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: Teicoplanin

Ref: TFORD/MB/018	**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.*	
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1. Summary Information on Teicoplanin

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Teicoplanin
Brand Name	Celplanin VIAL, Ticogem VIAL, Zyplanin VIAL, Zicoplanin VIAL, Trueplan INJ
Category/ Type	Antibiotic
Drug Bank ID/Link	DB06149 https://www.drugbank.ca/drugs/DB06149
Mode of Action	Teicoplanin inhibits peptidoglycan polymerization, resulting in inhibition of bacterial cell wall synthesis and cell death in Gram positive bacteria.
Therapeutic Target	D-Ala-D-Ala moiety of NAM/NAG peptide subunits of peptidoglycan (Note-Target for viral inhibition is reported to be human Cathepsin L)
Host or Virus Directed?	Virus
Currently Approved for which Indication(s)	Indicated for use in serious Gram+ve infections; serious staphylococcal infections in patients sensitive or unresponsive to penicillins and cephalosporins; CAPD (continuous ambulatory peritoneal dialysis) related peritonitis; prophylaxis in orthopaedic surgery at risk of Gram-positive infection.
Approved Dose	Can be given either IV (bolus or 30 minute infusion) or IM. Duration of therapy depends on type and severity of the infection and clinical response of the patient. Adult or elderly patients with normal renal function: Prophylaxis: Single dose of 400mg i.v. at induction of anaesthesia. Moderate infections: Loading dose - Single iv or im injection of 400mg on first day. Maintenance Dose - Single im or iv injection of 200mg daily. Severe infections: Loading dose - Three iv injections of 400mg administered 12 hours apart. Maintenance Dose - Single im or iv injection of 400mg daily. Severe infections and neutropenia patients: 10mg/kg every 12 hours for first 3 doses, thereafter 10mg/kg im or iv as single dose each day. Moderate infections: 10mg/kg every 12 hours for first 3 doses, thereafter 6mg/kg IM or IV as single dose each day.

	Neonates: Loading dose is 16mg/kg followed by a daily dose of 8mg/kg. CAPD: After single iv loading dose of 400mg, if patient is febrile then 20mg/l per bag in 1st week, 20mg/l in alternate bags in 2nd week; 20mg/l in overnight dwell bag only during 3rd week. Adult and elderly patients with renal insufficiency: Dosage reduction is not required until the fourth day of treatment. From the fourth day of treatment, in patients with mild renal insufficiency, creatinine clearance 40-60ml/min, Targocid dose should be halved (initial unit dose every two days or administering half of this dose once a day); in severe renal insufficiency: creatinine clearance less than 40ml/min and in haemodialysed patients, Targocid should be one-third of the normal (initial unit dose every third day or one third of this dose once a day)
Route of Administration	Intravenous injection, Intramuscular injection
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	Teicoplanin does not have dose-related adverse effects in the dose range 3-10 mg/kg. https://doi.org/10.1093/jac/27.suppl_B.69
Adverse events/Side effects reported at the current approved dose	Skin and subcutaneous tissue disorders: *Common:* Rash, erythema, pruritus. *Uncommon:* Red man syndrome (e.g. Flushing of the upper part of the body). Renal and Urinary disorders: *Common:* Blood creatinine increased General disorders and administration site conditions: *Common:* Pain, pyrexia Investigations: *Uncommon:* Transaminases increased (transient abnormality of transaminases), blood alkaline phosphatase increased (transient abnormality of alkaline phosphatase), blood creatinine increased (transient rise of serum creatinine)
Reported Drug-Drug Interactions	The risk or severity of bleeding can be increased when Teicoplanin is combined with (R)-Warfarin, Hydroxycoumarin, Acenocoumarol, Clorindione, Diphenadione *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.ema.europa.eu/en/documents/referral/targocid-article-30-referral-annex-iii_en.pdf
Current TRL level of the Drug	TRL-9 (Approved Drug)
Has the drug been repurposed for any other indication before?	No data reported until 8th April 2020.
Is the Drug being sold in India?	Yes
Indian Manufacturer(s)	Cipla, Lupin, Biocon, Macleods, Biosans Lifecare.
International Manufacturer(s)	Celon Pharma, Aspen Pharmacare, Fada Pharma, CJ Cheil Jedang, Daiko Seiyaku, Fuji Seiyaku, Generics UK.
Price of the Drug in India	Rs. 1400-1700/400mg injection
Information About the Candidate for COVID-19	
Repurposing Claim	New Indication (COVID-19) + New Dose (not confirmed)
Rationale for Repurposing for COVID19/MoA?	1. In-vitro studies show that in Coronaviruses (MERS) Teicoplanin acts on an early stage of the viral life cycle by inhibiting the low-pH cleavage of the viral spike protein by Cathepsin L in the late endosomes, thereby preventing the release of genomic viral RNA and continuation of the virus replication cycle. 2. It has also shown to be efficacious against other viruses like Ebola, Influenza, HIV, Hepatitis C, Flavivirus. https://www.sciencedirect.com/science/article/pii/S0924857920300947#bib0007 3. Studies show that the target sequence that serves as the

	cleavage site for cathepsin L is conserved in SARS-CoV-2 spike protein. https://www.biorxiv.org/content/10.1101/2020.02.05.935387v1
Proposed use as Primary or Adjuvant?	Primary
Pre-Clinical Data available for COVID-19	In-vitro studies show that Teicoplanin blocks SARS-CoV-2 entry in a mammalian cell line .The IC_{50} in vitro was 1.66 µM, which is much lower than the concentration reached in human blood (8.78 µM for a daily dose of 400 mg). https://www.biorxiv.org/content/10.1101/2020.02.05.935387v1
Status of Clinical Trials	No Ongoing Trials
Trial Details	Data not available
Key Data from Clinical Trials	Data not available
TRL Level for COVID19	TRL < 5 (Not completed Phase I)
IP Status	(see table below)

Status/ Molecule	Teicoplanin
Pending applications	201917027117 Title: Glycopeptide Antibiotic Constructs Assignee: The university of Queensland Priority date: 09/12/2016 Publication date: 06/09/2019 201817041113 Title: Stabilized Glycopeptide Antibiotic Formulations Assignee: Xellia Pharmaceuticals aps Priority date: 09/05/2016 Publication date: 01/03/2019 Status: Request for Examination: 25/03/2020
Approved and Active applications	Not available
Expired or Lapsed application	IN263491 Title: A Glycopeptide Antibiotic Composition Comprising Glycosylated (a) and Deglycosylated (b) Forms of one Glycopeptide Antibiotic Assignee: Xellia Pharmaceuticals aps Priority date: 17/09/2003 Grant date: 30/10/2014 Expected expiry: 17/09/2024 Status: Ceased Date Of Cessation:19/09/2016 IN220278 (No .pdf available on WIPO site) Title: Monthly Doses for Treatment of Streptococcus Pneumoniae Infections Assignee: Eli Lilly and Company Priority date: 03/05/1999 Grant date: 21/05/2008 Expected expiry: 19/04/2020 Status: Ceased: 20/04/2009 IN216350 Title: Glycopeptide Antibiotic Derivatives Assignee: Chiron Corporation, K.U. Leuven Research and Development Priority date: 30/08/2002 Grant date: 12/03/2008 Expected expiry: 01/09/2023 Status: Ceased: 01/09/2009 IN259388 Title: A Method for Purification of a Glycopeptide Antibiotic Assignee: Xellia Pharmaceuticals aps Priority date: 27/10/2004 Grant date: 11/03/2014 Expected expiry: 27/10/2025 Status: Ceased: 27/10/2016

	1209/KOLNP/2014 Title: Process of Purification of Teicoplanin Assignee: Lek Pharmaceuticals D.D. Priority date: 11/11/2011 Publication date: 16/10/2015 Status: Abandoned section 21(1) 1208/KOLNP/2014 Title: Process of Purification of Teicoplanin Assignee: Lek Pharmaceuticals D.D. Priority date: 11/11/2011 Publication date: 16/10/2015 Status: Abandoned section 21(1) of the Patent Act 1836/KOLNP/2007 (Divisional to (528/KOLNP/2005)) Title: A Composition Containing Gycopeptide Antibiotic or Derivative Thereof Assignee: Chiron Corporation, K.U. Leuven Research and Development Priority date: 30/08/2002 Publication date: 10/08/2007 Status: Abandoned section 21(1)
Other Key References	1. Potential Treatments for COVID-19; a Narrative Literature Review. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7085862/ 2. Treatment of Covid-19 Infection. A Rationale for Current and Futur Pharmacological Approach. https://www.ecronicon.com/ecprm/pdf/ECPRM-09-00577.pdf

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

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