THEMES AND RECOMMENDATIONS

- Federal policymakers should view the advance market commitment strategy followed with outpatient COVID-19 treatments as a success that should be built upon. This approach substantially reduced manufacturer risk and resulted in multiple drugs becoming available in a relatively short time at prices that were aligned with clinical benefit. The framework for drug price negotiation between the government and drug makers during a pandemic should be made more transparent so that the public is aware of the parameters that the federal government considers in pricing negotiations.

- The FDA needs to establish a clear and effective pathway for supporting evaluation of repurposed drugs. This may include proactive outreach to study investigators to invite applications and providing technical assistance during application development as well as consider internal FDA application initiation and development in cases where there is not a clear external sponsor.

- The federal government should work with states and other policymakers to adopt policy changes needed to improve the effectiveness of its "test-to-treat" program. Test-to-treat sites are greatly needed to more immediately link diagnosis with treatment. Further, test-to-treat sites, which offer the convenience of co-located services, may differentially benefit individuals with low incomes since these individuals may have lower means to make multiple visits to access testing and treatment. Given the need for rapid and broad distribution of treatment during pandemic, the federal government should consider working with states and professional stakeholders to broaden the functional scope of practitioners who can prescribe COVID-19 treatments. It may be possible to use telemedicine or other means to accomplish this goal, but allowing pharmacists to prescribe under certain circumstances should also be considered.

- When COVID-19 drug pricing and payment moves from federal contracts into private markets, manufacturers and payers should work together to explore innovative approaches for coverage and pricing that minimize the use of restrictive coverage access as a means of cost control. Manufacturers should price treatments so they are affordable to private insurance systems and patients. Given the need to treat COVID-19 rapidly upon symptom onset, payers should ensure that any prior authorization process leads to immediate coverage for an available and appropriate treatment and does not risk having patients not fill their prescriptions.

- Future research is needed to understand the epidemiology of long COVID and the impact of different prevention and treatment strategies on this condition as well as to define and measure the effects of treatments on a more inclusive set of patient-centered and societal outcomes.

"The evidence on outpatient treatments for COVID-19 must be viewed as highly sensitive to the evolving landscape of COVID-19 variants and vaccination status in the US. As indicated by the votes from the independent appraisal committee, the current evidence was judged more persuasive for Paxlovid and fluvoxamine than for molnupiravir, but clinical trials are ongoing for all three treatments. At their current negotiated price (molnupiravir, and Paxlovid) or their generic market price (fluvoxamine), these drugs appear to have prices reasonably aligned with patient benefits. One of the key lessons to be learned from the development of these drugs is that the federal government's advance market commitment mechanism was effective in reducing the financial uncertainty that could have deterred manufacturers from bringing a drug to market, and ultimately resulted in multiple drugs becoming available in a relatively short time at prices that were aligned with clinical benefit. That experience has many lessons for the future of US policy in preparing for future pandemics." **– ICER's President, Steven Pearson, MD, MSc**

Clinical Analyses

KEY CLINICAL BENEFITS STUDIED IN CLINICAL TRIALS

COVID-19 is an infectious respiratory disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of April 2022, there have been over 80 million confirmed COVID-19 cases and 980,000 COVID-19 deaths in the United States (US). The severity of the disease is classified into four levels. Most symptomatic COVID-19 patients have mild or moderate disease and do not require hospitalization. Patients who develop severe or critical disease require hospitalization with respiratory support. Many factors can increase the risk for developing severe or critical COVID-19. Some of the most common risk factors are older age, obesity, cardiovascular disease, and chronic obstructive pulmonary disease.

This evaluation is considered an Institute for Clinical and Economic Review (ICER) Special Assessment because the epidemiological landscape and evidence base for potential treatments for COVID-19 are both rapidly evolving and will continue to change throughout and beyond the course of this review. This constantly shifting landscape is a dominant contextual reality. However, due to the unprecedented immediacy and scale of COVID-19, and the near-term policy decisions that will be made across multiple treatment options, ICER believes that an independent review of existing evidence on comparative clinical effectiveness and value of these treatment options will be helpful to all stakeholders.

ICER is presenting a full evaluation of clinical and economic outcomes of four treatments for mild-to-moderate COVID-19 among outpatients at high risk of progression to severe disease: molnupiravir, Paxlovid™, and fluvoxamine. The scope of the review had aditionally included two monoclonal antibody treatments REGEN-COV and sotrovimab. However, neither treatment currently has emergency use authorization (EUA) from the Food and Drug Administration (FDA) for use in any U.S. region due to substantially reduced activity against the Omicron variant and Omicron BA.2 subvariant, respectively. Around the time of posting of the Draft Evidence Report, the FDA granted EUAs for remdesivir and bebtelovimab for our population of interest. Further, peginterferon lambda is seeking EUA based upon recent positive trial results. While these treatments emerged too late for us to consider in the revised Evidence Report, we note that the interactive economic model will now be available on ICER Analytics. Decisionmakers can input clinical and economic data on other emerging treatments to generate cost-effectiveness results and suggested health-benefit price benchmarks.

Molnupiravir is an oral ribonucleoside analog that causes viral genome replication errors. Nirmatrelvir/ritonavir (Paxlovid) is a combination oral drug that inhibits SARS-CoV-2-3CL protease, an enzyme necessary to produce other functional SARS-CoV-2 proteins. Fluvoxamine is an oral selective serotonin reuptake inhibitor (SSRI) with FDA approval for the treatment of obsessive-compulsive disorder. One hypothesized mechanism of action for fluvoxamine in the treatment of COVID-19 is through modulation of the body's inflammatory response. Molnupiravir, and Paxlovid currently have EUAs from the FDA. Fluvoxamine is available on the US market while university-based researchers are pursuing an EUA specifically for the treatment of COVID-19.

Studies of all three therapies were conducted in overlapping timeframes but with potentially important differences in location (US vs. overseas), and in the spectrum and relative prevalence of SARS-CoV-2 variants within the population. None of the clinical trials were performed at a time when the Omicron variant was present. Within this context, trial results demonstrated that, if given within a limited number of days following initial symptoms of COVID-19, all

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three drugs of interest were superior to placebo in reducing hospitalization related to the acute infection. Molnupiravir and Paxlovid significantly reduced the relative risk of hospitalization or death from any cause compared to placebo by 30%, and 88%, respectively. Fluvoxamine reduced the relative risk of COVID-19-associated acute care (i.e., retention in a COVID-19 emergency setting or transfer to tertiary hospital due to COVID-19) by 32% over placebo. A per-protocol analysis of fluvoxamine limited to individuals who did not stop treatment (i.e., had greater than 80% adherence) suggested substantially greater efficacy (66% relative risk reduction) in reducing acute care use.

Molnupiravir and Paxlovid were well tolerated and had low discontinuation rates in their Phase III clinical trials. However, each drug has some notable risks. With molnupiravir there were important safety considerations given laboratory evidence suggesting it may be mutagenic, teratogenic, and toxic to growing bone and cartilage. Based on a short five-day course of therapy, the FDA considers molnupiravir to have low risk for mutagenicity, but the EUA label limits usage to individuals 18 years and older who are not pregnant or breastfeeding and who are without alternative COVID-19 treatment options. The FDA also recommends that men of reproductive potential who are sexually active with individuals of childbearing potential should abstain from sex or use a reliable method of contraception for the duration of treatment and for at least three months after the last dose of molnupiravir. Molnupiravir is only authorized for individuals for whom alternative COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate.

Paxlovid is a combination therapy containing ritonavir. Ritonavir has many known drug-drug interactions that pose a safety risk. These include interactions with certain anticoagulants, antiplatelets, antiarrhythmics, anticonvulsants, and immunosuppressants.These interactions may be more common among certain patients who are at particularly high risk for severe COVID-19 disease (e.g., immunosuppressed patients). Paxlovid is not recommend for patients with severe renal or hepatic impairment.

As an SSRI, fluvoxamine also carries an FDA drug class warning for increased risk of suicidal thinking for children, adolescents, and young adults taking antidepressants for major depressive disorder and other psychiatric disorders. The risk of adverse events in the fluvoxamine arm was similar to the risk in the

Table 1. Number and Percentage of Hospitalizations or Deaths in Key Phase III Trials

Intervention (Trial)	Hospitalization or Death from Any Cause, n/N (%)		Death, n/N (%)	
	Intervention	Placebo	Intervention	Placebo
Molnupiravir (MOVe-OUT)	48/709 (6.8)	68/699 (9.7)	1/709 (0.1)	9/699 (1.3)
Paxlovid (EPIC-HR)	8/1,039 (0.8)	66/1,046 (6.3)	0/1,039 (0)	12/1,046 (1.1)
Fluvoxamine (TOGETHER)	79/741 (11)*	119/756 (16)*	17/741 (2.3)	25/756 (3.3)

n: number, N: total number
*Observed in a COVID-19 emergency setting (for more than six hours) or hospitalized.

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placebo arm of the Phase III TOGETHER trial as well as to the risks in intervention arms in the Phase III trials for the other drugs of interest. However, there was a sizeable percentage of individuals who stopped treatment due to tolerability in both the fluvoxamine and placebo arms of the TOGETHER trial (11.3% and 8.4%, respectively).

While further evidence on all three treatments of interest continues to be gathered and analyzed, the COVID-19 landscape has been evolving so rapidly that currently available data cannot be expected to have evaluated the safety and effectiveness of these drugs in the real-world US population as of the date of this report. Important uncertainties that must be considered include: 1) the rapid evolution of SARS-CoV-2 leading to variants with treatment resistance and with different morbidity and mortality impacts; 2) the enrollment of predominantly unvaccinated patients who were generally healthier and lower risk than those in the general population; and 3) the uncertain generalizability of data related to hospitalization rates and other health care resource utilization from studies conducted prior to the advent of the Omicron variant and based predominately or exclusively in countries outside of the US. Such issues are compounded by the early phase of evidence generation in which only one Phase III trial has been conducted for each drug in the population of interest at this time.

Substantial differences in patient populations across the Phase III trials preclude us from making direct comparisons or formal quantitative indirect comparisons of safety and effectiveness across the drugs of interest. For example, molnupiravir trials enrolled substantially larger proportions of individuals with obesity compared to the fluvoxamine and Paxlovid trials. Further, as noted, large variability in the countries of recruitment and the timing of trial enrollment periods reduce study comparability. The Phase III trials also defined outcomes differently. In particular, data from the fluvoxamine TOGETHER trial appears to be the least comparable to others since this trial used a distinct composite primary outcome of retention in a COVID-19 emergency setting for more than six hours or transfer to a hospital. Keeping this context of substantial uncertainty in mind, ICER Evidence Ratings shown in Table 2 should be viewed with corresponding caution, particularly when making inferences between the comparative effectiveness of the different agents.

Table 2. Evidence Ratings

Treatment	Comparator	Evidence Rating
Molnupiravir*	Usual care	C+
Paxlovid	Usual care	B+
Fluvoxamine	Usual care	C+

*Note: Population excludes individuals who are pregnant or who have childbearing potential.

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LONG-TERM COST EFFECTIVENESS

To estimate the cost effectiveness of each outpatient treatment, we used estimates of relative treatment effectiveness from each intervention's pivotal trial and applied those estimates to a common "usual care" comparator arm synthesized by pooling across the usual care arms of each pivotal trial. This approach was considered optimal given how disparate the results were in the usual care arms across the pivotal trials, reflective of the differences in the background patient population, timing of study in relation to COVID-19 variants, and differences in health care practices across the different countries in which the trials were conducted. Base-case results were calculated from the health care sector perspective over a lifetime time horizon. We acknowledge the societal perspective may have particular relevance when the government is paying for the treatments outside of usual health care cost budgets.Therefore, we present results from a modified societal perspective as a scenario analysis. All treatments had base-case estimates lower than $100,000 per quality-adjusted life year (QALY) gained and equal-value life year (evLY) gained from both perspectives at their current price set by government negotiation or the generic marketplace. Results were particularly sensitive to assumptions regarding the relative effectiveness of the intervention and the background rate of hospitalization within the common usual care comparator arm. Table 3 reports health-benefit price benchmarks for each treatment from the base-case health care sector perspective and the scenario modified societal perspective. The current treatment course price listed is based on government negotiation or the generic marketplace; the pricing and value considerations for these treatments will shortly transition to the private market.

These treatments also have important potential benefits that may not be fully captured or evaluated in the economic model, including the potential for preventing further spread of SARS-CoV-2. We modeled quantitatively the potential impact on improving hospital intensive care unit (ICU) capacity but, in addition, effective outpatient treatments may help address the disparate burden of the pandemic in disadvantaged communities and help provide psychological reassurance, allowing for broader opening of schools and workplaces. There are also important relative disadvantages of each drug when considered against other options. These disadvantages are described in Section 5 of the Final Evidence Report.

In conclusion, assessment of the evidence on outpatient treatments for COVID-19 must be viewed as highly sensitive to the evolving landscape of COVID-19 variants and vaccination status in the US. The available data come from single pivotal trials, all conducted in settings not reflective of the health care patterns and the background risk of progression to severe disease occurring in the current Omicron wave of infections in the US. With these limitations in mind, current evidence does suggest that the drugs of interest reduce hospitalizations among patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease. Numbers of deaths in the pivotal trials are too small to draw firm conclusions. There are no short-term data suggesting serious concerns for side effects of these drugs when limited to the populations for which they are indicated. And at their current negotiated price (molnupiravir and Paxlovid) or their generic market price (fluvoxamine), these drugs appear—at this time—to have prices reasonably aligned with patient benefits. To the degree that hospitalization from mild-moderate COVID-19 is reduced with the Omicron (or future) variant, and to the degree these treatments are used in lower-risk populations, including patients with full vaccination, their cost effectiveness would be reduced.

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Table 3. Perspective: Health Care Sector, Health-Benefit Price Benchmarks for Outpatient Treatments for COVID-19

Treatment*	Treatment Course Price	Treatment Course Price at $50,000/ QALY	Treatment Course Price at $100,000/ QALY	Treatment Course Price at $150,000/ QALY
Molnupiravir	$707	$560	$1,200	$1,900
Paxlovid	$529	$1,660	$3,600	$3,600
Fluvoxamine	$12	$600	$1,300	$2,000

Treatment*	Treatnent Course Price	Treatment Course Price at $50,000/ evLYG	Treatment Course Price at $100,000/ evLYG	Treatment Course Price at $150,000/ evLYG
Molnupiravir	$707	$590	$1,300	$2,000
Paxlovid	$529	$1,750	$3,800	$5,800
Fluvoxamine	$12	$630	$1,400	$2,100

evLYG: equal value of life years gained, QALY: quality-adjusted life year

*We advise against comparing between interventions given the systematic differences in the trial populations and design.

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Table 3 Continued. Perspective: Modified Societal, Health-Benefit Price Benchmarks for Outpatient Treatments for COVID-19

Treatment*	Treatment Course Price	Treatment Course Price at $50,000/ QALY	Treatment Course Price at $100,000/ QALY	Treatment Course Price at $150,000/ QALY
Molnupiravir	$707	$830	$2,200	$3,600
Paxlovid	$529	$2,400	$6,500	$10,600
Fluvoxamine	$12	$880	$2,400	$3,800

Treatment*	Treatment Course Price	Treatment Course Price at $50,000/ evLYG	Treatment Course Price at $100,000/ evLYG	Treatment Course Price at $150,000/ evLYG
Molnupiravir	$707	$890	$2,300	$3,800
Paxlovid	$529	$2,600	$6,900	$11,100
Fluvoxamine	$12	$950	$2,500	$4,000

evLYG: equal value of life years gained, QALY: quality-adjusted life year

*We advise against comparing between interventions given the systematic differences in the trial populations and design.

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POTENTIAL BUDGET IMPACT

A potential budget impact analysis was not conducted for this Special Assessment. Due to the narrow margins of cost and survival benefit, a potential budget impact analysis was not considered policy relevant.

Public Meeting Deliberations

VOTING RESULTS

Voting on Clinical Effectiveness and Contextual Considerations

- A majority (11-2) found current evidence is **not adequate** to demonstrate a net health benefit when molnupiravir is compared to symptomatic care alone.
- All panelists (13-0) found that current evidence is **adequate** to demonstrate a net health benefit when Paxlovid is compared to symptomatic care alone.
- A slight majority (7-6) found that current evidence is **adequate** to demonstrate a net health benefit when fluvoxamine is compared to symptomatic care alone.

During their deliberations, panel members also weighed the therapies' other potential benefits, disadvantages, and contextual considerations. Voting highlighted the following as particularly important for payers and other policymakers to note:

- Effective outpatient treatments for mild-moderate COVID-19 may help reduce population spread of COVID-19.
- Effective outpatient treatments for mild-moderate COVID-19 may reduce the number of hospitalized patients enough to increase capacity to treat non-COVID-19-related conditions.
- Effective outpatient treatments for mild-moderate COVID-19 will help address the disparate burden of the pandemic in disadvantaged communities.
- Effective outpatient treatments for mild-moderate COVID-19 may help provide psychological reassurance allowing for broader opening of schools and workplaces.
- Molnupiravir cannot be used in people who are attempting to conceive or who are pregnant.
- Paxlovid has many drug-drug interactions that may limit the number of patients who can use it.
- Fluvoxamine affects a different phase in COVID-19 pathophysiology and therefore it may be possible to combine its use with other agents.

After reviewing the clinical evidence and considering the treatments' other potential benefits, disadvantages, and contextual considerations noted above, the Midwest CEPAC evaluated the long-term value for these treatments. All three treatments had prices that fell below the level of ICER's health benefit price benchmarks derived from cost-effectiveness modeling:

- Due to uncertainty in the net health benefit for molnupiravir, a majority of panelists voted that it represents "low-to-intermediate" long-term value for money.
- A majority of panelists found that Paxlovid represents "high" long-term value for money.
- A majority of panelists found that fluvoxamine represents "intermediate-to-high" long-term value for money.

About ICER

The Institute for Clinical and Economic Review (ICER) is an independent nonprofit research institute that produces reports analyzing the evidence on the effectiveness and value of drugs and other medical services. ICER's reports include evidence-based calculations of prices for new drugs that accurately reflect the degree of improvement expected in long-term patient outcomes, while also highlighting price levels that might contribute to unaffordable short-term cost growth for the overall health care system.

ICER's reports incorporate extensive input from all stakeholders and are the subject of public hearings through three core programs: the California Technology Assessment Forum (CTAF), the Midwest Comparative Effectiveness Public Advisory Council (Midwest CEPAC) and the New England Comparative Effectiveness Public Advisory Council (New England CEPAC). These independent panels review ICER's reports at public meetings to deliberate on the evidence and develop recommendations for how patients, clinicians, insurers, and policymakers can improve the quality and value of health care.

For more information about ICER, please visit ICER's website (www.icer.org).