Lisa McGee's (VaxxChoice) Report on Remdesivir

Remdesivir
https://patentimages.storage.googleapis.com/a0/e3/91/7154d14f054b0d/US20180346504A1.pdf

Chemical compound structure: Remdesivir
https://pubchem.ncbi.nlm.nih.gov/compound/Remdesivir

Summary:
Remdesivir is an antiviral nucleotide analogue used for therapy of severe novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) infection. Remdesivir therapy is given intravenously for 3 to 10 days and is frequently accompanied by transient, reversible mild-to-moderate elevations in serum aminotransferase levels but has been only rarely linked to instances of clinically apparent liver injury, **its hepatic effects being overshadowed by the systemic effects of COVID-19.**

Datasheet: GHS Classification – NIH has removed the information for public access.
https://pubchem.ncbi.nlm.nih.gov/compound/Remdesivir_-_datasheet=LCSS&section=GHS-Classification

Globally Harmonized Systems of Classification and Labelling of Chemicals (GHS)
https://unece.org/sites/default/files/2021-09/GHS_Rev9E_0.pdf

Department of Veterans Affairs Office of Procurement, Acquisition and Logistics National Acquisition Center - Federal Supply Schedule Service
https://www.naspo.org/wp-content/uploads/2020/07/Contract-Announcement-COVID19-Drug-Remdesivir-Added-to- FSS-July-6-2020.pdf

REMDESIVIR - FDA (meta disclaimer)
https://www.biorxiv.org/content/10.1101/2020.01.30.927574v1.full.pdf

Nucleotide Analogues as Inhibitors of Viral Polymerases
https://api.fda.gov/drug/ndc.json?search=product_ndc:"61958-2901"

DESCPRITION Remdesivir is an **investigational** nucleotide analog with broad-spectrum antiviral activity. Remdesivir has demonstrated in vitro and in vivo activity in animal models against the viral pathogens MERS and SARS, which are also coronaviruses and are structurally similar to COVID-19. The limited preclinical data on remdesivir in MERS and SARS indicate that remdesivir may have potential activity against COVID-19
https://www.probes-drugs.org/compound/PD122226

Vendors:
Cayman Chem
*Application of the substance / the mixture For research use only - not for human or veterinary use.
https://cdn.caymanchem.com/cdn/msds/30354m.pdf

Description: Remdesivir is a nucleoside analogue with antiviral activity. It inhibits Middle East respiratory syndrome coronavirus (MERS-CoV)- or severe acute respiratory syndrome coronavirus (SARS-CoV)-infected HAE cultures with EC50 values of 74 nM and 69 nM. It inhibits murine hepatitis virus (MHV) with an EC50 of 30 nM in delayed brain tumor (DBT) cells. It is a delayed chain terminator with in vitro and animal model activity against multiple coronaviruses, and in vitro activity against SARS-CoV-2.

****HAE cultures with EC50 values of 74 nM and 69 nM – Created to study Remdesivir:**
1. Long-Term Modeling of SARS-CoV-2 Infection of *In Vitro* Cultured Polarized Human Airway Epithelium
https://pubmed.ncbi.nlm.nih.gov/33158999/

2. HAE cultures with EC50 values of 74 nM and 69 nM – Created to study Remdesivir:
SARS-CoV-2 infection of airway cells causes intense viral and cell shedding, two spreading mechanisms affected by IL-13
https://www.pnas.org/doi/pdf/10.1073/pna

An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice
https://www.science.org/doi/10.1126/scitranslmed.abb5883

FOR RESEARCH ONLY! - Remdesivir Disclaimer: FOR RESEARCH USE ONLY! Not to be used on humans. Do not take internally. Wear gloves and mask when handling the product! Avoid contact by all modes of exposure.

***PRE COVID 19**
Agostini, M.L., Andres, E.L., Sims, A.C., et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS- 5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio. 9(2) (2018).
https://www.biovision.com/remdesivir-24508.html

Studies re: Viral Polymerase and the Proofreading Exoribonuclease.
1. **Translational shutdown and evasion of the innate immune response by SARS-CoV-2 NSP14 protein**
https://www.pnas.org/doi/10.1073/pnas.2101161118

2. Characterization of the SARS-CoV-2 ExoN (nsp14–nsp10) complex: implications for its role in viral genome stability and inhibitor identification
https://academic.oup.com/nar/article/50/3/1484/6509090?login=false

Linked Proteins: **There are 3 linked proteins – this is the human protein (house mouse and pig are the others)**

O15118 NPC intracellular cholesterol transporter 1 (human) -
Intracellular cholesterol transporter which acts in concert with NPC2 and plays an important role in the egress of cholesterol from the endosomal/lysosomal compartment (PMID: 9211849, PMID: 9927649, PMID: 10821832, PMID: 18772377, PMID: 27238017, PMID: 12554680). May play a role in vesicular trafficking in glia, a process that may be crucial for maintaining the structural and functional integrity of nerve terminals (Probable).

(Microbial infection) Acts as an endosomal entry receptor for ebolavirus.
An NPC intracellular cholesterol transporter 1 that is encoded in the genome of human.

Linked Genes: There are 3 linked proteins - this is the human protein (house mouse and pig are the others)

4864 NPC1 - NPC intracellular cholesterol transporter 1 (human) -
This gene encodes a large protein that resides in the limiting membrane of endosomes and lysosomes and mediates intracellular cholesterol trafficking via binding of cholesterol to its N-terminal domain. This protein transports low-density lipoproteins to late endosomal/lysosomal compartments where they are hydrolyzed and released as free cholesterol. *Defects in this gene cause Niemann-Pick type C disease, a rare autosomal recessive neurodegenerative disorder characterized by over accumulation of cholesterol and glycosphingolipids in late endosomal/lysosomal compartments.[provided by RefSeq, Aug 2009]

The NPC1 gene provides instructions for making a protein that is located within the membrane of compartments in the cell called lysosomes and endosomes, which digest and recycle materials. While the exact function of this protein is unclear, it plays a role in the movement of cholesterol and other types of fats (lipids) within cells and across cell membranes.

DIP-201132E Interactors: Niemann-Pick C1 protein Envelope glycoprotein
Envelope glycoprotein: Envelope glycoprotein (Ebola virus - Mayinga, Zaire, 1976)
https://pubchem.ncbi.nlm.nih.gov/protein/Q05320

Evidence of the two Interactors:
https://dip.doe-mbi.ucla.edu/dip/DIPview.cgi?ID=DIP-201132E

Associated disease: Niemann Pick Disease
https://medlineplus.gov/genetics/condition/niemann-pick-disease/

DISEASE: Niemann-Pick disease type C
https://www.kegg.jp/entry/H00136

Linked Chemicals: There are 61 linked chemicals.
https://pubchem.ncbi.nlm.nih.gov/patent/US-2018346504-A1 - section=Linked-Chemicals

Compound Substances: There are 80 compound substances:
https://pubchem.ncbi.nlm.nih.gov/patent/US-2018346504-A1 - section=PubChem-Substances

*These chemicals and compound substances are all toxic to the system. They are complex, and need to be broken down further, by an expert.

Remdesivir: Dangers - Irritant and Health Hazards:
GHS Hazard Statements
H302 (25%): Harmful if swallowed [Warning Acute toxicity, oral]
H315 (25%): Causes skin irritation [Warning Skin corrosion/irritation]
H319 (25%): Causes serious eye irritation [Warning Serious eye damage/eye irritation]
H335 (25%): May cause respiratory irritation [Warning Specific target organ toxicity, single exposure; Respiratory tract irritation]
H372 (50%): Causes damage to organs through prolonged or repeated exposure [Danger Specific target organ toxicity, repeated exposure]
H373 (50%): Causes damage to organs through prolonged or repeated exposure [Warning Specific target organ toxicity, repeated exposure]

Hepatotoxicity
In human volunteer studies, remdesivir therapy given for 7 to 14 days was associated with minor serum aminotransferase elevations (less than 5 times ULN) but without other evidence of hepatic injury. In controlled trials of remdesivir in patients hospitalized with COVID-19, rates of serum ALT elevations were similar or lower in patients receiving remdesivir than in those on placebo. Nevertheless, in most uncontrolled studies and case series, between 10% and 50% of patients treated with remdesivir developed transient, mild-to-moderate serum ALT and AST elevations within 1 to 5 days of starting therapy without changes in serum bilirubin or alkaline phosphatase levels. Elevations above 5 times ULN were reported in up to 9% of patients in several clinical trials, but the abnormalities resolved with discontinuation and were not associated with clinically apparent injury. With more widespread use of remdesivir for COVID-19, rare instances of marked ALT elevations with jaundice have been reported, but largely in patients who were critically ill with multi-organ failure or sepsis, or who had received other potentially hepatotoxic agents such as intravenous amiodarone presents in up Confounding the issue is that serum aminotransferase elevations are common during symptomatic SARS-CoV-2 infection to 60% of patients and being more frequent in patients with severe disease and in those with the known risk factors for COVID-19 severity such as male sex, older age, higher body mass index and diabetes. ***Thus, serum aminotransferase elevations are common during remdesivir therapy but are generally asymptomatic, fully reversible and not associated with jaundice**. **With more widespread use of this antiviral in patients without severe or critical illness and with longer courses of therapy, features of hepatotoxicity may become more evident.**
Likelihood score: D (possible uncommon cause of clinically apparent liver injury).

***Causes of serum aminotransferase**
Mildly Elevated Liver Transaminase Levels: Causes and Evaluation
https://www.aafp.org/pubs/afp/issues/2017/1201/p709.html

Bilirubin - Bilirubin is a byproduct of broken-down old red blood cells. When red blood cells finish their life cycles in your body, they break down and pass through your bloodstream to your liver for processing.
https://my.clevelandclinic.org/health/diagnostics/17845-bilirubin

Amiodarone - Amiodarone is a benzofuran derivative, anti-arrhythmic drug used commonly in a variety of settings. Most known for its approved indication in life-threatening ventricular arrhythmias, it is also used off-label in the outpatient and inpatient setting for atrial fibrillation. Because of its ability to cause serious toxicity and possibly death, amiodarone use should be reserved for its approved indications, according to prescribing information.

Benzofuran -
Flammable liquid and vapor [Warning Flammable liquids]
Suspected of causing cancer [Warning Carcinogenicity]
Causes damage to organs through prolonged or repeated exposure - warning Specific target organ toxicity, repeated exposure. https://pubchem.ncbi.nlm.nih.gov/compound/benzofuran - section=Safety-and-Hazards

Linked Taxonomies (viruses/bacterium) These are extremely alarming.

11620	Lassa Mammarenavirus
11623	Lymphocytic Choriomeningitis Mammarenavirus
11628	Machupo Mammarenavirus
11629	Mopeia Mammarenavirus
11631	Tacaribe Mammarenavirus
12331	Rice Stripe Tenuivirus
42764	Oliveros Mammarenavirus
45219	Guanarito Mammarenavirus
45220	Flexal Mammarenavirus
45221	Latino Mammarenavirus
45223	Tamiami Mammarenavirus
46919	Whitewater Arroyo Mammarenavirus
49891	Pirital Mammarenavirus
55096	Ippy Mammarenavirus
55097	Mobala Mammarenavirus
144752	Allpahuayo Mammarenavirus
192848	Bear Canyon Mammarenavirus
208899	Cupixi Mammarenavirus
483046	Dandenong Virus
499556	Chapare Mammarenavirus
649188	Lujo Mammarenavirus
694009	Severe Acute Respiratory Syndrome-Related Coronavirus
1335626	Middle East Respiratory Syndrome-Related Coronavirus
2169991	Argentinian Mammarenavirus

2169992	Brazilian Mammarenavirus
2169993	Cali Mammarenavirus
2169994	Paraguayan Mammarenavirus
2169996	Serra do Navio Mammarenavirus

***EXTREMELY TOXIC: Chemical Structure - Remdesivir:**
CRYSTALLINE FORMS OF (S)-2-ETHYLBUTYL2-(S)-([(2R,3S,4R,5R)-5 (4-AMINOPYRROLO [2,1-F1 [1,2,4 TRIAZIN -7-YL)-5-CYANO -3,4 DIHYDROXYTETRAHYDROFURAN-2-YL) METHOXY)(PHENOXY) PHOSPHORYL)AMINO)PROPANOATE
https://pubchem.ncbi.nlm.nih.gov/patent/US-2021163523-A1

***There are 48 Linked Chemical Compounds that are extremely toxic**
https://pubchem.ncbi.nlm.nih.gov/patent/US-2021163523-A1 - section=Linked-Chemicals

Methods for creating synthetic DNA mimic this process through the use of a validated technology: phosphoramidite chemistry, which has stood the test of time. https://www.twistbioscience.com/blog/science/simple-guide-phosphoramidite-chemistry-and-how-it-fits-twist-biosciences-commercial

Phosphoramidite
https://pubchem.ncbi.nlm.nih.gov/compound/phosphoramidite

Phosphoramidite -
https://www.benchchem.com/product/b1245037

On-demand synthesis of phosphoramidites
https://www.nature.com/articles/s41467-021-22945-z