

The Pill Box

Issue: Second, Apr– Jun 2021

Dear Readers,

The purpose of this bulletin is to disseminate some important information related to drugs and medical devices likely to be of interest to everyone, involved directly or indirectly in patient care. The current issue highlights recent drug approvals, new drugs approved under emergency use for COVID-19 and COVID-19 vaccines options being considered in India. Feedback and suggestions, if any, may be sent at email Id: thepillboxafmc@gmail.com.

New restricted emergency use for COVID-19 Monoclonal antibody combination (Casirivimab and Imdevimab)

The antibody cocktail (Casirivimab 1200 mg and Imdevimab 1200 mg) launched in India at Rs 59,750/dose, developed by Roche and Regeneron. It is a virus neutralizing therapy directed against two subunits of spike protein S1 and S2 of SARS-CoV-2. Giving only one antibody may lead to escape of virus rendering treatment ineffective. Treatment should be started as soon as possible after the patient receives a positive report of Covid RTPCR or Rapid antigen within 10 days of symptom onset. It has shown to reduce the risk of hospitalisation and fatality by 70% and shortening the duration of symptoms by four days. Indications: Mild to moderate COVID-19 in adults and paediatric patients (Age 12 years or older weighing at least 40 Kg) at high risk of clinical progression to severe disease and/or hospitalization who meet at least one of following criteria: Obese with BMI > 35, chronic kidney disease, diabetes mellitus, immuno-compromising condition, currently receiving immunosuppressive treatment, age > 65 years, age > 55 years and have CAD/ HTN/COPD/ILD. It is not found to be beneficial in hospitalized patients with severe COVID-19. Possible side effects include: anaphylaxis and infusion-related reactions, fever, chills, hives, itching and flushing.

Other monoclonal antibody for COVID-19: Bamlanivimab, Regdanvimab.

Reference: FDA & product literature

New Drugs Corner

Ibrexafungerp

MOA: Glucan synthase inhibitor

Indication: Adult and post-menarchal pediatric females with vulvovaginal candidiasis (VVC).

Infigratinib

MOA: Kinase inhibitor

Indication: Adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a fibroblast growth factor receptor 2 (FGFR2) fusion.

Sotorasib

MOA: Inhibitor of the RAS GTPase family

Indication: Adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC).

Pegcetacoplan

MOA: A complement inhibitor

Indication: Adult patients with paroxysmal nocturnal hemoglobinuria (PNH).

Viloxazine

MOA: selective norepinephrine reuptake inhibitor

Indication: Attention Deficit Hyperactivity Disorder in paediatric patients (6 to 17 years)

Reference: USFDA

The Pill Box Quiz: 02

Instructions:

Scan the QR code to get the questions and correct answers with explanation.



SCAN ME



New restricted emergency use for COVID-19 2-Deoxy-D-Glucose (2-DG)

2-DG or 2-DEGE (synthetic glucose analogue) blocks glycolysis in initial stage and cause depletion of ATP as well as glucose derivatives required for protein glycosylation resulting in misfolded proteins leading to endoplasmic reticulum stress. It also inhibits anabolic reprogramming of host cells which is essentially required for fast viral multiplication. Moreover, this molecule selectively accumulates more in viral infected cells due to high glucose demand of these cells. It is used as adjunct therapy in the acute treatment of patients with moderate to severe COVID-19 disease in the hospital setting. 12 months is proposed shelf life when stored at controlled room temperature (below 30° C). Dose and Regimen: 45 mg/kg body weight AM and 45 mg/kg body weight PM twice daily (interval of at least 12 hours between doses) for not more than 10 days. It is advisable to exercise caution while using this drug in patients with hepatic or renal impairment and daily random blood sugar monitoring is recommended in diabetics as long as patients takes the drug. Insufficient data available to conclude on drug-drug interactions or its safety and efficacy in children and pregnancy.

How to prepare one dose: 2-DEGE is supplied as powder (white to off white colour) filled in sachets containing 2.34 g and 5.85 g of pure 2-Deoxy-D-Glucose. Measure and record patients body weight in kg. Within 1 hour prior to intended dose administration, completely dissolve the contents of one 2-DG sachet in 100 ml of potable water. Volume of 2-DG solution to be administered to the patient as one dose = $0.77 \times (\text{body weight of patients in Kgs})$ mL. Measure out the dose volume as calculated in a clean glass and ask the patient to drink the entire volume. Discard the remaining solution from the 100 ml prepared. Preferably should be taken on empty stomach fasting for at least 3 hours prior to administration. Reference: FDA product literature.

Potential molecule

New peptides allow cannabis-derived drugs to fight pain in mice without side effects

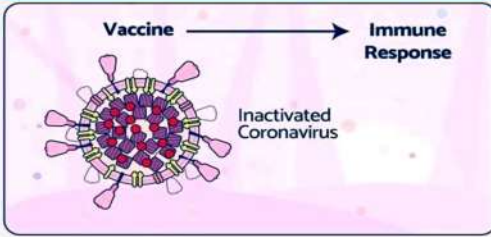
There is a lack of safe and effective drugs to treat moderate chronic or neuropathic pain. Cannabis-derived drugs have an excellent opportunity to provide relief in such cases, but their therapeutic use limited by side effects, including problems with memory and other cognitive functions. THC produces analgesia by binding to cannabinoid type 1 (CB1) receptors. Also, these receptors interact with serotonin receptor 5HT2A causing memory loss when THC is present. Based on molecular dynamics simulations and current pharmaceutical chemistry strategies, the researchers have developed a small peptide with high stability, allowing oral administration while increasing its ability to cross the blood-brain barrier to access and act on brain cells. After administering mice with the peptide orally, along with an injection of THC, they assessed pain threshold and memory capacity. Mice treated with both THC and the optimized peptide obtained the benefits of THC in relieving pain and also showed better memory compared to those treated with THC alone.

Journal reference: Gallo, M., et al. (2021) orally Active Peptide Vector Allows Using Cannabis to Fight Pain While Avoiding Side Effects. Journal of Medicinal Chemistry.

COVID-19 vaccines: A glimpse

COVID-19 vaccines are a critical tool in the battle against COVID-19. There are over 200 vaccine candidates for COVID-19 being developed and produced by different manufacturers around the world. Few of approved for restricted emergency use are shown below:-

BBV152/Covaxin BHARAT BIOTECH India



Inactivated Virus Vaccine

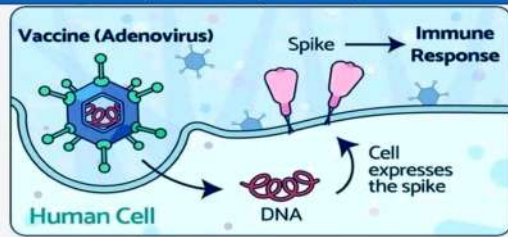
SARS-CoV2 is chemically inactivated (with a chemical called beta-propiolactone) so it cannot replicate but all the proteins remain intact.

Efficacy: 81% (original strain)
 --% (B1.351 "SA" variant)

Dosing: 2 dose - 28 days apart

Storage: +2-8°C

ChAdOx1/ AZD1222 (Covishield) OXFORD/ASTRAZENECA India



Viral Vector Vaccine

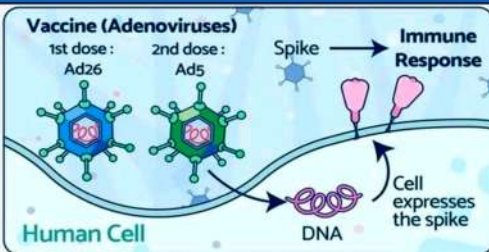
dsDNA encoding for the Spike protein is protected in a safe virus. The infected cell expresses the Spike protein which leads to an immune response.

Efficacy: 82% (original strain)
 10% (B1.351 "SA" variant)

Dosing: 2 doses - *12 weeks apart

Storage: +2-8°C - 6 Months

Sputnik V/ Gam-Covid-Vac GAMALEYA Russia



Viral Vector Vaccine

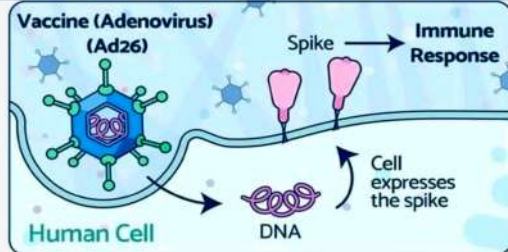
dsDNA encoding for the Spike protein is protected in a safe virus. The infected cell expresses the Spike protein which leads to an immune response.

Efficacy: 91% (original strain)
 --% (B1.351 "SA" Variant)

Dosing: 0.5 mL - 2 doses - 21 days apart

Storage: +2-8°C - 6 months
-20°C for 2 years

jNj-78436735/ Ad26.COVS JOHNSON&JOHNSON USA



Viral Vector Vaccine

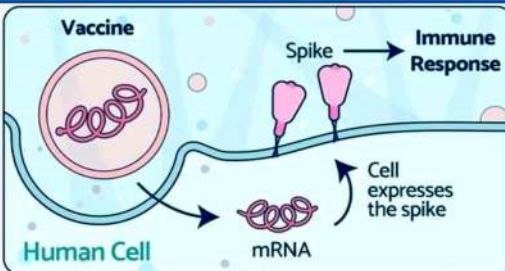
dsDNA encoding for the Spike protein is protected in a safe virus. The infected cell expresses the Spike protein which leads to an immune response.

Efficacy: 72% (original strain-US)
 moderate to severe cases 57% (B1.351 "SA" variant)

Dosing: 1 dose

Storage: +2-8°C - 3 months
-20°C - 2 Years

mRNA-1273 MODERNA USA



Encapsulated mRNA Vaccine

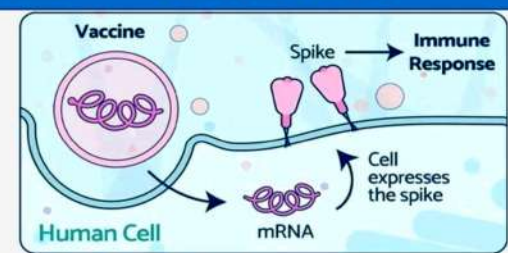
mRNA encoding for the spike protein is protected in a lipid nanoparticle (like a soap bubble). Once absorbed, the cell expresses the spike protein resulting in an immune response.

Efficacy: 94% (original strain)
 -- % (B1.351 "SA" variant)

Dosing: 0.5 mL - 2 doses - 28 days apart

Storage: -20°C - 6 months
+2-8°C - 30 days

BNT162b2 BIONTECH/PFIZER USA



Encapsulated mRNA Vaccine

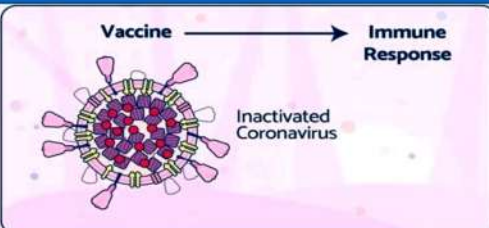
mRNA encoding for the Spike protein is protected in a lipid nanoparticle (like a soap bubble). Once absorbed, the cell expresses the Spike protein resulting in an immune response.

Efficacy: 95% (original strain)
 --% (B1.351 "SA" variant)

Dosing: 0.3 mL - 2 doses - 21 days apart

Storage: -70°C - 6 months
+2-8°C for 5 Days

BBIBP-CoV SINOPHARM China



Inactivated Virus Vaccine

SARS-CoV2 is chemically inactivated (with a chemical called beta-propiolactone) so it cannot replicate but all the proteins remain intact.

Efficacy: 79% (original strain)
 --% (B1.351 "SA" variant)

Dosing: 2 dose - 21 days apart

Storage: +2-8°C

NVX-CoV2373 NOVAVAX USA



Subunit Vaccine

Nanoparticles are coated with synthetic spike proteins. An additional element called adjuvant is added which allows to boost the immune reaction.

Efficacy: 96% (original strain)
 86% (B1.1.7 "UK" Variant)
 55% (B1.351 "SA" Variant)

Dosing: 2 doses - 21 days apart

Storage: +2-8°C - 6 months
-20°C for 2 years



We have been talking about Covishield, Covaxin and Sputnik V - the three Covid-19 vaccines being administered in India. Following are the other vaccines currently in the pipeline in India.

COVOVAX: Pune-based Serum Institute of India (SII) is manufacturing the US biotechnology company 'Novovax' protein-based Covid-19 vaccine NVX-CoV2373 under the name 'Covovax'. Bridging studies for Covovax are underway in India. It is expected to be rolled out in two to three months.

BBV154: Bharat Biotech's intranasal vaccine BBV154 creates an immune response at the site of infection (nasal mucosa), block both infection and transmission of Covid-19. Currently under Phase I trials.

HGC019: Pune-based Gennova Biopharmaceuticals has developed India's first mRNA Covid-19 vaccine called HGC019 and is in Phase I trials. Likely to be launched early next year.

ZyCoV-D: Zydus Cadila, Gujarat is producing an intradermal Covid-19 vaccine called ZyCoV-D. First indigenously developed DNA vaccine candidate, likely to be rolled out in two to three months.

CORBEVAX: Hyderabad-based Biological E has developed a protein sub-unit vaccine called Corbevax, currently undergoing Phase 3 clinical trials. Expected to be rolled out between August and December. The government likely to pay an advance of Rs 1,500 crore to reserve 30 crore doses of Corbevax.

PTX-COVID19-B: It is an mRNA vaccine currently under development in Canada. Biological E to manufacture the Canadian company's mRNA Covid-19 vaccine in India.

JANSSEN: Janssen approved for use in the United States, the European Union, Thailand and South Africa. Biological E has a deal to produce about 600 million doses of the vaccine in India.

Common controversies & facts

-Efficacy of current vaccines against new variants: The current vaccines should be effective against new variants (B.1.1.7, B.1.351, P.1, B.1.617) but cannot be commented upon precisely. Data continues to be collected and analysed on new variants of the COVID-19 virus by different agencies.

-Apprehension about Side-effects following vaccination: The chances of side effects occurring after vaccination varies with vaccine type. Typical side effects: pain at the injection site, fever, fatigue, headache, muscle pain and chills; last no longer than a few days. Individual to report to local health providers if side effects last more than three days or experience any unexpected side effects.

-Changing time-gap between two doses: An interval of 21–28 days (3–4 weeks) between doses were recommended based on initial clinical trials of vaccine candidates performed with the shortest possible duration between doses. The interval may be extended on the basis of evidence generated.

-Use of different vaccines for two doses: Few clinical trials are ongoing in some countries looking at interchangeability, which means the first dose with one vaccine and the second dose with a different vaccine. At present, not enough data available to recommend interchangeable two dose schedules. WHO recommends a vaccine from same manufacturer be used for both doses if one require two doses.

WHO has not advocated any particular vaccine, specific attributes and handling requirements to be considered by countries to find the vaccines that are most suitable for their circumstances.

Getting vaccinated is safer than getting infected.