Average duration of hospital stay, Number of occurrence of secondary infections	
NCT04337359 (Novartis)	Expanded Access study, Managed Access Program	Data not available	No combination Dose: Data not available Stage: Detailed inclusion/exclusion criteria on trial site	Data not available	No
ChiCTR2000029580	Prospective, single blind, randomized controlled clinical trial	Data not available	Ruxolitinib+ Mesenchymal Stem Cells Dose: Data not available Stage: Data not available	Data not available	No

Key Data from Clinical Trials	Data not available
TRL Level for COVID19	TRL>7 (Ph III trial)
IP Status	**Status/ Molecule** **Ruxolitinib** Pending applications 5153/DELNP/2015 Title: Sustained- Release Dosage Forms Of Ruxolitinib Assignee: Incyte Corporation Priority Date: 15/11/2012 Publication date: 01/01/2016 Status: Reply to FER: 31/10/2019 201741043524 Title: Improved Process For The Preparation Of (R)-3-(4-(7h-Pyrrolo[2,3d]Pyrimidin-4-Yl)-1h-Pyrazol-1-Yl)-3-Cyclopentylpropanenitrile Phosphate Assignee: MSN Laboratories Private Limited Filing Date: 05/12/2017 Publication Date: 07/06/2019 201641026603 Title: Enzymatic process for the preparation of Ruxolitinib and its intermediates Assignee: Dr. Reddy's Laboratories Limited, Chirotech Technology Ltd. Filing Date: 04/08/2016 Publication date: 09/02/2018 201617001982 Title: PIM Kinase Inhibitor Combinations Assignee: Novartis Ag Priority Date: 08/08/2013 Publication Date: 12/08/2016 5639/CHE/2015 Title: Improved Process For The Preparation Of (R)-3-(4-(7h-Pyrrolo[2,3-D]Pyrimidin-4-Yl)-1h-Pyrazol-1-Yl)-3-Cyclopentylpropanenitrile Phosphate Assignee: MSN laboratories Pvt Ltd Filing Date: 25/10/2015 Publication Date: 28/04/2017 3623/CHE/2015 Title: Preparation Of Ruxolitinib And Its Intermediates Assignee: Dr. Reddy's Laboratories Limited Filing Date: 15/07/2015 Publication date: 20/01/2017 2369/CHE/2015 (No .pdf on WIPO site) Title: Process For The Preparation Of Amorphous (R)-3-(4-(7h-Pyrrolo[2,3-D]Pyrimidin-4-Yl)-1h-Pyrazol-1-Yl)-3

	Expired or Lapsed application Not applicable
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
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.

Disclaimer
This Molecule Brief is a compilation of information available openly with no opinions or judgments or recommendations. This document is meant to compile high-quality information that can form the basis for informed discussion and decision-making. It is not meant to reflect the Government's position or that of any specific organization or individual. This information should also not be interpreted as guidance for clinical case management.