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: Ribavirin+IFN-β

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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 Ribavirin+IFN-β

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Ribavirin (Co-administered with Interferon-beta)
Brand Name	Tribavirin, Copegus, Rebetol, Ribasphere
Category/ Type	Antiviral – nucleoside analog
Drug Bank ID/Link	DB00811 https://www.drugbank.ca/drugs/DB00811
Mode of Action	Inosine-5'-monophosphate dehydrogenase 1 inhibitor. Ribavirin is a prodrug that is metabolized into nucleoside analogs that blocks viral RNA synthesis and viral mRNA capping. Ribavirin is a guanosine analog that interferes with the replication of RNA and DNA viruses. However, the anti-viral activity of ribavirin is not limited to interfering with polymerases; that is, the structure of ribavirin also interferes with RNA capping that relies on natural guanosine to prevent RNA degradation. Moreover, to further promote the destabilization of viral RNA, ribavirin inhibits natural guanosine generation by directly inhibiting inosine monophosphate dehydrogenase, in a pathway that is vital for the production of the guanine precursor to guanosine.
Therapeutic Target	RdRp RNA-dependent RNA polymerase, PLpro inhibitor
Is action Host or Virus directed?	Virus & Host (Immunomodulatory)
Currently Approved for which Indication(s)	HCV infection
Approved Dose	200, 400, 600 mg tablets, 6g/vial inhalation, 40mg/mL oral solution. For HCV, 200- 1200 mg 800 mg/d PO divided q12h x48 weeks; Co-administered with PEG-Interferon-alpha-2a (Pegasys)
Route of Administration	Oral & Inhalation
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	Data with doses tested is not available. Pharmacokinetics data reports the terminal half-life of ribavirin following administration of a single oral dose of 1200 mg is about 120 to 170 hours. The average time to reach Cmax was 2 hours after oral administration of 1200 mg ribavirin. The oral bioavailability is 64% following a single oral dose administration of 600mg ribavirin.

Adverse events/Side effects reported at the current approved dose	• Fatigue/asthenia, pyrexia, myalgia, and headache • Ribavirin-induced anemia is a dose-dependent adverse effect where reduced hemoglobin levels can be seen within the first 1-2 weeks in therapy. • Additionally, its adverse effect profile can be significant (anemia), particularly at the dosages for which it has been tested for MERS (~800-3600mg/day).
Reported Drug-Drug Interactions	• Co-administered with PEG-Interferon-alpha-2a (Pegasys) • Contraindicated (1), Serious - Use Alternative (3), Monitor Closely (3), Minor (1). • Nucleoside Reverse Transcriptase Inhibitors (Didanosine, Zidovudine), Drugs metabolized by Cytochrome P450 (Azathioprine) *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021511s023lbl.pdf
Current TRL level of the Drug	TRL9; Approved Drug
Has the drug been repurposed for any other indication before?	Not approved. Tested at a pre-clinical level for Candida strains, Nasopharyngeal Carcinoma
Is the Drug being sold in India?	Yes (Generic Versions)
Indian Manufacturer(s)	Aurobindo Pharma Ltd.
International Manufacturer(s)	Merck Sharp Dohme, Schering, Teva, Zydus Pharms, AMRIUS, Euticals Group SpA, Bidachem S.p.A, Chengdu Brilliant Pharmaceutical Co, China, Erredue S.P.A. IT 24040 Isso, Mayo Clinic, Nortec Quimica, Orgamol Pharma Solutions
Price of the Drug in India	Rs. 1100-1400/- Pack of 140 Tablets
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed) + New RoA (IV and oral- not confirmed)
Rationale for Repurposing for COVID19/MoA?	• Pre-clinical evidence shows that Ribavirin has activity against a range of DNA and RNA viruses; ED50 ranges from 1 to 100 µg/mL when tested in cell lines. • Ribavirin has a well-established history of usage in emergency clinical management plans for Coronaviruses, in which the greatest benefit has been reported with early administration upon presentation with pneumonia and before sepsis or organ system failure. • Note - While the drug has significant activity against coronaviruses in laboratory testing, the dose required to achieve that activity in patients may not have been reached in prior practice. The risk of hematologic toxicity at high doses likely outweighs potential clinical benefit, and therefore Ribavirin was not considered a viable candidate for further investigation by the World Health Organization research and development plan for SARS-CoV-2 given lack of in vitro efficacy, toxicity profile, and poor outcomes. COVID-19 Treatment: A Review of Early and Emerging Options Novel coronavirus treatment with ribavirin: Groundwork for evaluation concerning COVID-19 Shown to be effective for MERS in clinical studies. Trials on MERS are completed with positive results as mentioned below: • Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Results: The therapy was not associated with reduction in 90-day mortality or in faster MERS-CoV RNA clearance. https://www.ncbi.nlm.nih.gov/pubmed/31925415

	• Ribavirin and interferon alfa-2a for severe MERS coronavirus infection: a retrospective cohort study. Results: In patients with severe MERS-CoV infection, ribavirin and interferon alfa-2a therapy is associated with significantly improved survival at 14 days, but not at 28 days. Further assessment in appropriately designed randomised trials is recommended. https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(14)70920-X/fulltext
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	1. Ribavirin inhibits SARS-CoV-2 infection of Vero E6 cells. Ribavirin (EC_{50}) = 109.50 μM (which was over 100 times less potent than remdesivir), half-cytotoxic concentration (CC_{50}) > 400 μM, selectivity index (SI) > 3.65) along with penciclovir and favipiravir were required to reduce the viral infection. https://www.nature.com/articles/s41422-020-0282-0#Fig1 2. 3 Molecular docking studies show Ribiavirin can bind to SARS-CoV-2 RdRps. Results from 1 study - The half-maximal Effective Concentration (EC50) for Ribavirin against COVID-19 is 109.5 μM, can bind to both COVID-19 and SARS HCoV RdRps with good binding energy (−6.5 up to −9.0 kcal/mol), number of H bonds 13; https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7089605/pdf/main.pdf https://www.ncbi.nlm.nih.gov/pubmed/32222463 https://www.sciencedirect.com/science/article/pii/S2211383520302999
Status of Clinical Trials	Ongoing (See details below)
Trial Details	0 Completed + 3 Ongoing

Trial ID/Link	Type of Trial	No. of patients	Combination/Dose/ Stage of Disease	Primary and Secondary Measures	Has data from the trial been published (Yes/No)
NCT04276688	Open-label randomized controlled trial	70	Lopinavir/ ritonavir + Ribavirin + Interferon Beta-1B Dose- 400 mg/2times/daily/14 days Stage - Symptom duration < 10 days	Time to negative NPS, Time to negative saliva, clinical improvement, Hospitalisation, Mortality, Immune reaction, Adverse events, Time to negative all clinical specimens	No
ChiCTR2000030922	Prospective, open-label, controlled, multicenter cohort study	30	Group 1: Long-acting interferon alpha-2a (135ug) + ribavirin Group 2: Abidol + ribavirin Dose, Stage details - Not available	Primary: COVID-19 nucleic acid negative conversion rate, Causal mortality, All-cause mortality. Secondary: Causal mortality, Adverse events (Exacerbation of pneumonia, Impaired liver function, Myelosuppression)	No
ChiCTR2000029387	Parallel randomized	108	Group 1: Ribavirin + Interferon alpha-1b, Arm Group 2: lopinavir / ritonavir + interferon alpha-1b, Group 3: Ribavirin + LPV/r+Interferon alpha-1b Dose, Stage details - Not available	Primary: The time to 2019-nCoV RNA negativity in patients, Secondary: mortality on day 28, The rate of 1. negative 2019-nCoV RNA results at day 14, 2. aggravation, 3. adverse events, 4. discontinuations due to adverse events	No

<table>
<tr><td>Key Data from Clinical Trials</td><td>Data not available</td></tr>
<tr><td>TRL Level for COVID19</td><td>TRL > 6 (Ph II Trials)</td></tr>
<tr><td>IP Status</td><td>
<table>
<tr><th>Status/ Molecule</th><th>Ribavirin + Interferon-beta</th></tr>
<tr><td>Pending applications</td><td>4542/DELNP/2014
Title: Compositions And Methods For Treating Hepatitis C Virus
Assignee: Gilead Pharmasset Llc
Priority Date: 29/11/2011
Publication date: 06/02/2015
Status: Petition under rule 137: 11/02/2020</td></tr>
<tr><td>Approved and Active applications</td><td>NA</td></tr>
<tr><td>Expired or Lapsed application or Status not known</td><td>4287/DELNP/2012
Title: Dosage Regimens For HCV Combination Therapy Comprising Bi201335, Interferon Alpha And Ribavirin
Assignee: Boehringer Ingelhim International Gmbh
Priority Date: 30/10/2009
Publication date: 13/11/2015
Status: Application withdrawn
2489/DELNP/2011
Title: Combination Of HCV Ns3 Protease Inhibitor With Interferon And Ribavirin
Assignee: Boehringer Ingelhim International Gmbh
Priority Date: 17/09/2008
Publication date: 30/03/2012
Status: Abandoned section 21(1)
1286/DELNP/2009
Title: Liposome Treatment Of Viral Infections
Assignee: United Therapeutics Corporation
Priority Date: 02/08/2006
Publication date: 22/05/2009
Status: No update on Indian patent site
3225/KOLNP/2007
Title: Compositions And Methods For Treating Or Preventing Flaviviridae Infections
Assignee: Boehringer Ingelhim International Gmbh
Priority Date: 09/02/2005
Publication date: 21/03/2008
Status: Abandoned section 21(1)
906/KOLNP/2006
Title: Combination Therapy For HCV Infection
Assignee: Vertex Pharmaceuticals Incorporated
Priority Date: 11/10/2003
Publication date: 20/04/2007
Status: Abandoned section 21(1)
855/CHENP/2006
Title: Method Of Treating Viral Infections
Assignee: Horward Smith & associates
Priority Date: 13/08/2003
Publication date: 29/06/2007
Status: No update on Indian patent site
4243/DELNP/2007
Title: Treatment of Hepaatitis C in the Asian Population
Assignee: Laboratories Serono S.A.,
Priority Date: 16/12/2004
Publication date: 31/08/2007
Status: No update on Indian patent site</td></tr>
</table>
</td></tr>
<tr><td>Other Key References</td><td>1. https://www.ncbi.nlm.nih.gov/pubmed/31307986
2. https://cancerres.aacrjournals.org/content/79/13_Supplement/2190
3. Inhibition of novel b coronavirus replication by a combination of interferon-a2b and ribavirin.</td></tr>
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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.

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