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: Oseltamivir

Ref: TFORD/MB/010	**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 Oseltamivir

Information About the Candidate for Approved Indication(s)	
Common Name of Drug	Oseltamivir
Brand Name	Tamiflu®
Category/ Type	Antiviral
Drug Bank ID/Link	DB00198 (APRD01148) https://www.drugbank.ca/drugs/DB00198
Mode of Action	Oseltamivir is a reversible competitive inhibitor of influenza neuraminidase. Virion release from infected cells and spread with the respiratory tract are inhibited due to blockade of this enzyme.Oseltamivir activity reduces viral shedding and infectivity. http://www.antimicrobe.org/drugpopup/oseltamivir.htm
Therapeutic Target	Viral neuraminidases of influenza A (including pandemic H1N1) and influenza B
Is action Host or Virus directed?	Virus
Currently Approved for which Indication(s)	• Treatment of acute, uncomplicated influenza in patients 2 weeks of age and older who have been symptomatic for no more than 2 days. • Prophylaxis of influenza in patients 1 year and older.
Approved Dose	• Treatment of influenza : Adults and adolescents (13 years and older) - 75 mg twice daily for 5 days • Prophylaxis of influenza : Adults and adolescents (13 years and older) - 75 mg once daily for at least 10 days
Route of Administration	Oral
Safety Profile of drug (dose range in which it has been tested to be safe in humans)	75 mg once/twice daily for at least 10 days https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf
Adverse events/Side effects reported at the current approved dose	Nausea, diarrhea, insomnia, vomiting, headache and skin rashes https://www.ncbi.nlm.nih.gov/pubmed/16192481
Reported Drug-Drug Interactions	• Entecavir • Influenza virus vaccine, h1n1, live • Influenza virus vaccine, live, trivalent

	• Methotrexate • Pemetrexed • Probenecid • Tafamidis • Warfarin *(Clinicians need to note relevant drug-drug interactions depending on nature of use)*
Link to Datasheet	https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021087s062lbl.pdf https://www.fda.gov/media/76542/download
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)	Cipla, Hetero, Natco API Manufacturers: Lupin, Mylan, Jubilant Generics, Cadila, Matrix http://www.medlineindia.com/antibiotic/oseltamivir.html
International Manufacturer(s)	Roche https://www.gilead.com/news-
Price of the Drug in India	Rs.450- 500 per pack of 10 tablets/capsules
Information about the candidate for COVID19	
Repurposing Claim	For COVID-19 with or without antibiotics, corticosteroids and antiviral drugs
Rationale for Repurposing for COVID19/MoA?	1. Known antiviral activity against influenza and initial report from Huang and colleagues in Wuhan where patients with COVID-19 received oseltamivir in addition to broad spectrum antimicrobials. https://academic.oup.com/ofid/advance-article-pdf/doi/10.1093/ofid/ofaa105/32961870/ofaa105.pdf 2. Clinical trials for Oseltamivir are ongoing for COVID-19 (details below)
Proposed use as Primary or Adjuvant?	Adjuvant
Pre-Clinical Data available for COVID-19	No data to suggest *in vitro* activity of Oseltamivir against SARS CoV-2.Coronaviruses do not utilize neuraminidase for the budding stage of reproduction and therefore no activity is expected. https://www.nebraskamed.com/sites/default/files/documents/covid-19/antiviral-and-pharmacotherapy-information.pdf?date=03242020
Status of Clinical Trials	3 Ongoing Phase III and IV
Trial Details	See details below

Trial ID/Link	Type of Trial	Number of patients	Combination/ Dose/Stage of Disease	Primary and Secondary Measures	Has data from the trial been published (Yes/No)
NCT04261270	Randomized, Open, Controlled Small Sample Clinical Study	60	ASC09F+ Oseltamivir Ritonavir+ Oseltamivir Dose - 75mg/once a day Stage: Data not available	Primary- Rate of comprehensive adverse outcome Secondary- Time of clinical remission, Rate of no fever, Rate of no cough, Rate of no dyspnea, Rate of no need for oxygen inhalation, Rate of undetectable viral RNA, Rate of mechanical ventilation, Rate of ICU admission, Rate and time of CRP,ES,Bio chemical criterion(CK,ALT,Mb) recovery	No
NCT043	Prospective,	80	Group 1:	Primary- SARS-CoV-2 eradication	No

03299	Open Label, Randomized, Multicenter Study		Oseltamivir + Chloroquine, Group 2: Darunavir+ Ritonavir+ Oseltamivir Group 3: Lopinavir+ Ritonavir + Oseltamivir Dose - 300mg (or 4-6 mg/kg) per day – Oseltamivir Stage: Data not available	time [Time Frame: Up to 24 weeks] Eradication of nasopharyngeal SARS-CoV-2 Secondary- Number of patients with Death, Number of patient with Recovery adjusted by initial severity in each arm, Number of day With ventilator dependent adjusted by initial severity in each arm, Number of patient developed Acute Respiratory Distress Syndrome After treatment [Time Frame: Up to 24 weeks] Other Outcome Measures: Number of patient with Acute Respiratory Distress Syndrome Recovery [Time Frame: Up to 24 weeks] Acute Respiratory Distress Syndrome Recovery rate	
NCT04255017	Open, Prospective/Retrospective, Randomized Controlled Cohort Study	400	Group1: Arbidol hydrochloride (0.2g once, 3 times a day,2 weeks) Group 2: Oseltamovir (75mg once, twice a day,2 weeks) Group 3: Lopinavir/ Ritonavir (500mg once, twice a day,2 weeks) Stage: Mild and severe	Primary Outcome Measures : 1. Rate of disease remission [Time Frame: two weeks] A: For mild patients : fever, cough and other symptoms relieved with improved lung CT; B:For severe patients : fever, cough and other symptoms relieved with improved lung CT,SPO2> 93% or PaO2/FiO2>300mmHg (1mmHg=0.133Kpa) 2. Time for lung recovery [Time Frame: two weeks] Compare the average time of lung imaging recovery after 2 weeks of treatment in each group. Secondary Outcome Measures : 1. Rate of no fever [Time Frame: two weeks] 2. Rate of respiratory symptom remission [Time Frame: two weeks] 3. Rate of lung imaging recovery [Time Frame: two weeks] 4. Rate of CRP,ES,Biochemical criterion(CK,ALT,Mb) recovery [Time Frame: two weeks] 5. Rate of undetectable viral RNA [Time Frame: two weeks]	No
ChiCTR2000029592 (Prophylaxis)	Retrospective case-control cohort study	Cohort1- 66 family members Cohort 2- 124 healthcare workers	No combination Dose: 200mg, Tid, 5-10 days Stage: Post exposure prophylaxis	Delay time of PEP after the diagnosis or primary case in family and health care workers cohorts with or without Arbidol	Yes

Key Data from Clinical Trials	A recent publication indicates that, "Oseltamivir was not as successful as Arbidol to reduce the infection risk (Post Exposure Prophylaxis –PEP) of the novel coronavirus in hospital and family settings. Following observations were made– i) 45 family members used Arbidol PEP and 1 became infected

<table>
<tr><td></td><td>ii) 21 family members use Oseltamivir and 12 became infected
iii) 55 health workers used Arbidol PEP and 1 became infected
iv) 68 health workers used Oseltamivir and 7 became infected
Study: ChiCTR2000029592
http://www.chinaxiv.org/user/download.htm?id=30258</td></tr>
<tr><td>TRL Level for COVID19</td><td>TRL-8 (Phase III/IV)</td></tr>
<tr><td>IP Status</td><td>
<table>
<tr><th>Status/ Molecule</th><th>Oseltamivir</th></tr>
<tr><td>Pending applications</td><td>4109/MUM/2014
Title: A Process For Preparation Of Ethy (1r,5r,6r)-5-(1-Ethylpropoxy)-7-Azabicyclo [4,1,0] Hept-3-Ene-3-Carboxylate
Assignee: Sequent Scientific Limited
Filing Date: 22/12/2014
Publication date: 24/06/2016
Status: FER sent on 19/03/2020</td></tr>
<tr><td>Approved and Active applications</td><td>IN314403
Title: New Process For The Synthesis Of Methyl 3-Epi-Shikimate And Oseltamivir
Assignee: National University Corporation Okayama University
Filing Date: 25/10/2011
Grant date: 21/06/2019
Expected expiry date: 25/10/2031
IN303314
Title: Novel Salts Of Ethyl (3r,4s,5r)-4,5-Imino-3-(1-Ethylpropoxy) - 1-Cyclohexene-1- Carboxylate
Assignee: MSN Laboratories Limited,
Filing Date: 19/08/2009
Grant date: 20/11/2018
Expected expiry date: 19/08/2029
IN284534
Title: Pharmaceutical Composition Comprising Oseltamivir Phosphate
Assignee: Chugai Seiyuku Kabushiki Kaisha, F.Hoffmann-La Roche Ag
Priority Date: 20/02/2006
Grant date: 23/06/2017
Expected expiry date: 20/02/2027
IN224636 (No .pdf available on WIPO site)
Title: Process For Preparing a 4,5-diamino shikimic acid
Assignee: F. Hoffmann-la roche ag
Filing Date: 01/12/2000
Grant date: 21/10/2008
Expected expiry date: 01/12/2020
IN286011
Title: Process For The Preparation Of Shikimic Acid Useful For Production Of Avian Flu Drug Tamiflu (Oseltamivir)
Assignee: CSIR
Filing Date: 12/03/2010
Grant date: 02/08/2017
Expected expiry date: 12/03/2030</td></tr>
<tr><td>Expired or Lapsed application or status not known</td><td>IN288276
Title: Nitro Group-Containing Ether Compound And Method For Producing Same
Assignee: National University Corporation Okayama University
Priority Date: 09/06/2009
Grant date: 11/10/2017
Expected expiry date: 08/06/2030
Status: Patent ceased: Renewal discontinued: 08/12/2019
IN209070
Title: Process For Preparing Neuraminidase Inhibitor Ro-64-0796</td></tr>
</table>
</td></tr>
</table>

Assignee: F. Hoffmann-la roche ag
Filing Date: 08/06/2000
Grant date: 20/08/2007
Status: Patent ceased: Renewal discontinued: 10/06/2019
IN209362 (No .pdf available on WIPO site)
Title: A Process For The Preparation Of 4, 5-Diamino Shikimic Acid Derivative Of Formula Assignee: F. Hoffmann-la roche ag
Priority Date: 10/04/2000
Grant date: 27/08/2007
Status: Patent ceased: Renewal discontinued: 09/04/2019
IN209362
Title: Process From Shikimic Acid To Oseltamivir Phosphate
Assignee: F. Hoffmann-la roche ag
Priority Date: 18/09/2007
Grant date: 15/06/2017
Status: Patent ceased: Renewal discontinued: 09/09/2019
IN275216
Title: Process For Producing Oseltamivir Phosphate And Intermediate Compound
Assignee: Tokyo University Of Science Educational Foundation Administrative Organization
Priority Date: 30/05/2008
Grant date: 29/08/2016
Expected expiry date: 28/05/2029
Status: Patent ceased: Renewal discontinued: 28/11/2019
1262/KOL/2014
Title: Oseltamivir Compositions
Assignee: Lupin Atlantis Holdings Sa
Priority Date: 01/12/2014
Publication date: 26/08/2016
Status: No status update on Indian patent site
201611038603
Title: Pharmaceutical Composition Comprising Oseltamivir Phosphate And Process Of Preparation Thereof
Assignee: Jubilant Generics Limited
Filing Date: 11/11/2016
Publication date: 18/05/2018
Status: No status update on Indian patent site
1262/KOL/2014
Title: Oseltamivir Compositions
Assignee: Lupin Atlantis Holdings Sa
Filing Date: 01/12/2014
Publication date: 26/08/2016
Status: No status update on Indian patent site
3788/CHE/2011
Title: Improved Process For The Preparation Of Pure Crystalline Form A Of Oseltamivir Phosphate
Assignee: Mylan Laboratories Ltd
Filing Date: 01/12/2014
Publication date: 03/01/2014
Status: No status update on Indian patent site
2512/CHE/2011
Title: A composition for treating swine-flu and a process for formulating the same
Assignee: JSS college of pharmacy
Filing Date: 27/07/2011
Publication date: 22/03/2013
Status: Abandoned section 21(1)
1861/MUM/2011
Title: Novel Salt Of Oseltamivir

Assignee: Cadila Healthcare Ltd
Filing Date: 2/06/2011
Publication date: 04/01/2013
Status: Abandoned section 21(1)
124/CHE/2011
Title: Improved Process For The Preparation Of Oseltamivir Phosphate And Its Intermediates Thereof
Assignee: Matrix Laboratories Ltd
Filing Date: 14/01/2011
Publication date: 07/02/2014
Status: No status update on Indian patent site
3989/CHENP/2010
Title: Polymorphic Forms Of Oseltamivir Phosphate
Assignee: F.Hoffmann-La Roche Ag
Priority Date: 04/01/2008
Publication date: 17/12/2010
Status: Abandoned section 21(1)
733/DELNP/2009
Title: Isoquinuclidine Derivative And Method For Manufacturing 1-Cyclohexene-1-Carboxylic Acid Derivative By Using The Same
Assignee: The University Of Tokyo
Priority Date: 28/06/2006
Publication date: 20/08/2010
Status: No status update on Indian patent site
3285/CHENP/2008
Title: Epoxide Intermediate In The Tamiflu Synthesis
Assignee: F. Hoffmann-La Roche AG
Priority Date: 28/12/2005
Publication date: 06/03/2009
Status: No status update on Indian patent site
1191/CHENP/2006
Title: Process For Obtaining Pure Oseltamivir
Assignee: Hetero Drugs Ltd
Filing Date: 06/04/2006
Publication date: 17/08/2007
Status: No status update on Indian patent site
1724/CHE/2005
Title: Improved Process Form Oseltmivr Phosphate
Assignee: Hetero Drugs Ltd
Filing Date: 25/11/2005
Publication date: 05/10/2007
Status: No status update on Indian patent site
396/DEL/1996 (No .pdf available on WIPO site)
Title: Carbocyclic Compound
Assignee: Gilead Sciences, Inc.
Priority Date: 27/02/1995
Status: Application Was Rejected Vide Controller's Order Dated 23/03/2009
514/DEL/2007 (Div of 396/DEL/1996) (No .pdf available on WIPO site)
Title: Carbocyclic Compound
Assignee: Gilead Sciences, Inc.
Priority Date: 27/02/1995
Status: Application Refused Vide Order Dated 12/06/2012 By The Controller
1132/DEL/1999 (No .pdf available on WIPO site)
Title: Novel Selective Inhibitors Of Viral Or Bacterial Neuraminidases
Assignee: Gilead Sciences Inc
Priority Date: 27/02/1995
Status: Abandoned Under 21(1)
IN190983 (No .pdf available on WIPO site)
Title: A Process For Preparing Neuraminidase Inhibitors Capsule
Assignee: Gilead Sciences
Priority Date: 17/09/1997

	Grant Date: 12/04/2004 Status: Patent Term Expired:17/09/2018 1525/CHE/2011 Title: Improved Process For The Preparation Of Oseltamivir Phosphate And Its Intermediates Thereof Assignee: Matrix Laboratories Ltd Filing Date: 03/05/2011 Publication date: 21/06/2013 Status: Abandoned Under 21(1)
Other Key References	1.https://pubchem.ncbi.nlm.nih.gov/compound/oseltamivir#section=Metabolite-References 2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4375804/

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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