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: Enoxaparin

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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 Enoxaparin

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Enoxaparin
Brand Name	Lovenox
Category/ Type	Anti-coagulant
Drug Bank ID/Link	DB01225 (APRD00068) https://www.drugbank.ca/drugs/DB01225
Mode of Action	Enoxaparin, a Low Molecular Weight Heparin (LMWH), binds to and accelerates the activity of antithrombin III. By activating antithrombin III, enoxaparin preferentially potentiates the inhibition of coagulation factors Xa and IIa. Factor Xa catalyzes the conversion of prothrombin to thrombin, so enoxaparin's inhibition of this process results in decreased thrombin and ultimately the prevention of fibrin clot formation https://www.drugbank.ca/drugs/DB01225
Therapeutic Target	Antithrombin III, Coagulation factor X
Is action Host or Virus directed?	Host
Currently Approved for which Indication(s)	Deep vein Thrombosis (Prophylaxis and Treatment), Pulmonary embolism, Myocardial infarction, Acute Coronary syndromes
Approved Dose	Deep vein thrombosis with or without pulmonary embolism - 1mg/kg every 12 hours
Route of Administration	Subcutaneous and Intravenous (Bolus) injection
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	Data not available
Adverse events/Side effects reported at the current approved dose	Bleeding, Anemia, Thrombocytopenia, Elevation of serum aminotransferase, diarrhea, nausea, ecchymosis, fever, edema, peripheral edema, dyspnea, confusion, and injection site pain https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020164s085lbl.pdf
Reported Drug-Drug	Risk of hemorrhage due to anticoagulants,

Interactions	platelet inhibitors including acetylsalicylic acid, salicylates, NSAIDs (including ketorolac tromethamine), dipyridamole, or sulfinpyrazone https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020164s085lbl.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/2009/020164s085lbl.pdf http://products.sanofi.us/Lovenox/Lovenox.pdf
Current TRL level of the Drug	TRL-9; Approved drug
Has the drug been repurposed for any other indication before?	Data not available
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	INTAS, Ranbaxy, Lupin, Abbott- India, Cipla, Biocon Ltd, Torrent Pharma, Micro Labs, Sanofi- Aventis
International Manufacturer(s)	Sanofi- Aventis
Price of the Drug in India	Rs.500/40mg Injection
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	• Severe COVID-19 is reported to be associated with coagulopathy, markedly elevated D-dimer associated with poor prognosis. The effect of SARS-CoV2 infection on pulmonary coagulation and fibrinolysis is considered to be mediated by various proinflammatory cytokines. https://www.sciencedirect.com/science/article/pii/S0140673620302117?via%3Dihub https://www.sciencedirect.com/science/article/pii/S0140673620301835?via%3Dihub https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1736644 https://journals.lww.com/ccmjournal/Abstract/2006/03000/Pulmonary_coagulopathy_as_a_new_target_in.42.aspx • The WHO and Indian MoHFW Clinical Management Guidelines recommend the use of Heparin to reduce incidence of venous thromboembolism and its treatment. https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected https://www.mohfw.gov.in/pdf/GuidelinesonClinicalManagementofCOVID1912020.pdf
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	Data not available
Status of Clinical Trials	6 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?
NCT04345848	Randomized, Open label clinical trial	200	Participants will be treated with prophylactic doses of subcutaneous low-molecular-weight heparin (enoxaparin) or unfractionated heparin, from admission until the	1. Primary: Risk of thrombosis and all- cause mortality 2. Secondary: Arterial thrombosis, Venous thromboembolism, Disseminated intravascular coagulation, All-cause mortality, Sepsis induced coagulopathy	No

			end of hospital stay or clinical recovery. If hospitalized in the intensive care unit, they will receive an augmented thromboprophylaxis regimen as standard of care		
NCT04359277	Open labelled randomized trial	1000	Enoxaparin Higher Dose Non-intubated patients with a Cr Clearance of > 30, 1mg/kg q12 SQ hours for weight 50-150kg, 0.75mg/kg q12 SQ hours for weight >150kg or BMI >40 AntiXA testing will be done after fourth injection only for participants with BMI >40 or weight > 150 kg as per institutional policy	1. Primary: All- cause mortality, Incidence of Cardiac arrest, Deep vein thrombosis, Pulmonary embolism, Myocardial infarction, Hemodynamic shock, Arterial thromboembolism 2. Secondary: Renal failure, Hypercoagulability, Incidence of major bleeding	No
NCT04377997	Randomized, Open-Label	300	Enoxaparin Dose: Data not available Stage: COVID-19 Patients With an Elevated D-Dimer	Primary: Number of patients with the composite efficacy endpoint of death, cardiac arrest, symptomatic deep venous thrombosis, pulmonary embolism, arterial thromboembolism, myocardial infarction, or hemodynamic shock. [Time Frame: 12 weeks]	No
NCT04366960	Randomized, Open-Label	2712	Enoxaparin Dose: 40 mg o.d or 40 mg b.i.d. Stage: Hospitalized COVID-19 Patients	Primary: Incidence of venous thromboembolism detected by imaging [Time Frame: 30 days] Secondary: In hospital major complications [Time Frame: 30 days] Number of deep venous thrombosis events [Time Frame: 30 days] Sequential organ failure assessment [Time Frame: 30 days] Maximum sequential organ failure assessment (SOFA) score comparison C-reactive protein [Time Frame: 30 days] Interleukin-6 [Time Frame: 30 days] D-dimer [Time Frame: 30 days] hs-troponin levels [Time Frame: 30 days] Acute Respiratory Distress Syndrome [Time Frame: 30 days] Hospital stay [Time Frame: 30 days] Right ventricular function	No

				[Time Frame: 30 days] Number of pulmonary embolism events [Time Frame: 30 days]	
NCT04360824	Randomized, open-label	170	Enoxaparin Dose: 40 mg o.d or 40 mg b.i.d. Stage: Hospitalized COVID-19 Patients	Primary: Mortality [Time Frame: 30 Days post intervention] Secondary : Major Bleeding [Time Frame: 30 Days post intervention] Arterial Thrombosis [Time Frame: 30 Days post intervention] Venous Thromboembolism [Time Frame: 30 Days post intervention] ICU admission, intubation/ventilation [Time Frame: 30 Days post intervention] Packed Red Blood Cell Transfusions [Time Frame: 30 Days post intervention] Platelet Transfusions [Time Frame: 30 Days post intervention] Fresh Frozen Plasma Transfusions [Time Frame: 30 Days post intervention] Cryoprecipitate Transfusions [Time Frame: 30 Days post intervention] Prothrombin Complex Concentrate Transfusions [Time Frame: 30 Days post intervention]	No
NCT04354155	Open Label	38	Enoxaparin Dose: Twice-daily low-dose Enoxaparin thromboprophylaxis (starting dose, 0.5 m/gkg subcutaneously q12 hours, adjusted to achieve a 4 hour post-dose anti-factor Xa level of 0.20-0.49 anti-Xa U/mL) Stage: COVID-19 children with symptoms	Primary : Safety of in-hospital thromboprophylaxis [Time Frame: Day 30] Secondary : Median twice-daily enoxaparin dose [Time Frame: 4 hours post initial dose]	No

Key Data from Clinical Trials	No published data from Clinical Trials. Data from 2 Retrospective Studies are detailed below. • Retrospective Study from China, March 2020: 449 patients with severe COVID-19 enrolled into the study, 99 of them received heparin (mainly with low molecular weight heparin) for 7 days or longer. D-dimer, prothrombin time, and age were positively, and platelet count was negatively, correlated with 28-day mortality in multivariate analysis. No difference in 28-day mortality was found between heparin users and nonusers (30.3% vs 29.7%, *P* = .910). But the 28-day mortality of

	heparin users was lower than nonusers in patients with SIC score ≥4 (40.0% vs 64.2%, *P* = .029), or D-dimer >6-fold of upper limit of normal (32.8% vs 52.4%, *P* = .017). Authors conclude - Heparin treatment appears to be associated with better prognosis in severe COVID-19 patients with coagulopathy. https://onlinelibrary.wiley.com/doi/10.1111/jth.14817 • Retrospective Study from China, April 2020: 42 patients with COVID-19 (21 of whom were treated with low molecular weight heparin (LMWH), and 21 without LMWH) that were retrospectively analysed. Changes in the percentage of lymphocytes in the LMWH group before and after LMWH treatment were significantly different from those in the control group (p=0.011, respectively). Changes in the levels of D-dimer and fibrinogen degradation products (FDP) in the LMWH group before and after LMWH treatment were significantly different from those in the control group (p=0.002;p=0.035). In the LMWH group, IL-6 levels were significantly reduced after LMWH treatment (p=0.006). Besides, the changes in IL-6 levels in the LMWH group before and after LMWH treatment were significantly different from those in the control group (p=0.031). Authors conclude - LMWH improves the coagulation dysfunction of COVID-19 patients and exerts anti-inflammatory effects by reducing IL-6 and increasing lymphocyte %. https://www.medrxiv.org/content/10.1101/2020.03.28.20046144v3
TRL Level for COVID19	TRL>7 (Phase III trial)
Other Key References	None

IP Status

Status/ Molecule	Enoxaparin
Pending applications	201741044415 Title: Process for the preparation of low molecular weight heparin Assignee: Biological E. Ltd. Filing date: 11/12/2017 Publication date: 14/06/2019 Status: FER issued on 28/02/2020
Approved and Active applications	Not applicable
Expired or Lapsed application or examination request not filed	1054/CHENP/2008 Title: Methods for performing percutaneous coronary intervention Assignee: Aventis Pharma S.A Priority date: 02/09/2005 Publication date: 05/06/2009 Status: No updates on Indian patent site 312/MUM/2013 Title: Prefilled syringe containing Enoxaparin Inventors: Agrawal, Pawan, Agrawal, Zameer Filing date: 04/02/2013 Publication date: 14/11/2014 Status: No updates on Indian patent site IN/PCT/2002/00684/DEL Title: Novel therapeutic use of Enoxaparin Assignee: Aventis Pharma S.A Priority date: 06/01/2000 Publication date: 02/02/2007 Status: No updates 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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