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: Nitazoxanide

Ref: TFORD/MB/026	**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.*	
Circulation restrictions: *Non-confidential. Open Access. If you use this information in any other document or communication, please credit is as "Molecule Brief: Nitazoxanide, Task Force on Repurposing of Drugs for COVID19, India, June 2020".*	

1. Summary Information on Nitazoxanide

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Nitazoxanide
Brand Name	Alinia
Category/ Type	Anti-parasitic and Anti-viral
Drug Bank ID/Link	DB00507 https://www.drugbank.ca/drugs/DB00507
Mode of Action	• Anti-parasitic: Disruption of the energy metabolism by inhibition of the pyruvate: ferredoxin/flavodoxin oxidoreductase (PFOR) cycle. Nitazoxanide also induces lesions in cell membranes and depolarizes the mitochondrial membrane while inhibiting quinone oxidoreductase NQO1, nitroreductase-1 and protein disulphide isomerase enzymes. It also inhibits glutathione-S-transferase (a major detoxifying enzyme) and modulates the Avr-14 gene, encoding for the alpha-type subunit of glutamate-gated chloride ion channel present in nematodes. • Anti-bacterial: It inhibits pyruvate dehydrogenase in E Coli, disrupts the membrane potential and pH homeostasis in the Mycobacterium tuberculosis, suppresses the chaperone/usher (CU) pathway of the gram-negative bacteria, and stimulates host macrophage autophagy in tuberculosis patients. • Anti-viral: Suppresses viral replication by inhibiting the maturation of the viral hemagglutinin and the viral transcription factor immediate early 2 (IE2) as well as by activating the eukaryotic translation initiation factor 2α (an antiviral intracellular protein) • Anti-cancer: Inhibits tumor cell progression by altering drug detoxification (glutathione-S-transferase P1), unfolded protein response, autophagy, anti-cytokines activity, and c-Myc inhibition. https://www.drugbank.ca/drugs/DB00507
Therapeutic Target	Pyruvate-flavodoxin oxidoreductase https://www.drugbank.ca/drugs/DB00507
Is action Host or Virus directed?	Virus
Currently	Treatment of Diarrhea caused by *Giardia lamblia* or *Cryptosporidium*

Approved for which Indication(s)	*parvum*
Approved Dose	500 mg twice daily with food for 3 days
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	500 mg every 12 hour for 3 days
Adverse events/Side effects reported at the current approved dose	Asthenia, fever, pain, allergic reaction, pelvic pain, back pain, chills, chills and fever, flu syndrome and others https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021818lbl.pdf
Reported Drug-Drug Interactions	44 moderate drug interactions *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021818lbl.pdf
Current TRL level of the Drug	TRL-9; Approved drug
Has the drug been repurposed for any other indication before?	Tested as an investigational therapy for Influenza https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4584294/
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Cubit, Piramal, Ascent Corporation, Unichem, Alembic, Glenmark, Lupin, Mankind Pharma
International Manufacturer(s)	Romark Pharmaceuticals
Price of the Drug in India	Rs. 45/- /(500mg tablet)
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	Anti-viral activity: • Nitazoxanide has shown anti-viral activity against SARS, MERS, Dengue Virus Type 2, Japanese Encephalitis Virus, and Yellow Fever Virus in-vitro. https://www.ncbi.nlm.nih.gov/pubmed/25108173 https://www.sciencedirect.com/science/article/pii/S1876034116300181 • Clinical Study: A Phase II 2b/III, randomized, placebo-controlled trial using Nitazoxanide on Uncomplicated Influenza patients showed significant viral suppression and reduction in illness duration by 1 day. NCT01227421 https://pubmed.ncbi.nlm.nih.gov/24852376/ Anti-inflammatory activity: • Nitazoxanide reduces plasma IL-6 levels by 90% as compared to controls in an in-vivo mouse model for inflammation. https://www.sciencedirect.com/science/article/pii/S1567576912000689 https://www.sciencedirect.com/science/article/pii/S1876034116300181#bib0085
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	An in-vitro study shows Nitazoxanide, inhibits SARS-CoV-2 infection of VeroE6 cells at low-micromolar concentrations (EC_{50} = 2.12 µM; CC_{50} > 35.53 µM; SI > 16.76)

	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7054408/
Status of Clinical Trials	10 ongoing trials
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?
NCT04341493	Randomized	86	Nitazoxanide + HCQ Other arms - HCQ Dose: HCQ - 400 mg PO every 12 hours for two days and then 200 mg PO every 12 hours for four days Nitazoxanide - 500 mg PO every 6 hours for six days Stage: Data not available	Primary: Mechanical ventilation requirement Secondary: Data not available	No
NCT04360356	Double blind randomized controlled parallel study	100	Ivermectin + Nitazoxanide Dose: Nitazoxanide 500 mg twice daily orally with meal for 6 days + Ivermectin 200 mcg/kg once orally Stage: Newly diagnosed COVID-19 patients	Primary: Number of Patients with COVID-19-negative PCR Secondary: Number of patients with improved respiratory rate, number of patients with improved PaO2 number of patients with normalized Serum IL6, number of patients with normalized Serum TNFα, number of patients with normalized Serum iron, number of patients with normalized Serum ferritin, number of patients with normalized International normalized ratio "INR" for prothrombin time, number of patients with normalized complete blood count "CBC", mortality rate among treated patients	No
NCT04361318	Double blind randomized controlled parallel study	100	HCQ + Nitazoxanide Dose: 200 mg of HCQ orally three times daily for 10 days + 500 mg Nitazoxanide orally twice daily for 6 days Stage: Newly diagnosed COVID-19 patients	Primary: Number of patients with COVID-19-negative PCR Secondary: Number of patients with improved respiratory rate, Number of patients with improved PaO2, Number of patients with normalized Serum IL6, Number of patients with normalized Serum TNFα, Number of patients with normalized Serum iron, Number of patients with normalized Serum ferritin, Number of patients with normalized International normalized	No

				ratio "INR" for prothrombin time, Number of patients with normalized complete blood count "CBC", Mortality rate among treated patients	
NCT04351347	Randomized, Open label	60	Nitazoxanide Other Arms – Chloroquine Ivermectin Dose: Data not available Stage: Data not available	Primary: Number of patients with virological cure Secondary: Data not available	No
NCT04348409	Multicentre, Parallel, Randomized, Double-blind	50	Nitazoxanide Dose:600 mg BID for 7 days Stage: Moderate Disease	Primary: Viral load Secondary: Evolution of acute respiratory syndrome, Change in Clinical Condition, Hospital discharge, Rate of mortality within 21-days, Need of mechanical ventilation	No
NCT04359680 (Prophylaxis)	Randomized, Double-Blind, Placebo Controlled Trial	800	Nitazoxanide Dose: Two 300 mg tablets orally twice daily for 6 weeks. Stage: Pre and Post exposure, Healthcare workers	Primary outcome measures: The proportion of subjects with symptomatic laboratory-confirmed COVID-19 identified after start of treatment and before the end of the 6-week treatment period. The proportion of subjects with symptomatic laboratory-confirmed VRI identified after the start of treatment and before the end of the 6-week treatment period. Secondary outcome measures: not mentioned	No
NCT04343248 (Prophylaxis)	Randomized, Double-Blind, Placebo Controlled, Trial	600	Nitazoxanide Dose: Two 300 mg tablets orally twice daily for 6 weeks Stage: Pre and Post exposure, Elderly Residents of Long-Term Care Facilities	Primary: Symptomatic laboratory-confirmed COVID-19, symptomatic laboratory-confirmed VRI Secondary: not mentioned	No
NCT04345419	Randomized	120	Nitazoxanide Other Arms – Chloroquine Azithromycin, Favipiravir, Ivermectin Dose: Data not available Stage: Data not available	Primary: Number of patients with decreased viral load Secondary: Data not available	No
NCT04392427	Randomized, Sequential Assignment	100	Nitazoxanide+ Ribavirin + Ivermectin + Zn Supplement	Primary: Negative test result for COVID-19 Secondary: Not	No

			Dose: Nitazoxanide, Ivermectin and Ribavirin 200 mg or 400 mg for 7 days Stage: Data not available	mentioned	
NCT04382846	Randomized, open label	80	1. Nitazoxanide + Azithromycin 2. Nitazoxanide + Ivermectin 3. Nitazoxanide + Ivermectin + Azithromycin Dose: Data not available Stage: Data not available	Primary: Number of patients with virological cure Secondary: Data not available	No

Key Data from Clinical Trials	Data not available
TRL Level for COVID19	TRL>7; (Phase III/IV Trials)
Other Key References	None

IP Status

Status/ Molecule	Nitazoxanide
Pending applications	201721009758 Title: Therapeutic agent for phosphodiesterase inhibition and its related disorders Assignee: Novalead Pharma Inc. Filing date: 23/03/2017 Publication date: 12/07/2019 Status: Pending 201821006534 Title: Process for the preparation of Nitazoxanide Assignee: Amneal Pharmaceuticals Company GmbH Filing date: 21/02/2018 Publication date: 23/08/2019 Status: Pending 201841040410 (No link on WIPO site) Title: Improved process for the preparation of 2-acetyloxy-N-(5-nitro-2-thiazolyl) benzamide (Nitazoxanide) Assignee: Biophore India Pharmaceuticals Pvt. Ltd. Filing date: 26/10/2018 Publication date: 01/05/2020 Status: Pending
Approved and Active applications	264839 Title: Viral Hepatitis Treatment Assignee: Romark Laboratories, L.C. Priority date: 09/01/2006 Grant date: 23/01/2015 Expected expiry date: 09/01/2027 298233 Title: Controlled release pharmaceutical formulations of Nitazoxanide Assignee: Romark Laboratories L.C. Priority Date: 13/02/2009 Grant date: 28/06/2018 Expected expiry date: 12/02/2030
Expired or Lapsed application or	783/CHE/2010 Title: Pharmaceutical composition comprising Nitazoxanide

examination request not filed	Filing Date: 24/03/2010 Publication Date: 06/07/2012 Status: Abandoned under section 21(1) Assignee: RA Chem Pharma Limited

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/ .

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.