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Task Force on Repurposing of Drugs (TFORD) for COVID19
S&T Core Group on COVID19 constituted by PSA to GoI

Molecule Brief: Dexamethazone

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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 Dexamethazone

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Dexamethasone
Brand Name	Decadron
Category/ Type	Immunomodulator
Drug Bank ID/Link	DB01234 (APRD00674) https://www.drugbank.ca/drugs/DB01234
Mode of Action	Dexamethasone is a synthetic adrenal corticosteroid with potent anti-inflammatory properties. In addition to binding to specific nuclear steroid receptors, dexamethasone also interferes with NF-kB activation and apoptotic pathways. Glucocorticoids/Adrenal corticosterioids are known to inhibit neutrophil apoptosis and de-margination, phospholipase A2 which decreases the formation of arachidonic acid derivatives, NF-Kappa B and other inflammatory transcription factors. They promote anti-inflammatory genes like interleukin-10. Downstream effects lasts over hours to days. Lower doses of corticosteroids provide an anti-inflammatory effect, while higher doses are immunosuppressive. https://www.drugbank.ca/drugs/DB01234 https://pubchem.ncbi.nlm.nih.gov/compound/Dexamethasone
Therapeutic Target	• Glucocorticoid Receptor (Agonist) Other reported targets: • Nuclear receptor subfamily 0 group B member 1 (Stimulator) • Annexin A (Agonist) • Nitric Oxide Synthase, inducible (Negative modulator) • Nuclear receptor subfamily 1 group 1 member 2 (Agonist) https://www.drugbank.ca/drugs/DB01234
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	• Allergic states • Dermatologic diseases • Endocrine disorders • Gastrointestinal diseases • Hematologic disorders

	• Respiratory diseases
Approved Dose	For oral administration: initial dosage varies from 0.75 to 9 mg a day depending on the disease being treated
Route of Administration	Oral, Injection
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	Safety dose: varies as per indication
Adverse events/Side effects reported at the current approved dose	Allergic reactions, Cardiovascular, Dermatologic, Endocrine, Fluid and electrolyte disturbances, Gastrointestinal, Musculoskeletal, Metabolic, Neurological/Psychiatric, Ophthalmic
Reported Drug-Drug Interactions	A total of 632 drugs are known to interact with dexamethasone. • 100 major drug interactions • 482 moderate drug interactions • 50 minor 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/2004/11664slr062_decadron_lbl.pdf
Current TRL level of the Drug	TRL 9; Approved drug
Has the drug been repurposed for any other indication before?	No
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Daksh Pharmaceuticals, Wockhardt, GLS Pharma, Cadila, Zydus Novartis, Wyeth
International Manufacturer(s)	Merck Sharp & Dohme
Price of the Drug in India	Rs. 2.73 (0.5mg for 10 tablets)
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	Pre-clinical evidence for other Coronaviruses: 1. In-vivo studies in a SARS-CoV rat model for pulmonary inflammation shows Dexamethasone effectively alleviates the pulmonary inflammatory reaction. https://www.ncbi.nlm.nih.gov/pubmed/16409721 2. In-vivo studies in Porcine respiratory coronavirus (PRCV)-infected conventional pigs shows 1-2 doses of Dexamethasone given in the acute phase of the infection effectively alleviates early pro-inflammatory responses in respiratory CoV infections. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2293053/ Clinical Evidence: 1. A retrospective comparison of 17 patients treated with early pulsed-dose methylprednisolone with 55 patients treated with low-dose hydrocortisone or methylprednisolone conducted in Hong Kong, suggested that treatment utilizing early pulsed dosing decreases supplemental oxygen requirement and the need for future pulsed-dose rescue therapy, while also improving radiologic outcome and fever resolution. However, no significant difference in overall mortality or intensive-care unit admission was observed. https://www.atsjournals.org/doi/full/10.1164/rccm.200306-766OC

	2. In a trial with 16 non ICU cases of SARS-CoV, plasma SARS-Cov RNA concentrations was significantly higher in patients who received initial hydrocortisone treatment (*n* = 9), as compared to those who received placebo (*n* = 7). However, there was no difference in the median time for SARS-CoV to become undetectable in plasma - 12 days (11–20 days) for treated versus 8 days (8–15 days) placebo. https://www.sciencedirect.com/science/article/pii/S1386653204001957 3. Corticosteroids have been tested in clinical trials of patients with viral pneumonia and ARDS. Based on results of these trials, The Surviving Sepsis Clinical Management Guidelines for COVID-19 makes the following recommendations: • In adults with COVID-19 and refractory shock, recommend using low-dose corticosteroid therapy ("shock-reversal"), over no corticosteroid therapy • In mechanically ventilated adults with COVID-19 and ARDS, recommend using systemic corticosteroids, over not using corticosteroids Note – The document specifies that this is a weak recommendation due to low quality evidence. https://www.esicm.org/wp-content/uploads/2020/03/SSC-COVID19-GUIDELINES.pdf 4. Dexamethasone (low dose) is one of the Treatment Arms in UK's Recovery Trial https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001113-21/GB
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	Data not available
Status of Clinical Trials	12 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?
NCT04327401	Open-label, Randomized, Controlled Trial	290	Dexamethasone Dose: 20mg IV 1x/day for 5 days, followed by 10mg IV 1xd for 5 days + standard treatment Stage: Data not available	Primary: Ventilator-free days Secondary: Evaluation of the clinical status, All-cause mortality, Mechanical ventilation duration, Sequential Organ Failure Assessment (SOFA) Score	No
NCT04325061	Multicenter, randomized, controlled, open-label trial involving	200	Dexamethasone Dose: 20 mg/iv/daily/from Day 1 of randomization during 5 days, followed by 10 mg/iv/daily from Day 6 to 10 of randomization Stage: Mechanically ventilated adult patients with ARDS caused by confirmed	Primary: 60-day mortality Secondary: Ventilator-free days	No

			COVID-19 infection		
NCT04347980	Multicentre, Randomized Controlled Trial	122	Dexamethasone + Hydroxychloroquine (HCQ/DXM) Dose: Standardized ventilatory management + administration of HCQ + DXM at a rate of 20 mg intravenously for 15 min once a day for 5 days (D1 to D5) then at a rate of 10 mg per day from D6 to D10. If the patient is extubated before the 10th day, he will receive his last dose of DXM before. Stage: Data not available	Primary : Day-28 mortality Secondary: Ventilator-free days, Intensive Care Unit mortality, Day-60 mortality, Nosocomial pneumonia, Bacteremia	No
NCT04344730	Randomized	550	Dexamethasone, Dexamethasone + Standard Oxygen, Dexamethasone + Continuous positive airway pressure, Dexamethasone + High-Flow Nasal Oxygen Dose: Dexamethasone 20 mg / 5 ml, solution for injection in ampoule of 5mL. 10 days in all groups Stage: Patients admitted in ICU for severe COVID-19 infection, Non-mechanically ventilated patients	Primary: The time-to-death from all causes, The time to need for mechanical ventilation (MV) Secondary: Viiral load in the respiratory tract, Number of patient with at least one episode of healthcare-associated infections, Number of days alive without mechanical ventilation, Measure of SOFA score, Number of days alive without renal replacement therapy, Lengths of ICU-stay, Lengths of hospital-stay, Number of patients with severe hypoxemia, Number of patients with cardiac arrest within 1 hour after intubation	No
NCT04360876	Single-center, Phase 2a, pragmatic, randomized, double-blinded, placebo-controlled	90	Dexamethasone Dose: Intravenous 20mg daily for 5 days followed by 10mg daily for 5 days Stage: Patients with the hyper-inflammatory sub-phenotype of ARDS due to COVID-19 pneumonia	Primary: Ventilator Free Days (VFD) at Day 28. Secondary: Clinical Status at day 14 as measured by World Health Organization (WHO) 7-point ordinal scale Clinical Status at day 28 as measured by WHO 7-point ordinal scale In-Hospital Mortality at day 28 In-Hospital Mortality at day 90 Time to Mortality to day 28 ICU-free days to day 28 Hospital Length of Stay among survivors to day 90 Severity of ARDS to day 10 Days to resolution of fever Change in C-Reactive Protein (CRP) level from baseline to day 10 Vasopressor-free days to day	No

				28 Renal replacement-free days to day 28, Duration of mechanical ventilation to day 28 Oxygenation-free days to day 28 Incidence of New Mechanical Ventilation to day 28 Change in sequential organ failure assessment (SOFA) score from baseline to day 10 In-hospital adverse events to day 28, discontinuation of study drug infusion	
NCT04366115	Randomized, Double-Blind, Placebo-Controlled, Phase 1/2 study	126	Dexamethasone sodium phosphate Dose: Single IV infusion at 10 mg/ml in normal saline over 1 hour to patients. Stage: Patients with severe or life-threatening COVID-19 infection	Primary: Dose-Limiting Toxicities, 28 day all-cause mortality will be a primary end point for Phase 1 and 2 Secondary: Data not available	No
NCT04380818	Multi-central Prospective Study: non randomized	106	Corticosteroids (methyl prednisolone / dexamethasone/ prednisone) Other Arms - Corticosteroids + HCQ + Ritonavir-lopinavir + Tocilizumab + Azithromycin, Heparin) Dose: Data not available Stage: Data not available	Primary outcome measures: Efficacy of low-dose pulmonary irradiation assessed by change in PAFI O2 by 20% Secondary outcome measures: Number of participants with treatment-related adverse events as assessed by CTCAE v5.0, change of the radiological image, overall mortality, measure of pro-inflammatory interleukins, measure of transforming growth factor (TGF-b), measure of tumor necrosis factor alpha (TNF-a), Determining over expression of pro-inflammatory selection, Determining cell adhesion molecules (CAMs) , Measure of marker of oxidative stress PON-1	No
NCT04381936 (Recovery)	Randomized, open label	12000	Dexamethasone Other Arms - Hydroxychloroquine, Lopinavir-Ritonavir, Azithromycin, Tocilizumab Dose: Liquid or tablets or intravenous: 6 mg once daily for 10 days. Stage: Data not available	Primary: All-cause mortality Secondary: Duration of hospital stay, need for (and duration of) ventilation, need for renal replacement	Yes (Interim/News/Preprint)
2020-001113-21 (Recov	Randomized Evaluation of COVID-19 Therapy	1000	Dexamethasone Other Arms - Hydroxychloroquine, Lopinavir-Ritonavir,	Primary: Effect of study treatments on death within 28 days of randomization (with subsidiary analyses of cause of	No

ery)			Azithromycin, Tocilizumab Dose: 6 mg : Intravenous, oral use Stage: Data not available	death). Secondary objectives: Effects of study treatments on duration of hospital stay and on need for (and duration of) ventilation or renal replacement therapy.	
2020-001333-13	Randomized controlled trial	Data not available	Dexamethasone + Hydroxychloroquine Other Arms – Hydroxychloroquine Dose: Data not available Stage: Patients with ARDS caused by COVID-19	Primary: Mortality on D28 Secondary: Ventilator-free days, Mortality in intensive care unit, Mortality on D60, Number of episodes of pneumonia and bacteremia	No
2020-001457-43	Randomized	Data not available	Dexamethasone + oxygen support Dose: Intravenous: 20 mg/ 5mL Stage: ICU patients with Covid-19 pneumonia	Primary: Time-to-death from all causes within the first 60 days after randomization and the time to need for mechanical ventilation (MV) Secondary: The cycle threshold for SARS-CoV-2 PCR at baseline, day 7 and day 10 in samples of the same origin Proportion of patients with at least one episode of any healthcare-associated infection between randomization and D28 Number of days alive without mechanical ventilation at day 28 Number of days alive without renal replacement therapy at day 28	No
IRCT20120225009124N4	Randomized	105	Intervention 1: Dexamethasone + IV-IG + Interferon beta Intervention 2: Standard treatment for COVID19 + dexamethasone + IV-IG + Interferon beta Dose: Data not available Stage: Patients with severe COVID-19 disease. Intervention 1: At time of admission Intervention 2: 48 hours after admission	Primary: Improvement in SpO2 (increasing in level of SpO2 to levels higher than 90%): After finishing the intervention Secondary: Duration of stay in hospital, intubation, mortality	No

Key Data from Clinical Trials	• A Meta-analysis study using clinical data of SARS and MERS and COVID-19 patients administered with cortiocosteroids shows use of corticosteroids in critically ill patients with COVID-19 does not improve or worsen mortality https://www.medrxiv.org/content/10.1101/2020.04.17.20069773v1

	• Interim data from Recovery Trial (Pre-print): 2104 patients randomly allocated to receive dexamethasone were compared with 4321 patients concurrently allocated to usual care. Overall, 454 (21.6%) patients allocated dexamethasone and 1065 (24.6%) patients allocated usual care died within 28 days (age-adjusted rate ratio [RR] 0.83; 95% confidence interval [CI] 0.74 to 0.92; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.0% vs. 40.7%, RR 0.65 [95% CI 0.51 to 0.82]; p<0.001), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (21.5% vs. 25.0%, RR 0.80 [95% CI 0.70 to 0.92]; p=0.002), but did not reduce mortality in patients not receiving respiratory support at randomization (17.0% vs. 13.2%, RR 1.22 [95% CI 0.93 to 1.61]; p=0.14). Conclusions: In patients hospitalized with COVID-19, dexamethasone reduced 28-day mortality among those receiving invasive mechanical ventilation or oxygen at randomization, but not among patients not receiving respiratory support. https://www.medrxiv.org/content/10.1101/2020.06.22.20137273v1
TRL Level for COVID-19	TRL>7 (Phase III/IV trials)
Other Key References	None

IP Status

Status/ Molecule	**Dexamethasone**
Pending applications	2171/MUMNP/2013 Title: Dose guides for injection syringe Assignee: Icon Bioscience Inc. Priority date:25/04/2011 Publication date:24/10/2014 Status: Pending. Reply to FER: 11/05/2020 2318/CHE/2015 Title: Dexamethasone unidirectional aqueous bi-layered buccal muco adheshive patch with sodium saccharine as release enhancer; a non-invasive treatment approach of oral sub-mucous fibrosis Inventor: Dr. P. K. Lakshmi Filing date: 07/05/2015 Publication date: 11/11/2016 Status: Pending. Request for examination filed on: 06/05/2019 3324/MUMNP/2015 Title: Use of sustained release dexamethasone in post cataract surgery inflammation Assignee: Icon Bioscience Inc. Priority date: 24/05/2013 Publication date :08/07/2016 Status: Pending. Reply to FER on: 26/04/2019
Approved and Active applications	224993 (Orange Book Listed -US6899717) Title: An apparatus for implanting an ocular implant at a location in a patient's eye Assignee: Allergan, Inc. Priority Date: 18/09/2002 Grant Date:31/10/2008 Expected expiry date: 18/09/2023 326873 Title: A medicinal fusidic acid cream made using sodium fusidate and incorporating a biopolymer, and a corticosteroid - Dexamethasone Acetate, and a process to make it Inventor: Sulur, Subramaniam Vanangamudi Filing date:22/02/2010 Grant date:13/12/2019 Expected expiry date: 22/02/2030
Expired or Lapsed application or	1107/KOLNP/2005 Title: Biodegradable ocular implant Assignee: Allergan, Inc.,

examination request not filed	Priority date: 09/01/2003 Publication date:13/07/2007 Status: Patent application refused 5168/DELNP/2007 Title: Virus recovery medium, use thereof and viral diagnostic kit including same Inventor: Alexander Robert Priority date: 14/01/2005 Publication date:17/08/2007 Status: No update on Indian patent site 1035/KOLNP/2010 Title: Dexamethasone formulations in a biodegradable material Assignee: Warsaw Orthopaedic, Inc., Medtronic, Inc Priority date: 18/04/2008 Publication date:09/07/2010 Status: Abandoned under section U/S 21(1) 3574/MUM/2010 Title: Immune booster preparation Inventor: Raviraj Sadhuprasadji Pande Filing date:30/12/2010 Publication date:18/02/2011 Status: No update on Indian patent site 3234/DEL/2011 Title: A novel muco adhesive dexamethasone bio – nano-suspension for targeting to brain via ear Inventor: N.V. Satheesh Madhav Filing date: 14/11/2011 Published date: 27/09/2013 Status: No update on Indian patent site 321/MUM/2013 Title: A Dexamethasone prefilled syringe Inventor: Agrawal, Pawan, Agarwal, Zameer Filing Date: 04/02/2013 Publication date:12/12/2014 Status: No update on Indian patent site

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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