MSF Access Campaign

Access Challenges to COVID-19 Therapeutic Candidates

Briefing Document

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Contents

INTRODUCTION

The current global pandemic of COVID-19, caused by infection with the novel coronavirus SARS-CoV-2, poses an unprecedented global health challenge. There are no proven effective cures or vaccines to date. More than 70 therapeutic candidates are in different stages of clinical trials. The World Health Organization (WHO) launched the international Solidarity Trial on selected therapeutic candidates. Once safety and efficacy of any of the candidate therapeutics are demonstrated, ensuring access to the effective therapeutics for all people will be an immediate challenge facing all countries. To ensure universal access to effective COVID-19 medicines in a timely manner, massive production and sufficient supply of quality-assured medicines, and equitable allocation based on public health needs, will be required at both international and national levels.

This briefing document aims to provide an up-to-date analysis of the main access challenges associated with selected priority therapeutic candidates for COVID-19 treatment. For each candidate, key information including medical attributes, patents and other exclusivity rights, supply situation, and pricing are provided. A colour-coded summary table indicates levels of supply constraints. All information is collected from publicly available sources and analysed independently by MSF Access Campaign. The choice of the selected priority candidates and the related information will be updated regularly (please refer to last updated date at top of document).

This briefing document offers only a shortlist of candidate therapeutics; a number of other medicines are also under evaluation in numerous clinical trials around the world.

OVERCOMING EXCLUSIVITY BARRIERS TO COVID-19 THERAPEUTICS

Multiple barriers may hinder rapid and ample production and sufficient supply of effective and affordable therapeutics. At the centre is the use of intellectual property (IP) and other exclusivities to restrict manufacturing and supply options, delaying competition that would lower drug prices and increase patient access. Market dominance including monopolies

held by pharmaceutical corporations through patents and other types of IP and regulatory exclusivities may prevent other manufacturers from increasing global manufacturing capacity. These exclusivities may also enable companies to charge high prices and profiteer from the pandemic or prioritise wealthier countries over ones with less financial capacity. Also, the absence of platforms for open sharing and the right to use of know-how, data and IP can impact technology transfer and access to critical technologies, and may further delay the development and eventual regulatory approval of affordable generic or biosimilar products.

Patents

Patents are territorial rights granted by national government agencies allowing for a maximum 20-year monopoly for the patent holder. However, in some countries, this monopoly could be further extended beyond 20 years through patent terms extensions and other exclusivities. Once granted, a patent can exclude anyone from using, producing and selling the concerned product without the permission of the patent holder. Companies often apply for multiple patents on the same medicine to prolong the market monopoly – known as "patent evergreening". They can also apply for patents on additional medical indications of a repurposed medicine. Companies could engage in secret bilateral voluntary licensing of its IP and technology to specific manufacturers while excluding others despite the potential need to ramp up global production. Transparency and accountability are lacking with respect to their actions or license agreements, in particular whether they are aligned with global public health needs and inclusion of all countries or not.

Data and Market Exclusivity

In addition to patents, companies may also apply for or may receive exclusive rights during the regulatory process, including but not limited to data exclusivity and market exclusivity associated with orphan drug status of the medicine. Data exclusivity prohibits regulatory agencies (within a fixed period of time, and when reviewing registration dossiers submitted by generic or biosimilar producers) from registering generic or biosimilar medicines even if they do not directly rely on the test data submitted by the originator company. In some countries, regulators will refuse to review dossiers of generic-drug companies without data from the originator company being submitted first, which some companies are reluctant to do in low- and middle-income countries that are not part of their commercial markets. Moreover, some countries allow for data exclusivity for a new medical indication for an old repurposed medicine. Market exclusivity associated with orphan drug status and other designations prevent any alternative producers from supplying the concerned medicine for a certain period of time. Both data exclusivity and market exclusivity provide additional monopoly power alongside patents and may delay product competition and availability of affordable generic formulations of a medicine, even after the 20-year term of the patent is over.

Policy and Legal Safeguards

To overcome barriers of market dominance and access to patented health technologies and products needed for COVID-19 treatments, countries can make use of a range of public health safeguards enshrined in international law. In particular, flexibilities are contained in the World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and the Doha Declaration on the TRIPS Agreement and Public Health. Important measures that can be adapted at national, regional and international levels include but are not limited to:

- Suspending the application and enforcement of patents and other IP on essential health technologies, materials and products concerning COVID-19.
- Issuing compulsory licenses or government-use licenses to allow local production, importation and exportation of patented medical tools within a defined period of time, including exploring a regional approach to compulsory licensing to facilitate international collaboration and adapting expedited procedures to allow fast-track compulsory licenses.
- Adapting strict patentability criteria by excluding second medical uses, new forms and derivatives of known medicines from being patentable; especially, second medical uses of old medicines should be considered as methods of treatment and be excluded from patentability.
- Suspending the application of data exclusivity and other market exclusivities (or providing waivers), if existing in national or regional laws, to enable rapid regulatory approval of generic and biosimilar products.

- Applying a 'Bolar exemption' that allows alternate manufacturers to undertake development and seek marketing and regulatory approval of generic and biosimilar versions of patented medicines even during the patent term.
- Suspending certain obligations under bilateral or regional trade and investment agreements that may constrain a country's ability to issue a compulsory license, undermine strict patent examination criteria, and facilitate data or other exclusivities on medicines
- Stop all free trade agreement (FTA) negotiations during the pandemic. If FTAs are negotiated, restrictive IP provisions that could hinder timely and affordable access to medical technologies must be excluded. Before engaging in bilateral FTA negotiations, it is important to assess the impact of the restrictive IP provisions that are likely to be tabled on access to affordable medicines including for COVID-19 treatment.

The global impact of the COVID-19 pandemic also presents challenges and limitations of relying only on national strategies to ensure an effective global response. In this regard, countries should explore effective international collaborations and binding agreements under the United Nations to facilitate open sharing of technologies, know-how, data, and global non-exclusive rights to use and produce COVID-19 medicines.

For more information of MSF positions and recommendations in this regard, please visit: https://msfaccess.org/covid-19-action

DRUGS/TREATMENTS:

Dexamethasone

Medical and Clinical Trials

On 16 June 2020, the University of Oxford released interim results of the dexamethasone arm of the RECOVERY trial, a multicenter randomised clinical trial evaluating different candidate therapeutics for COVID-19 in more than 175 National Health Service (NHS) hospitals in the United Kingdom (UK). These results were later published in the *New England of Journal of Medicine*.

The results from more than 6,000 patients show that dexamethasone – a corticosteroid that has been used to treat many diseases for decades and has been on the World Health Organization (WHO) Model Essential Medicines List (EML) since 1977 – can be lifesaving for some people with severe or critical COVID-19 disease. The results show that the drug can decrease the risk of dying by one third for critical patients on mechanical ventilation and by one fifth for people requiring supplemental oxygen but not on mechanical ventilation. In the event that dexamethasone is not available, the drug may be substituted with an appropriately adjusted dose of other corticosteroids.

MSF will provide dexamethasone, as used in the RECOVERY trial (or appropriately adjusted doses of other corticosteroid drugs), to treat people in our care with COVID-19. MSF recommends providing ivermectin to all people receiving corticosteroids for COVID-19 to prevent disseminated strongyloidiasis, an unusual but life-threatening parasitic disease that is a well-known complication of corticosteroid treatment – especially in areas where MSF works. Ivermectin is also being investigated as a promising repurposed drug for COVID-19, but MSF is waiting for further results from ongoing studies before making a final assessment of its effectiveness as a COVID-19 treatment.

Dexamethasone may also be useful as part of combination regimens including other potential antivirals (like remdesivir) or other host directed therapies (like interferon), which remains to be formally tested in trials.

It is important that corticosteroids are used rationally, under proper medical guidance and timed correctly. People who are asymptomatic or who have a mild form of the disease (people not requiring supplemental oxygen) may not benefit from the drug and it may even have negative consequences in these cases. Dexamethasone must not be used as a means of preventing COVID-19.

The drug comes in different formulations: tablets of various strengths, liquid, and a solution for injection (there are also inhaled formulations that have not yet been adequately tested for COVID-19).

At the end of July, the European Medicines Agency (EMA) announced they started to review dexamethasone as a treatment for COVID-19. The drug is already recommended for routine care in the US and UK, and some other countries have included it in their national protocols. WHO is also in the process of preparing formal guidance on the drug.

Patents

Dexamethasone is widely available, free of patents and produced by multiple generic producers around the world. This is also the case for other corticosteroids which may be used as a substitute for dexamethasone if the drug is not available.

Pricing

Dexamethasone is a low-cost drug. Price hikes – if or when demand surges – would not be acceptable and should be monitored and challenged by the global health community.

Supply

Shortages of dexamethasone should theoretically not be a concern given that it is off-patent, widely available and produced by multiple generic producers around the world. However, as COVID-19 cases surge, demand may eventually outweigh supply – especially if projected needs are not well understood, the global supply situation is not transparent, and if global production is not ramped up to sufficient capacity. The UK placed an export ban on dexamethasone the day after the positive clinical trials for the drug were announced. Dexamethasone must be treated as a global public good. It must be equitably allocated based on internationally agreed medical and ethical criteria for distribution of COVID-19 medical tools and not hoarded or controlled by individual countries. Frontline healthcare workers in direct contact with people affected with this virus are at high risk of infection, and the availability of dexamethasone for treatment of healthcare workers must be guaranteed.

WHO is evaluating the global supply situation and their Prequalification Program has recently opened an expression of interest for dexamethasone, inviting additional generic suppliers of both active pharmaceutical ingredients (API) and final formulations of the drug to submit their products for quality assurance evaluation.

On 2 July, UNITAID announced that an advanced purchase of quality-assured dexamethasone would be made under the umbrella of the WHO Access to COVID-19 Tools Accelerator (ACT-A) , with an aim to support 4.5 million patients in low- and middle-income countries. UNICEF, the Global Fund to Fight AIDS, Tuberculosis and Malaria and others will be able to procure from this advanced bulk purchase.

Remdesivir

Overview

Remdesivir, first manufactured by pharmaceutical corporation Gilead Sciences, is one of the antiviral drugs currently in clinical trials for the treatment of COVID-19. It is a new experimental COVID-19 drug, initially developed for Ebola. It has not been approved for any other indication (besides COVID-19) anywhere in the world. Gilead holds primary patents on the drug in more than 70 countries that may block generic entry until 2031.

Gilead has a poor track record for facilitating affordable and sustained access to lifesaving treatments. MSF has seen firsthand what Gilead's greed does to people with HIV and hepatitis C all over the world as the company's prices and intellectual property strategies keep lifesaving medicines out of reach, particularly in middle-income countries who have been systematically excluded from the scope of its voluntary licenses. The company's recent actions with remdesivir provide scant assurance that the company can be trusted to act in the public interest (see 'Patents and Licenses' and 'Pricing' below).

Gilead should announce now that it will not enforce its patents that it has applied for and obtained over the last few years. When prevented or restricted by patents and other exclusivity rights enforced by Gilead, generic production could be prevented for years. Early entry of generic production is vital to secure alternative suppliers and increase global production capacity of the drug available to supply all countries around the world. There are concerns that Gilead's decision to keep full control over remdesivir via exclusive intellectual property and secret licensing agreements with

generic producers will lead to insufficient manufacturing capacity to supply for global needs as well as unaffordable prices for resource-limited countries.

Medical and Clinical Trials

Remdesivir, an antiviral drug that requires cold chain and must be given via intravenous route, was originally developed to treat Ebola virus but without positive results. In vitro studies against SARS-CoV-2, the virus that causes COVID-19, showed potent antiviral action. Preliminary results from a multi-country phase III randomised clinical trial have been published. This study included 1,063 hospitalised patients with severe COVID-19 and showed statistical evidence for a shorter time to recovery among those who received remdesivir (from 15 to 11 days), although there was no clear evidence of a survival benefit for the whole group (a subgroup analysis showed a potential survival benefit for patients requiring supplemental oxygen but not mechanical ventilation).

Additional studies have been published, including a clinical trial that didn't find any difference between a 5- and 10-day long treatment course, and a press release from Gilead with preliminary results from a trial among moderate cases showing that 5 days (but not 10 days) of remdesivir shortens the time to improvement as compared to those who did not receive the drug. While the drug still may be promising in certain populations, particularly if started earlier in the course of disease or in combination with other therapeutics, at this point it cannot be considered a game changer.

More recent results from an observational study presented at the 2020 International AIDS Conference and published in *Clinical Infectious Diseases* show that remdesivir has the potential to decrease the risk of dying for people with low levels of oxygen who are not on mechanical ventilation. Also, additional data presented regarding children showed a safety profile similar to adults.

Approvals of Gilead's remdesivir by regulatory agencies, in chronological order:

- US, 1 May 2020: The drug received approval for emergency use from the US Food and Drug Administration (US FDA) with the requirement that the US government control distribution and allocation within the US.
- Europe: The European Medicines Agency (EMA) has a rolling review of remdesivir, which includes a benefit-risk analysis, and the EMA has recommended expanding the compassionate use programme to patients not yet requiring ventilation, and to use a five-day course of treatment, based on available clinical trial data.
- Japan, 7 May 2020: The Japanese regulatory agency granted exceptional approval for remdesivir to be used for the treatment of severe COVID-19.
- UK, 26 May 2020: Remdesivir was approved by the UK regulatory agency for limited use to patients meeting certain criteria.
- Taiwan, 30 May 2020: The regulatory authority of Taiwan announced its approval of the drug.
- India, 2 June 2020, newspapers reported that India's regulatory authority had allowed restricted emergency use of remdesivir for severe patients.
- South Korea, 3 June 2020: South Korea announced approval of remdesivir for emergency use.
- Singapore, 11 June 2020: Singapore announced conditional approval.
- Europe, 3 July 2020: The EMA granted conditional marketing authorisation for use in adolescents and adults (12 years and older) with COVID-19 and requiring supplemental oxygen.
- US, 10 August 2020: Gilead submitted a New Drug Application to the US FDA for full approval of remdesivir.

Remdesivir is being tested as part of the ongoing World Health Organization (WHO)-sponsored multi-country randomised clinical trial ('SOLIDARITY') that launched in March 2020, as well as in other clinical trials in China, US and Europe.

Patents and Licenses

The primary patent on the base compound of remdesivir has been granted to Gilead in more than 70 countries, which, if enforced, will block the entry of generic producers until 2031. These patents set Gilead up to control the production and supply, and charge whatever they want during this global health crisis and for years to come. Gilead has also applied for secondary patents covering the use of remdesivir for the treatment of other coronaviruses (SARS, MERS) in many countries.

Despite the announcement of public health emergency declarations across the US since the end of February 2020, Gilead still sought an orphan drug designation from the US FDA on remdesivir that would have allowed for even longer monopoly control over the 20-year patents it had already filed. Gilead only gave up this special designation in late March following intense criticism from civil society groups and MSF. Gilead has yet to commit to not enforcing its patents globally despite an open request by more than 150 civil society organisations, including MSF, and individuals around the world.

If remdesivir is found to be effective and is approved, Gilead should not be allowed to enforce its patents nor claim any other types of exclusivities over remdesivir. No company should profiteer off this pandemic.

Several generic companies in China (BrightGene, CobenPharm, Hainan Haiyao, Sichuan Kelun, Hunan Warran), one Taiwanese research institute (National Health Institute) and one generic company in Bangladesh (Beximco) have announced that they already have the capacity to produce remdesivir, and some have proceeded to test their production of the active pharmaceutical ingredients and finished product.

However, Gilead has secretly negotiated and signed voluntary licenses with generic companies from Egypt, India and Pakistan, as the corporation has done in the past with HIV and hepatitis C medicines. On 12 May 2020, Gilead announced that it had entered into agreements with five generic manufacturers in India and Pakistan that can market generic versions of the drug in 116 countries and 11 territories, not 127 countries as announced by the company. On 13 June 2020, two more companies based in India and one in Egypt were added to the license. The licenses, however, exclude nearly half of the world's population[1], including most South American countries and a number of middle-income countries that have considerable manufacturing capacity, such as Brazil and Russia, where coronavirus cases are surging, and China, where the first coronavirus epicenter was located and a country that supported the first phase III clinical trials of remdesivir (which failed to show a benefit but was terminated early due to insufficient enrolment after outbreak control). Negotiated in the dark, there is no transparency around the terms and conditions of the agreements, including whether or not they are aligned with public health needs.

MSF has witnessed first-hand the impact that Gilead's corporate polices have had on people with hepatitis C. Gilead notoriously set the price for a hepatitis C treatment at an exorbitant US$1,000 per pill in 2013 in the US. Gilead then negotiated bilateral voluntary licenses with Indian manufacturing companies that excluded high- and middle-income countries like Brazil and China from receiving generic supply, leaving these countries to negotiate directly with the company, largely in secret, and having to pay higher prices.

The precedent set by Gilead should alert Member States and WHO that we cannot rely on the voluntary actions of companies in this pandemic and we must adopt binding measures to ensure global access to COVID-19 medical tools.

In addition, if required in the interest of public health, countries must make use of legal tools like 'compulsory licenses' to override patents during this pandemic and access the drug in the quantities needed. Already, Brazil, Canada, Chile, Ecuador, Germany and Hungary have taken steps to facilitate issuing of compulsory licenses for COVID-19 medicines, vaccines and other medical tools. Similarly, Israel issued a compulsory license for patents on another medicine they were investigating for COVID-19. On 4 August 2020, more than 30 state attorneys general in the US sent a joint letter to the US Department of Health and Human Services, the National Institutes of Health, and the FDA requesting that Gilead's monopoly on remdesivir be removed.

Pricing

On 29 June 2020 Gilead announced that remdesivir will be priced at US$2,340 for a five-day treatment course for most countries in their "commercial" market, and higher in the US, at US$3,120 per treatment. This price has drawn criticism for being too high, especially since a recent pricing study estimated the manufacturing cost of remdesivir to be less than US$9 for a five-day treatment course, suggesting that this potential COVID-19 treatment could be made available to all at an affordable price during this pandemic.

[1] Countries and regions excluded from the license include: Albania, American Samoa, Argentina, Bolivia, Bosnia-Herzegovina, Brazil, Bulgaria, Chile, China, Colombia, Congo, Ecuador, Gaza and the West Bank, Iran, Iraq, Jordan, Kosovo, Lebanon, Macedonia, Malaysia, Mexico, Montenegro, Paraguay, Peru, Romania, Russia, Serbia, Syria, Turkey, Uruguay, Venezuela, and Yemen.

Several generic licensees (Cipla, Mylan, Hetero, Jubilant and Zydus Cadila) that have signed with Gilead have now registered in India and started to produce generic remdesivir with prices varying from US$37.50 to US$72 per vial. However, their capacity to supply to low- and middle-income countries included in the territory of the license remains unknown.

Public Funding and Contributions

The R&D of remdesivir is the result of a massive collective effort, involving many actors and multiple public resources. Remdesivir was developed with considerable public funding, mainly from the US government. Millions of taxpayer dollars have been invested by different US public agencies including the US Department of Defense, Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and National Institute of Allergy and Infectious Diseases (NIAID) towards the development of remdesivir. US-based non-profit organisation Public Citizen estimates that taxpayers have contributed more than US$70.5 million to the development of remdesivir so far.

Public health authorities and regulatory bodies in many other countries have also supported the ongoing clinical trials. People with COVID-19 and healthcare workers are indispensable contributors, as the clinical trials would not be possible without them. It is unacceptable for remdesivir to be put under one company's exclusive control, especially considering that the drug was developed with considerable public funding for both early-stage research and clinical trials, and due to the extraordinary efforts and personal risks healthcare workers and patients have faced using the medicine in clinical trial settings. If its efficacy is demonstrated, patents on remdesivir should be overridden so that the drug can be affordable to everyone.

Supply

The US Department of Human Health and Services announced 29 June 2020 that it had secured half a million treatment courses of remdesivir, including 100% of Gilead's production for July, and 90% for August and September. Plans for Gilead to prioritise supply to the US beyond September are unclear. Given that the secret licenses Gilead signed with generic companies to produce generic versions of remdesivir leave out nearly half of the world's population (see the 'patents and licenses' section above), the US announcement means that there is very little or even no supply for any of the other countries in need of remdesivir where Gilead is supposed to provide. Furthermore, generic development and scale-up of production will take time and Gilead does not have any plan to sufficiently supply low- and middle-income countries' markets during this interim period while generics are coming on board. The European Union and UK have also since secured a small amount of supply from Gilead, paying US$74 million for 30,000 treatments to be supplied starting in August. The supply of medical tools for COVID-19 should be allocated equitably, based on public health needs, regardless of ability to pay high prices.

The corporation stated that it takes six months to produce remdesivir, and that they aim to produce more than 500,000 treatment courses by October 2020, and more than one million treatment courses by the end of 2020.

Following the emergency use authorisation by the US FDA, Gilead reported that a "donation" to the US government had concluded and that the allocation of 607,000 vials of remdesivir for the US had begun. It was unclear at that time how allocation to other countries would be determined. US media reported that the government's last shipment of the drug went out the week of 29 June.

The corporation stated that they have repurposed some of their own manufacturing facilities to focus on the drug and are collaborating with contract manufacturers, increasing their "network of external manufacturing partners around the world," and "building a geographically diverse consortium of pharmaceutical and chemical manufacturers to expand global capacity for raw materials and production." On 12 August 2020, two additional secret deals with Gilead were announced, this time with Pfizer (US) and Hikma Pharmaceuticals (UK), who will serve as contract manufacturers for remdesivir, with manufacturing sites in the US and Portugal, respectively. These contract manufacturers are part of a network Gilead has built to increase their manufacturing capacity, which they say will produce 2 million treatment courses by the end of 2020.

Gilead should make the data required for regulatory purposes on remdesivir publicly available and share samples of the drug as required so that more manufacturers can produce remdesivir to ensure sustainable and timely supply worldwide.

The capacity of the generic licensees that have signed with Gilead (Cipla, Mylan, Hetero, Jubilant and Zydus Cadila) to supply to low- and middle-income countries included in the territory of the license remains unknown.

Ensuring supply for low-resource settings and healthcare workers:

High-income countries must avoid overstocking or hoarding remdesivir, as this may limit its access in low-resource settings. Instead, a global coordination mechanism, led by the WHO, should be established to ensure that remdesivir is allocated based on public health and outbreak control needs, not the ability to pay high prices or the capacity to manufacture in-country.

If remdesivir is proven safe and effective, a network of manufacturers in different countries, including low- and middle-income countries, must be established and prepared for a rapid scale-up of supply. WHO and UN agencies should lead and coordinate an emergency preparedness and response mechanism to safeguard supplies to countries with weaker health systems and insufficient in-country manufacturing capacity.

Frontline healthcare workers in direct contact with people affected with this virus are at high risk. The availability of remdesivir for treatment of frontline healthcare workers must be guaranteed.

Tocilizumab

Overview

Roche and its subsidiary Genentech are the only global suppliers of tocilizumab, one of several potential treatments in the pipeline for COVID-19. The drug is being used in several countries for people with severe and critical cases of COVID-19, including in China, Italy, Spain and the US. The drug has been off-patent since 2017, but biosimilars are still under development.

To scale up production and ensure access, Roche/Genentech must disclose its manufacturing capacity and existing inventory and share its know-how, data and master cell line with any monoclonal antibody manufacturer, including existing developers of biosimilars of tocilizumab. Multiple sources of tocilizumab are needed to increase manufacturing capacity and decrease product price.

Medical and Clinical Trials

Tocilizumab is a monoclonal antibody therapy approved for the treatment of rheumatoid arthritis and the severe immune overreaction ('cytokine storm') caused by modern cancer treatments. The drug does not have any direct antiviral activity. Severe COVID-19 is characterised by a cytokine storm, which results in severe lung disease (acute respiratory distress syndrome [ARDS]). Tocilizumab may reverse the cytokine storm and ARDS not by direct action against the virus but by blocking interleukin-6 (IL-6), a substance produced by the body that boosts this exaggerated inflammatory response. Administered intravenously or subcutaneously, tocilizumab can be used in a single dose, and repeated one or two times if necessary.

Although the drug remains unapproved for the treatment of COVID-19, many cases have been treated off-label in different countries, with anecdotal reports and press releases showing promising results. While a few observational cohort or single arm trial studies in Europe and the US have provided some evidence suggesting that tocilizumab may be useful for severe or critical patients, two randomised clinical trials recently showed no impact for patients with severe pneumonia, raising doubts about the drug's effectiveness for COVID-19. More recent observational studies suggest that the combination of tocilizumab with a corticosteroid may be superior to treating with a single drug. Definitive results from randomised clinical trials studying combinations are eagerly awaited. Trials looking at tocilizumab for people with more advanced COVID-19 disease are also ongoing. The UK RECOVERY trial, which brought important evidence regarding the positive impact of dexamethasone and the lack of impact for hydroxychloroquine, is currently evaluating tocilizumab.

In addition, a similar product, monoclonal antibody therapy sarilumab (Kevzara, manufactured by Sanofi/Regeneron), is being tested in a clinical trial in the US and Italy. Interim negative results for a trial focusing on severe and critical patients, however, have dampened optimism around IL-6 focused therapies. Further trial results are needed before

definitive conclusions can be made. Other host-targeted medications, including monoclonal antibodies, that work to alleviate the cytokine storm are being trialled as well.

Patents

The primary patent on tocilizumab expired in 2017. Several biosimilars are under development, but none have been approved by a regulatory authority, meaning that despite being off-patent, Roche/Genentech continue to have de facto market exclusivity on the drug. Secondary patents on the drug, and other types of market exclusivities, are also of concern, and may hinder access to this potentially key COVID-19 treatment.

Pricing

A single vial (400mg/20mL) of tocilizumab is needed to treat a person with COVID-19. The price of one vial of tocilizumab (400mg/20mL) produced by Roche/Genetech is between US$400-800 in middle-income countries. In India, while the public sector's clinical management guidelines do not include the drug, tocilizumab is being prescribed in private sector hospitals to severe COVID-19 patients with cytokine-release syndrome (CRS) for over 60,000 Indian rupees (US$794) per vial. This high price creates a discriminatory system where only those who can afford the drug can get access through Roche's distributor Cipla, leaving many people empty handed. The price may be higher in high-income countries. The costs to manufacture tocilizumab could be estimated to be as low as US$40, given that the manufacturing costs of monoclonal antibodies are often below US$100 per gram when produced on a large-scale. Roche/Genentech should agree to sell tocilizumab for COVID-19 at a much more affordable price than they currently do.

Supply

The demand for tocilizumab is expected to be high, should its efficacy be demonstrated, with concerns that Roche/Genentech are unable to produce sufficient quantities of the drug to meet demand. Shortages were reported in India and Ecuador, among other countries. Roche/Genentech have donated vials of the drug to China, Italy, and Spain. The US Strategic National Stockpile acquired 10,000 doses on 23 March 2020, thus worsening the shortage crisis. On 28 March 2020, China announced it would donate 3,000 doses to Italy.

On supply and manufacturing, Roche/Genentech should take the following actions:

1. Disclose transparently its manufacturing capacity and existing inventory, and urgently scale up production.
2. Collaborate with additional manufacturers in high- and middle-income countries to quickly increase production in the short term.
3. Make publicly available its know-how, manufacturing secrets and master cell lines required to make the drug, so that manufacturers across the world can produce tocilizumab.

The development of biosimilars must also be expedited. There are several biosimilar candidates under development (in China, India, Switzerland, and Iran). They are not all at the same stage of development – some are at an advanced stage, but none have been approved. While these biosimilars were initially developed for rheumatoid arthritis, their repurposing for COVID-19 should be considered. Iran recently announced that its biosimilar version of tocilizumab is undergoing trials for COVID-19 and that its production can be scaled up. Roche/Genentech should facilitate access to its know-how and master cell lines, so that more manufacturers are able to produce tocilizumab, and competition can bring down prices and increase patient access.

Favipiravir

Medical

Favipiravir, produced by Fujifilm in Japan (originator manufacturer, brand name Avigan) and Hisun in China (generic manufacturer), is an oral antiviral drug used for years in Japan and other countries for influenza. It was tested against Ebola without positive results. Favipiravir has weak in vitro activity against SARS-CoV-2 and is currently recommended as an option for COVID-19 in Japanese guidelines. Studies so far have shown contradictory evidence and its potential role in treating COVID-19, if any, remains to be demonstrated in a proper powered randomised clinical trial. There are concerns of teratogenicity, which has been seen in animal species studied: both female and male patients treated with favipiravir

should be asked to implement strict contraception up to seven days after treatment. There are several generic companies in India working on this product including Aurobindo, Cipla, Mylan and Dr Reddy's Lab.

Patents

The primary patent for favipiravir expired in 2019.

Pricing

Fujifilm sells favipiravir at around US$3 per tablet. The price of a full treatment course (assuming a dosage of 600mg twice a day for 14 days) is therefore US$252. According to a recent pricing study, the manufacturing costs of a full treatment course may be as low as US$20, suggesting that this potential COVID-19 treatment could be made available to all at an affordable price during this pandemic.

Supply

Hisun's generic version of favipiravir has been approved by the Chinese FDA for the treatment of influenza and is being used off-label for COVID-19. The company is undertaking supplementary studies to register the drug for the new indication of COVID-19. Registration information in other countries is pending.

Manufacturers in India and Bangladesh have recently announced that they expect to be able to manufacture generic favipiravir. On 21 June 2020, Glenmark Pharmaceuticals received approval for production and sales of favipiravir in India.

Fujifilm have stocks of the drug and capacity to increase production. The drug is registered in Japan for the treatment of influenza. MSF could use the drug under 'compassionate use' or clinical trial conditions. Fujifilm is cautious about which countries they send the drug to, and they need to ensure it is not used in pregnant women. The Japanese government appears willing to collaborate with other countries to conduct clinical trials and increase production. The Japanese government has received about 50 requests from other governments and has since arranged for a donation, the logistics of which will be managed by United Nations Office for Project Services (UNOPS), to allocate the drug among countries in alignment with guidance for use by WHO.

SUMMARY TABLE

Access issues for selected candidate therapeutics for COVID-19*

Colour code:

- Green: Sufficient
- Yellow: Of concern
- Red: Critical (lacking access guarantees)

Drug	Price (USD)	Supply & Capacity	Intellectual Property Barriers	Regulatory Challenges
Dexamethasone	<$15 per treatment	Widely available and produced by generic companies Countries should refrain from hoarding and/or restricting export of dexamethasone to ensure global allocation and access	No longer patented	Registered globally for various treatment indications
Remdesivir (RDV) vials	Gilead's price: $2,340 for 5 days treatment ($3,120 in US). Generic prices: $225-432 for 5 days treatment Estimated cost to manufacture as low as $0.93 per day, $9 per treatment	Gilead donated >140,000 treatment courses of RDV to US, said they will produce 1 million treatment courses by end 2020. US government has been prioritised for vast majority of Gilead's supply until September 2020. Supply constraints beyond that time are unclear. Multiple generic manufacturers developing and scaling up RDV supply.	Gilead filed patents in >70 countries until 2031 Concluded negotiations for voluntary licensing with several generic companies in India, Egypt and Pakistan to supply 116 countries and 11 territories; excluded most Latin American countries, China, Russia, and Malaysia, among other LMICs	Approvals: • US: emergency use • EU: conditional use, certain criteria • Japan: severe cases • UK: limited use, certain criteria • Taiwan: severe cases • India: emergency use for severe cases • South Korea: emergency use • Singapore: conditional use
Tocilizumab, 400mg/20ml vials	Estimated cost to manufacture unknown Potentially <$40 for a 400mg vial, given cost of <$100 per g for same product category Priced at $400-800 per 400mg vial in MICs	Limited supply available from Roche/Genentech (sole supplier) No biosimilar yet approved but several in development	Primary patents expired Secondary patents may block biosimilar use in some countries	Approved for use in rheumatoid arthritis and cytokine storm associated with cancer therapy Regulatory approval for new indication may lead to new exclusivities for a limited period of time in some countries
Favipiravir (FPV) tablets	Estimated cost to manufacture as low as $1.45 per	Japan stockpiling enough for 2 million treatments	No longer patented Secondary patent for indication of COVID-19	Approved in Japan for influenza

	day, $20 per treatment Price from FujiFilm is $3 per tablet, $252 per treatment	Company increasing production to 100,000 treatments (14 days) by July 2020 and 300,000 by Sept 2020 20-100 treatments per country being supplied to about 50 countries via UNOPS One generic supplier in China and multiple in development in India	may be problematic in some countries	Regulatory approval for new indication may lead to new exclusivities for a limited period of time in some countries

LMIC = low- or middle-income country; MIC = middle-income country; UNOPS = United Nations Office for Project Services

*Disclaimer: The drugs selected here for analysis are in various stages of clinical trials. The information provided is being updated on a regular basis but may not be completely up to date due to rapid developments. Please refer to the last updated date at the beginning of the document.