Bulletin of Pharmaceutical Research 2022;12(1-3):175
An Official Publication of Association of Pharmacy Professionals
ISSN: 2249-6041 (Print); ISSN: 2249-9245 (Online)
DOI: 10.21276/bpr.2022.12.1

REVIEW ARTICLE

ORAL ANTIVIRAL MEDICINES FOR COVID-19

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Received: Jun 24, 2022 / Revised: Aug 30, 2022 / Accepted: Aug 31, 2022

In recent years, USFDA has granted Emergency Use Authorization (EUA) to three medications for oral treatment of Covid-19 infection, which is considered a breakthrough in Covid treatment after the only available vaccination option for prevention of this deadly disease. This study concisely portrays the basic structure and lifecycle of corona virus in context to the mechanism of action of oral anti-Covid-19 medications. Further, different comparative parameters of oral medicines are summarized to appraise appropriateness of their use in distinct patients groups.

Key words: Oral anti-Covid-19 medications, Covid-19 tablets, Covid-19 capsules, Molnupiravir, Paxlovid.

INTRODUCTION

SARS-CoV-2, a severe acute respiratory syndrome coronavirus-2, continues to be a threat to our society and global public health. The COVID-19 epidemic has rapidly spread across the globe, with 539,119,771 cases of COVID-19 and 6,322,311 deaths reported as of 22 June 2022 [1]. The most significant symptoms in COVID-19 patients are fever, dry cough, loss of sense of taste, lethargy, shortness of breath, and anosmia [2]. Mass vaccination is still going on population; however, studies have shown that even vaccinated people are infected with novel coronavirus variants. The World Health Organization (WHO) variants of concern (VOC) have included the alpha, beta, gamma, delta, delta plus and the omicron variants of SARS-CoV-2 [3]. Based on the COVID-19 public health emergency, the secretary of the Department of Health and Human Services (HHS) justified on March 27, 2020, the authorization of emergency use of unapproved drugs and biological products under section 564 of the Act (21 U.S.C. 360bbb-3) [4,5].

Food and Drug Administration (FDA) approved Remdesivir and also authorized the emergency use of other drugs including Casirivimab/imdevimab, Tixagevimab/Cilgavimab, Bebtelovimab, however, most of them require medically supervised intravenous (IV) administration. Therefore, drug companies put extra efforts to develop simple and low-cost oral coronavirus medication to protect unvaccinated people and to add extra protection for immuno-compromised patients that may not be fully protected after vaccination in the early stage of SARS-CoV-2.

First, FDA issued an Emergency Use Authorization (EUA) for the emergency use of two oral antiviral medicines on 22nd December 2021: Paxlovid (nirmatrelvir/ritonavir) and Lagevrio (Molnupiravir) [4,5]. Paxlovid (nirmatrelvir / ritonavir) and Lagevrio (Molnupiravir) oral medicines were approved for the early treatment of mild-to-moderate Covid-19 at high-risk to treat severe symptoms of Covid-19, including hospitalization or death.

Later, on May 10, 2022, FDA approved another oral medication Baricitinib. It is a drug already used for the treatment of rheumatoid arthritis in adults, but now, it has been approved for the treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extra-

corporeal Membrane Oxygenation (ECMO). The FDA has authorized the emergency use of baricitinib for the treatment of COVID-19 in children (2 to 18 years old) under EUA [6,7]. These oral medications are promising to add protection to patients with Covid-19. Before proceeding with the oral medications, understanding the basics of Covid-19 pathogenesis is necessary to develop the efficacious treatment and prevention strategies for Covid-19.

Corona virus: Basic structure and life cycle

COVID-19 spread between people *via* respiratory droplets and aerosols. Coronaviruses consist of four structural proteins; Spike glycoprotein (S), membrane (M), envelop (E) and nucleoprotein (N) [2,8,9]. Spike is composed of a transmembrane trimetric glycoprotein protruding from the viral surface. It has two subunits: S1 and S2. S1 is responsible for binding to the host cell receptor (Angiotensin converting enzyme 2, ACE2) highly expressed in lung, heart, ileum, kidney, bladder and S2 for the fusion of the viral and cellular membranes. In lung, ACE2 was highly expressed on lung epithelial cells [9]. Inside there is the viral RNA material whose genome length is about 26-32 Kilo base pairs (kb) [2].

As illustrated in **Figure 1**, five steps have been proposed for the life cycle of the virus with the host *i.e.* attachment, penetration, biosynthesis, maturation and release [9]. The Plaxlovid tablets work by blocking an enzyme central to SARS-CoV-2's replication cycle. Nirmatrelvir is an inhibitor of SARS-CoV-2 main protease (Mpro: also referred as 3CLpro).

The viral protease creates other proteins needed by the virus. Ritonavir does not have activity against SARS-CoV-2 but is included to inhibit the CYP3A which is involved in the metabolism of nirmatrelvir, and consequently increases the nirmatrelvir plasma concentrations to levels inhibiting SARS-CoV-2 replication [10,11].

Molnupiravir inhibits SARS-CoV-2 replication by viral mutagenesis. Molnupiravir is a prodrug, metabolized to the cytidine nucleoside analogue, 5′-isobutyrate ester of the ribonucleoside analog N4-hydroxycytidine (NHC). NHC is distributed into the cell, and it is phosphorylated to form a ribonucleoside triphosphate (NHC-TP). NHC-TP incorporation into SARS-CoV-2 RNA by the viral RNA polymerase, causes mutations that stop the virus from replicating. Some scientists worry the drug could cause mutations in people, but little evidence supports this concern. In general, these two drugs work in the biosynthesis step [11,12].

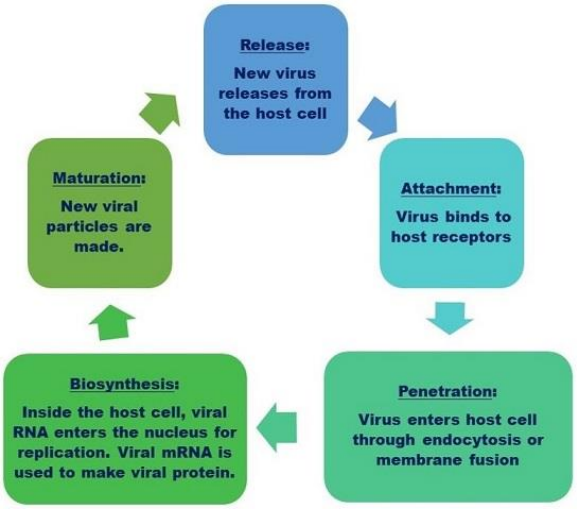


Fig. 1. Corona virus life cycle.

Baricitinib is a reversible Janus-associated kinase (JAK)-inhibitor that interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology. It prevents virus endocytosis and reduces viral assembly by inhibiting adaptor-related protein-2 (AP-2)–associated protein kinase 1 and cyclin-G-associated kinase enzymes in alveolar type 2 cells [13].

Based on the information of all drugs, Paxlovid seems to be the best treatment option during pregnancy, for pediatric patients (12 years of age and older) and for patients with a high risk of developing allergic reactions (anaphylaxis). On the other hand, Molnupiravir seems to be the better option for patients with renal and hepatic impairment and for patients who are receiving concomitant medications metabolized by CYP3A (drugs highly dependent on CYP3A or potent CYP3A inducers). Patients receiving Baricitinib should be monitored cautiously due to the significant serious adverse effect compared to Paxlovid and Molnupiravir, but it is the only available alternative for pediatric patients (2 to 18 years). Baricitinib can produce some abnormal laboratory analytes values (eGFR, Absolute Lymphocyte Count, Absolute Neutrophil Count, Aminotransferases), which may result in the discontinuation of the treatment during the hospitalization. Baricitinib is not recommended for use in patients who are on dialysis, have end-stage renal disease (ESRD), or acute kidney injury (eGFR). Benefits evaluation must be taken for patient with hepatic impairment.

Paxlovid (88%) demonstrates greater efficacy compared to Molnupiravir (30%) in reducing the

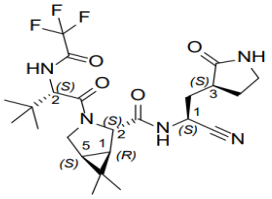
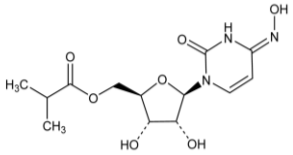
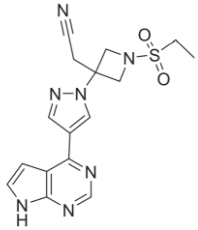
hospitalizations and deaths among people with Covid-19 who were at high risk of severe illness. Efficacy of Baricitinib was acceptable based on the following endpoints from clinical studies: the time to recovery within 29 days after randomization, clinical status on Day 15, the proportion of patients who died or progressed to noninvasive ventilation/high-flow oxygen or invasive mechanical ventilation within the first 28-days of the study, all-cause mortality by Day 28. Health care providers must take into consideration the efficacy and other factors when choosing the appropriate treatment. Despite the use of all three tablets in COVID-19, some important differences including the mechanism of action of three drugs must be taken into consideration when evaluating the treatment options in different patient populations. **Table 1** depicts a comparative summary of the Lagevrio (Molnupiravir), Paxlovid (Nirmatrelvir and ritonavir) and Olumiant (Baricitinib) oral medicines [4-18]. Besides EUA, a couple of reports have evaluated potential of combination therapy as well as repurposing approach in Covid-19 treatment [19,20].

Table 1. Comparative summary of oral antiviral medicines, Paxlovid (Nirmatrelvir/Ritonavir), Lagevrio (Molnupiravir) and Olumiant (Baricitinib).

Product	**Paxlovid (nirmatrelvir/ ritonavir)** [4,14,16-18]	**Lagevrio (Molnupiravir)** [5,12,17,18]	**Olumiant (Baricitinib)** [6,7,13,15]
Manufacturer	Pfizer, Inc.	Merck Sharp & Dohme Corp.	Eli Lilly and Corp.
Approved date	EUA: 12/22/21 Last update: 04/14/2022	EUA: 12/23/21 Last update: 03/23/2022	EUA: 05/10/2022 Last update: 06/13/2022
Use	Treatment of mild-to-moderate COVID-19 at high-risk to develop severe symptoms of COVID-19, including hospitalization or death.	Treatment of mild-to-moderate COVID-19 at high risk to develop severe symptoms of COVID-19, including hospitalization or death.	Treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).
Targeted population	Adults and pediatric patients (12 years of age and older)	Adults	Adults and children (2 to 18)
Initiation of treatment	Should be taken as soon as possible after a diagnosis of COVID-19 and within five days of symptom onset	Should be taken as soon as possible after a diagnosis of COVID-19 and within five days of symptom onset	Some laboratory analytes values must be monitored before starting the treatment and during the treatment. Avoid initiation or interrupt the treatment in patients with lymphopenia (ALC < 200 cells/mm^3) or neutron-penia (ANC < 500 cells/mm^3)
Duration of treatment	5 days	5 days	14 days or until hospital discharge, which occurs first
Limitations of Authorized Use	• Not for patients requiring hospitalization with severe or critical COVID-19 • Not use for prophylaxis for prevention of COVID-19 • Not use for longer than 5 consecutive days.	• Not for patients requiring hospitalization due to COVID-19 • Not use for prophylaxis for prevention of COVID-19 • Not use for longer than 5 consecutive days • Not for patients less than 18 years of age	• The treatment of COVID-19 in hospitalized adults requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or ECMO • The treatment of adult patients with rheumatoid arthritis and severe alopecia areata. • Not recommended for use in combination with other JAK inhibitors, biologic immunomodulators, cyclosporine or other potent immunosuppressants

Status	Prescription-only	Prescription-only	Prescription-only
Clinical studies	A total of 2,246 (≥18 years) subjects participated in the study EPIC-HR (NCT04960202), a Phase 2/3, randomized, double-blind, placebo-controlled study in non-hospitalized symptomatic adult subjects with a laboratory confirmed diagnosis of SARS-CoV-2 infection	A total of 1,433 (≥18 years) subjects participated in the study MOVe-OUT trial (NCT04575597), Phase 3, a randomized, double-blind, placebo-controlled study in non-hospitalized patients with mild-to-moderate COVID-19 who are at risk for progressing to severe COVID-19 and/or hospitalization	The efficacy and safety of Baricitinib were assessed in 2 Phase 3, randomized, double-blind, placebo-controlled clinical trials • COVID I (ACTT-2, NCT04401579): (N = 1033 patients) evaluated the combination of baricitinib 4 mg + remdesivir (n = 515) compared to placebo + remdesivir (n = 518). • COVID II (COV-BARRIER, NCT04421027): (N = 1525 patients) evaluated baricitinib 4 mg compared to placebo Baricitinib is being studied in an ongoing clinical trial in pediatric patients, based on extrapolation of ACTT-2 and COV-BARRIER, and safety data from ongoing clinical trials of Baricitinib in other pediatric conditions
Efficacy per clinical trials	88% reduction in hospitalizations/deaths	30% reduction in hospitalizations/deaths	Clinical trial (NCT04401579): • A better clinical status on Day 15 and a better time to recovery within 29 days were observed in baricitinib + remdesivir. • The proportion of patients who died by Day 29 was lower in baricitinib + remdesivir Clinical trial (NCT04421027): The proportion of patients who died by Day 28 was lower for baricitinib (8.1%)
Dosage forms and strengths	Tablets (two oval, pink, immediate-release, film-coated tablet debossed with “PFE” on one side and “3CL” on the other side): nirmatrelvir 150 mg Tablets (white, film-coated, ovaloid tablet debossed with the "a" logo and the code NK): ritonavir 100 mg	Capsules (Swedish orange, logo 82 printed in white ink): 200 mg	Tablet 1 mg (very light pink, round, debossed with “Lilly” on one side and “1” on the other) Tablet 2 mg (light pink, oblong, debossed with “Lilly” on one side, “2” on the other) Tablet 4 mg (medium pink, round, debossed with “Lilly” on one side and “4” on the other. Tablets contain a recessed area on each face of the tablet surface and are available for oral

			administration as debossed, film-coated, immediate-release tablets
Packaging	Blister card contains a morning and evening dose Include a total of 30 tablets (300 mg nirmatrelvir;100 mg ritonavir) or 20 tablets (150 mg nirmatrelvir; 100 mg ritonavir)	Includes 40 counts per bottle	Includes 30 counts per bottle
Administration and dose	• Two tablets of nirmatrelvir (300 mg) must be co-administered with one tablet of ritonavir (100 mg) • All three tablets must be taken at the same time twice daily for 5 days • Administer orally with or without food • The tablets should be swallowed whole	• Four capsules (800 mg) must be taken orally every 12 hours for 5 days • Administer orally with or without food. • Capsules should be swallowed whole	• 1 time a day by mouth with or without food. • 9 years of age and older: 4 mg • 2-8 years of age: 2 mg • Alternative mode of administration: tablets may be crushed to make a dispersion in water • It can be given via gastrostomy tube (G tube), nasogastric tube (NG tube) or orogastric tube (OG tube)
Important prescribing information	Patients with moderate renal impairment require a different dose of PAXLOVID 150 mg nirmatrelvir with 100 mg ritonavir	No dosage adjustment for renal and hepatic impairment	Dosage adjustment must be required for abnormal laboratory values, for patients with renal impairment and for patient taking strong OAT3 inhibitors (*e.g.* probenecid) Caution must be taken for patients with severe hepatic impairment, dosage adjustment is not known
Contra-indications	Individuals with significant hypersensitivity reactions to any component of Paxlovid Cautions must be taken for patients receiving concomitant medications metabolized by CYP3A (drugs highly dependent on CYP3A or potent CYP3A inducers), which may increase or decrease the plasma concentrations of nirmatrelvir or ritonavir affecting the virologic response	No contraindications due to limited available data	None
Drug interaction	Drugs highly dependent on CYP3A increase the plasma concentration of Plaxlovid causing a potentially serious and/or life-threatening reactions: alfuzosin, pethidine, piroxicam, propoxyphene, ranolazine,	None based on the limited available data	Strong OAT3 Inhibitors (*e.g.* probenecid) Medicines to treat rheumatoid arthritis: tocilizumab (Actemra®), etanercept (Enbrel®), adalimumab (Humira®), infliximab (Remicade®),

	amiodarone, dronedarone, flecainide, propafenone, quinidine, colchicine, lurasidone, pimozide, clozapine dihydroergotamine, ergotamine, methylergonovine, lovastatin, simvastatin, sildenafil, triazolam, oral midazolam. Potent CYP3A inducers can reduce nirmatrelvir or ritonavir plasma concentrations causing a potential loss of virologic response and possible resistance: apalutamide, carbamazepine, phenobarbital, phenytoin, rifampin, St. John's Wort (hypericum perforatum)		rituximab (Rituxan®), abatacept (Orencia®), anakinra (Kineret®), certolizumab pegol (Cimzia®), golimumab (Simponi®), tofacitinib (Xeljanz®, Xeljanz XR®), sarilumab (Kevzara®) Taking OLUMIANT with these medicines may increase your risk of infection
Pregnant or breastfeeding	There is no experience treating pregnant women or breastfeeding mothers	It is not recommended for treatment in this group	There is no experience treating pregnant women or breastfeeding mothers. Based on animal data, may cause fetal harm
Warnings and precautions	Not recommended in patients with severe renal and hepatic impairment. No pharmacokinetic or safety data are available for these patients	• Embryo-Fetal Toxicity: Molnupiravir is not recommended for use during pregnancy Molnupiravir caused harm to unborn babies on pregnant animals. Hypersensitivity reactions, including anaphylaxis have been reported with molnupiravir • Bone and Cartilage Toxicity: Molnupiravir is not authorized for use in patients less than 18 years of age because it may affect bone and cartilage growth	• Not recommended for End Stage Renal Disease, Patients on Dialysis, or Acute Kidney Injury • Increased risk of hypersensitivity and gastrointestinal perforations • Laboratory Abnormalities: Monitor for changes in lymphocytes, neutrophils, hemoglobin, liver enzymes, and lipids. Avoid use with live vaccines
Structures and molecular weight	 Nirmatrelvir is (1R,2S,5S)-N-((1S)-1-Cyano-2-((3S)-2-oxopyrrolidin-3-yl)ethyl)-3-((2S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3- azabicyclo	 Molnupiravir is {(2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2- oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate	 Baricitinib is a {1-(ethylsulfonyl)-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]azetidin-3-yl}acetonitrile.

	Molecular formula: $C_{23}H_{32}F_3N_5O_4$ Mol. wt.: 499.54 g/mol. 10-Hydroxy-2-methyl-5-(1-methylethyl)-1- [2-(1 methylethyl)-4- thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester, [5S-(5R*,8R*,10R*,11R*)] *Molecular formula:* $C_{37}H_{48}N_6O_5S_2$, Molecular weight: 720.95 g/mol	*Molecular formula:* $C_{13}H_{19}N_3O_7$ Molecular weight of 329.31 g/mol	*Molecular formula:* $C_{16}H_{17}N_7O_2S$ Molecular weight of 371.42 g/mol
Excipients or inactive ingredients	**Nirmatrelvir**: colloidal silicon dioxide, croscarmellose sodium, lactose monohydrate, microcrystalline cellulose, and sodium stearyl fumarate. The following are the ingredients in the film coating: hydroxy propyl methylcellulose, iron oxide red, polyethylene glycol, and titanium dioxide **Ritonavir**: anhydrous dibasic calcium phosphate, colloidal silicon dioxide, copovidone, sodium stearyl fumarate, and sorbitan monolaurate. The following are the ingredients in the film coating: colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, polyethylene glycol 400, polyethylene glycol 3350, polysorbate 80, talc, and titanium dioxide	**Molnupiravir**: croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate and microcrystalline cellulose and purified water. The capsule shell is made of hypromellose, red iron oxide and titanium dioxide. The capsule is printed with white ink made of butyl alcohol, dehydrated alcohol, isopropyl alcohol, potassium hydroxide, propylene glycol, purified water, shellac, strong ammonia solution and titanium dioxide	**Baricitinib:** croscarmellose sodium, ferric oxide, lecithin (soya), magnesium stearate, mannitol, microcrystalline cellulose, polyethylene glycol, polyvinyl alcohol, talc and titanium dioxide
Mechanism of action	Nirmatrelvir is an inhibitor of the SARS-CoV-2 main protease (Mpro) which prevent the production of polyprotein precursors, preventing viral replication Ritonavir inhibits the CYP3A-mediated metabolism of nirmatrelvir	Molnupiravir a prodrug, nucleoside analogue that inhibits SARS-CoV-2 replication by viral mutagenesis	Baricitinib is a reversible Janus-associated kinase (JAK)-inhibitor that interrupts the signaling of multiple cytokines implicated in COVID-19 immunopathology It prevents virus endocytosis and reduces viral assembly by inhibiting adaptor-related protein-2 (AP=2)–associated protein kinase 1 and cyclin-G-associated kinase enzymes in alveolar type 2 cells
Adverse effects	Dysgeusia, diarrhea, hypertension, and myalgia	Diarrhea, nausea, and dizziness	• Specifics for Covid-19: increases of liver

			enzymes, thrombocytosis, creatine phosphokinase increases, neutropenia, deep vein thrombosis, pulmonary embolism, and urinary tract infection • Increased risk of serious infections (bacterial, fungal, viral and other infections leading to hospitalization or death, including tuberculosis) • Increased risk of death in people 50 years of age and older who have at least 1 heart disease • Increased risk of certain cancers including lymphoma and lung cancer • Increased risk of major cardiovascular events such as heart attack, stroke or death in people 50 years of age and older who have at least 1 heart disease (cardiovascular) risk factor and taking a medicine in the class of medicines called JAK inhibitors, especially if you are a current or past smoker • Blood clots in the veins of your legs (deep vein thrombosis, DVT) or lungs (pulmonary embolism, PE) and arteries (arterial thrombosis) • Tears (perforation) in the stomach or intestines. • Changes in certain laboratory test results (low lymphocyte counts, low neutrophil counts and low red blood cell counts) • Allergic Reactions (rash, swelling of your lips, tongue, or throat, or hives)
Activity against SARS-Cov-2 variants	Alpha, beta, gamma, delta. Alpha, beta, gamma, and delta and omicron variants [14,16,17]	Alpha, beta, gamma, and delta and omicron variants [17,18]	Not specified

CONCLUSION

Despite some adverse effects and limitations in their use, oral anti-Covid 19 medications are boon for patients due to their ability to significantly reduce the hospitalizations and deaths while allowing the patients to adopt at-home treatment with easy self-administration option unlike the invasive parenteral administration that requires medical assistance. At the same time, it is essential to choose the correct treatment option based on patient population to get most out of these three EUA oral medications without the significant side effects.

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