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Expanded Access Programs, compassionate drug use, and Emergency Use Authorizations during the COVID-19 pandemic.

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The US Food and Drug Administration (FDA) Expanded Access (EA) Program, which allows for compassionate uses of unapproved therapeutics and diagnostics outside of clinical trials, has gained significant traction during the Coronavirus 2019 (COVID-19) pandemic. While development of vaccines has been the major focus, uncertainties around new vaccine safety and effectiveness have spawned interest in other pharmacological options. Experimental drugs can also be approved under the FDA Emergency Use Authorization (EUA) program, designed to combat infectious disease and other threats. Here, we review the US experience in 2020 with pharmacological EA and EUA approvals during the pandemic. We also provide a description of, and clinical rationale for, each of the EA- or EUA-approved drugs (e.g. remdesivir, convalescent plasma, propofol 2%, hydroxychloroquine, ruxolitinib, bamlanivimab, baricitinib, casirivimab plus imdevimab) during the pandemic and concluding reflections on the EA program and its potential future uses.

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has dramatically affected the global community and economy. In response to the pandemic, there has been great interest in developing novel therapies, including the use of repurposed drugs, to treat SARS-CoV-2. The quest for a vaccine through the unprecedented national Operation Warp Speed (OWS) effort has dominated the proposed COVID-19 mitigation process [1]. However, uncertainty surrounding the safety and effectiveness, as well as durability of protection, of a rapidly developed vaccine intervention has increased interest in pharmacological therapeutic options. Research into novel new therapeutics for the pandemic is underway. However, in addition, EA, or compassionate drug use of agents already approved for uses other than COVID-19, has gained significant attention [2]. EA describes the use of an investigational drug outside of a clinical investigation, and often requires a complex process of collaboration among governments, clinicians, and pharmaceutical companies [3]. Drugs used under EA have not been approved for their EA-intended use by the US Food and Drug Administration (FDA), the European Medicines Agency (EMA), or similar drug oversight and regulatory bodies [4]. Nonetheless, approved drugs can sometimes

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be used under EA, but not for the purpose(s) for which they were approved *a priori* [5]. Such use is commonly referred to as 'off-label' [5]. Off-label uses can already benefit from safety data from their approved uses. EA programs (EAP) can provide unavailable safety and efficacy data to the manufacturers and the scientific and regulatory organizations [6], although robust new evidence generation cannot always be ensured through EA approvals [7]. Thus, the adoption of such programs, while of significant importance particularly during emergency situations, such as a pandemic, nonetheless requires additional scrutiny of safety and efficacy.

It is preferable for the FDA and others that the use of investigational drugs by patients occurs in the context of clinical investigations, such as randomized controlled trials (RCTs), because these can generate data that lead to marketing approval and greater availability of the product [8]. However, it is sometimes not possible for certain patients to enroll in clinical investigations. A patient might be ineligible for available ongoing clinical trials, or there might not be any clinical trials in process for particular products of interest [9]. In such circumstances, it might be possible for the patient to receive the investigational drug through EA. EAPs are operational not only in the USA, but also in other countries, such as Australia, Belgium, Canada, France, Germany, Italy, The Netherlands, Romania, Spain, Switzerland, and the UK [10].

EA versus Emergency Use Authorization

Expanded access differs from EUA [11]. EUAs are medical countermeasures used to combat chemical, biological, radiological, nuclear, and infectious disease threats, and are issued by the FDA during public health emergencies to facilitate access to drugs, diagnostic tests, or other essential medical products when there are no adequate, approved, and available options [12]. The FDA evaluates the options rapidly using the evidence that is available, and carefully weighs the potential benefits and risks [12]. Once the FDA believes that sufficient evidence exists for safe administration, the availability of a product transitions from an EA to an EUA, and enrollment in EAPs is usually stopped. Patients who do not qualify for access under the EUA (e.g., children, adolescents, or pregnant women) might still be able to access the product through an EAP. The FDA responded to the COVID-19 pandemic using these pathways to bring therapies to patients, and revised its decisions when appropriate for public health (Fig. 1). Table 1 presents a summary of the differences between EA and EUA.

EA criteria

EA is intended for patients with immediately life-threatening or serious illnesses who lack other therapeutic options, and who cannot participate in conventional clinical trials. It is not intended to obtain information about the safety or effectiveness of a drug [13]. Investigational drugs could be available to certain patients via EA on a case-by-case basis and, for each case, the FDA must determine that it meets the following criteria (21 CFR 312.305 (a)): (i) the patient(s) to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat

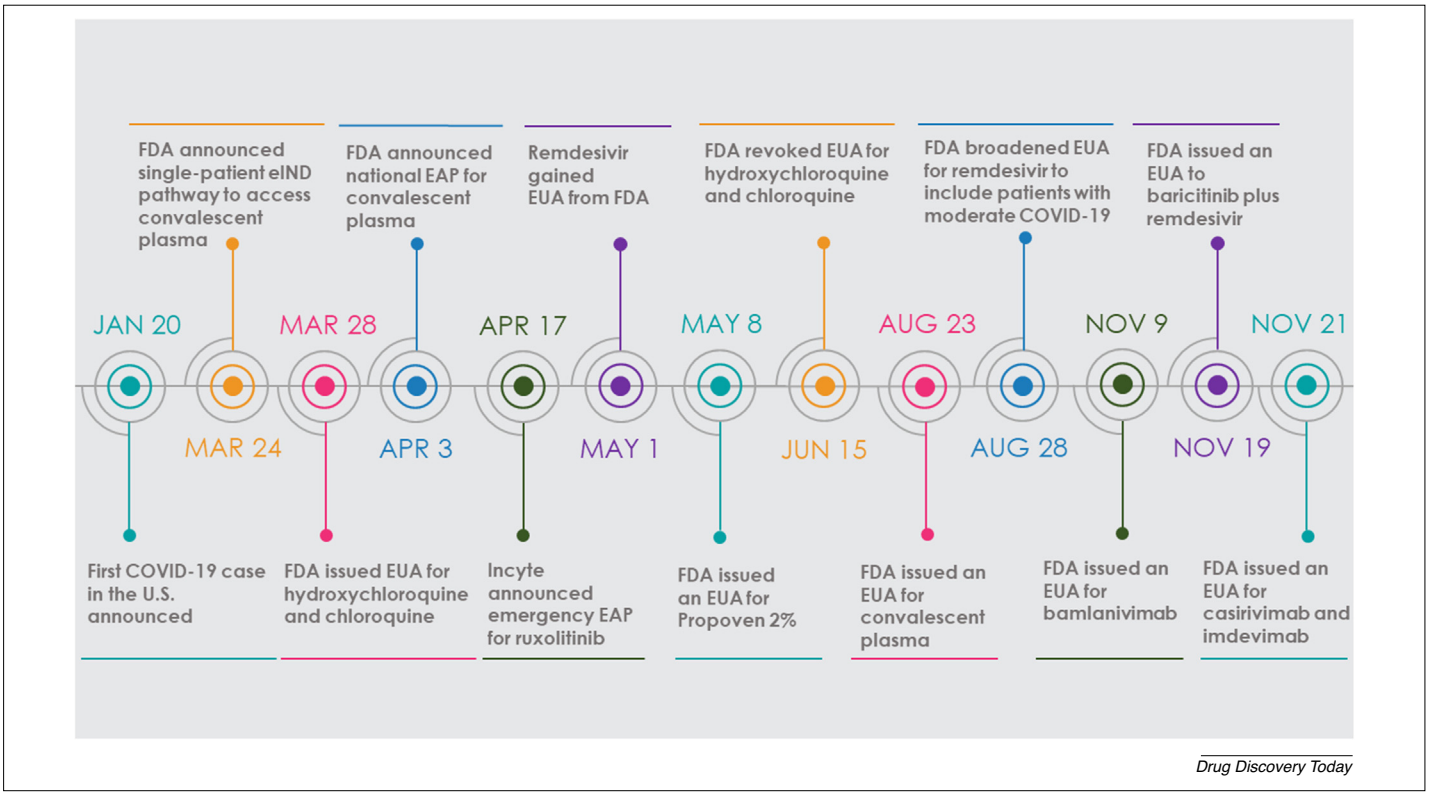

FIGURE 1

Expanded Access Program (EAP) and Emergency Use Authorization (EUA) announcements and initiation over the duration of the Coronavirus 2019 (COVID-19) pandemic. Abbreviations: eIND emergency investigational new drug; FDA, Food and Drug Administration.

TABLE 1

EA versus EUA regulatory provisions[a]

Provision	Expanded Access Program	Emergency Use Authorization
Criteria	EAP is available to qualified registered treating physicians at registered sites for patients who meet inclusion and exclusion criteria and provide informed consent; product is considered investigational	EUA allows product to be distributed and used by licensed physicians to treat patients with serious or life-threatening COVID-19; use of product is part of the practice of medicine
Informed consent	Required	Required
SAE reporting requirements	Federal and IND requirement	Required by 21 CFR 606.170
Information about product	Available in EAP protocol, informed consent form, and investigator's brochure, and provided to treating physician	Provided in a Fact Sheet by FDA to clinicians and patients
FDA IND requirement	Required	Not required
IRB approval	Required	Not required

[a] Abbreviations: CFR, code of federal regulations; IRB, institutional review board.

the disease or condition; (ii) the potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and (iii) providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the EA use or otherwise compromise the potential development of the EA use.

An 'immediately life-threatening disease or condition' is a stage of a disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment (21 CFR 312.300). Examples include: patients critically ill with COVID-19 (i.e., requiring mechanical ventilation or high-flow oxygenation, or requiring treatment in an intensive care unit; ICU), amyotrophic lateral sclerosis (ALS), and some advanced stages of cancer. A 'serious disease or condition' has substantial impact on day-to-day functioning (21 CFR 312.300). The morbidity does not have to be irreversible, but must be persistent or recurrent. Examples include multiple myeloma and chronic asthma. This determination is a matter of clinical judgement and is based on its impact on factors such as survival, day-to-day function, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one (21 CFR 312.300).

Do all patients who meet the criteria qualify for EA?

Even though a patient with COVID-19 might meet all these criteria to qualify for EA, there is no guarantee that they will receive the drug because of other factors associated with the final decision [14]. These factors include: (i) a licensed physician must be willing to manage the investigational drug with the patient(s), and take on the role of the investigator for the EA application. Without this the EA process cannot proceed; and (ii) the drug manufacturer must be willing to give the patient(s) access to that drug.

Additional barriers

EAPs are not available in many countries, which creates an agonizing barrier to patients and families who need urgent access to novel therapies. This creates political, social, and medical urgency for governments and regulatory agencies to optimize and implement these programs [15]. Moreover, in the USA, the FDA cannot require the manufacturer to offer patients access to investigational drugs [16]. The manufacturer might not be able to give access to their investigational drug for various regulatory reasons. For example, a manufacturer might be concerned that EA would interfere with marketing and regulatory approval. Another potential barrier to access is that the drug might be limited in production availability and supply. In this case, companies can set stringent selection criteria to offer the drug to patients with the most serious or life-threatening conditions.

Reimbursement for the EA drug is a complex issue. Insurance companies typically do not reimburse for experimental or research drugs and patients might be required to pay out-of-pocket [4], unless special arrangements have been made in advance for research trials. Pharmaceutical companies can also pay for such experimental or compassionate therapeutic options as they would for clinical trials in some circumstances. In the case of government reimbursement, the Centers for Medicare and Medicaid Services (CMS) can create an agreement for reimbursement for promising therapeutics in exchange for clinical data collection called Coverage with Evidence Development (CED), or through a CMS Innovation Center grant arrangement [17]. Alternatively, in the case of an emergency such as the current pandemic, the federal government can directly pay for drugs or vaccines through Congressional approval or an Executive Order.

Types of EA

There are three different categories of EA: (i) individual patient (21 CFR 312.310), which includes emergency use and non-emergency use; (ii) intermediate-size patient population (21 CFR 312.315); and (iii) treatment–EA (21 CFR 312.320) for widespread treatment. For each of these categories of EA, either an access protocol or access Investigational New Drug (IND) application can be submitted [18,19]. An access protocol is a regulatory submission submitted as a protocol amendment to an existing IND, usually for patients who do not fit the inclusion criteria for the clinical trial. Access IND is separate from any existing INDs and is intended only to make a drug available for compassionate treatment use, not research. This is usually used when there is an existing IND in effect for which the sponsor chooses not to add new patients to that IND.

Individual patient access

If only one patient is to be treated, the EA would fall under an individual patient IND [13]. In the case of an emergency, where

treatment is required before a written submission can be filed, FDA might allow the request to be done via telephone, email, or other rapid communication method, provided that the physician explains how the EA will meet the requirements, and agrees to submit a written submission within 15 working days of the initial authorization of the EA use. The physician must determine that the probable risk to the patient is not greater than the probable risk from the disease or condition (21 CFR 312.310). In addition, the FDA must determine that the patient cannot obtain the drug under another IND or protocol. Treatment is generally limited to a single course of therapy and a specific duration, unless the FDA specifically authorizes multiple courses of therapy. Individual access requires that the FDA and drug manufacturer review each patient's case separately. When a significant number of individual patient INDs for EA have been made, the FDA can request that the sponsor submit an intermediate-size patient population access or protocol, or a treatment access IND or protocol [20]. Owing to the overwhelmingly increased demand for remdesivir, Gilead transitioned from individual access to intermediate-size and treatment-EA to facilitate and expedite the process [10]. A similar path was followed for convalescent plasma, which was initially available through a single patient emergency IND (eIND) [21].When the EA therapeutic is a novel drug, it would appear appropriate to require higher scrutiny for adverse effects and safety-related complications than might be needed for therapeutics already approved for other clinical indications. In addition, when the dosage of such an already approved medication is higher for EA use than typically used for approved indications, additional safety scrutiny should also be required.

Intermediate-size patient population access

Intermediate-size patient population access is used to obtain access to a drug under development, a drug not under development, or an approved or related drug that is not available through marketing channels [22]. Patients who are not eligible for a clinical trial (e.g., have an exclusion criteria) or do not have access to a clinical trial (e.g., geographically distant) are included in this category. In addition, this type of EA might be requested if the drug has already been approved for a specific disease but is no longer marketed for safety reasons, has failed to meet conditions for marketing approval, or is in short supply (e.g., drug shortage with a foreign version of the drug) [23]. There has to be sufficient evidence that the drug is safe at the proposed dose and duration to justify a clinical trial with the approximate number of patients expected to receive the drug under EA (21 CFR 312.315). Also, there needs to be preliminary evidence of the effectiveness or plausible beneficial pharmacological effect of the drug to use it as a reasonable therapeutic option in the anticipated patient population. In addition, it must be stated whether the drug is being developed. If the drug is not actively being developed, the sponsor needs to provide an explanation as to why the drug cannot currently be deployed for the EA use, and under what circumstances the drug could be approved or deemed valuable for that use. If the drug is being studied in a clinical trial, an explanation is required as to why the patient population cannot be enrolled in the clinical trial, and under what circumstances that patient population could be enrolled (21 CFR 312.315(c)).

Treatment EA

The treatment EA category allows the investigational drug to be used for wide-spread treatment use [13]. The FDA must determine that the drug is being investigated in a controlled clinical trial under an IND designed to support a marketing application for the EA use, or all clinical trials of the drug have been completed (21 CFR 312.320). Additionally, the sponsor must demonstrate that it is actively pursuing marketing approval of the drug for the EA use. There must be sufficient evidence for the safety and effectiveness of the target drug to support the EA use for the serious disease or condition. This clinical evidence would normally comprise clinical trial data from Phase III, but alternatively could comprise compelling data from complete Phase II trials. In immediately life-threatening diseases or conditions, the scientific evidence to reasonably conclude that the investigational drug might be effective for the EA use, and would not expose the patient to an unreasonable and significant risk, would customarily comprise clinical data from Phase II or III trials, but could include more preliminary clinical evidence. The decision to transition to treatment-expanded access for remdesivir was based on the National Institute of Allergy and Infectious Diseases (NIAID) Phase III study and Gilead's global Phase III study, which evaluated the 5-day and 10-day dosing regimens of the drug [24].

Gaps and challenges associated with EAPs and EUA

There are several important gaps and challenges related to the use of drugs for the treatment of COVID-19 under an EUA or EAP. An EUA issued by the FDA might not be grounded on specific trials demonstrating efficacy and safety in humans. For hydroxychloroquine and chloroquine, the EUA was based on limited in vitro and anecdotal clinical data in case series [25], which makes it difficult to determine the certainty of the scientific evidence the FDA considered. Quickly relying on a drug that might appear to treat the condition could compound the situation further. An EUA could interfere with the collection of safety and efficacy data through continued robust and reliable clinical-evidence generation that would support the use of drugs to treat COVID-19 [26]. Thus, there might be more risk than benefit in prematurely issuing EUAs. EAPs usually involve single-group interventions without a comparison control group [27]. Consequently, overall safety and efficacy of a therapy cannot be accurately determined. The broad application of EAPs might also detract from the resources needed to conduct standard clinical trials, including patients, drugs, money, and data [28,29].

The EUA does not carry terms that are required to provide important information on the efficacy and safety of a drug [26]. Physicians are supplied with a fact sheet and are expected to report medication errors and serious adverse events (SAEs) through the MedWatch Adverse Event Reporting program of the FDA [30]. This system suffers from varying degrees of under-reporting and incomplete reports [31]. Developing a patient registry, run by the FDA and not the manufacturer, that contains information on patient demographics, the drug, and clinical outcomes could improve this system and the collection of needed data by requiring physicians to report safety data, which can then be made publicly available after the data are de-identified [26,32].

The provision of EUA to hydroxychloroquine and chloroquine, now rescinded, allowed for the access of these medication from the

federally secured stockpiles [33]. This led to a national shortage of hydroxychloroquine and chloroquine, which can be particularly problematic for chronic users of these drugs, such as patients with systemic lupus erythematosus and rheumatoid arthritis. The EUA also provides a waiver for current good manufacturing practices (GMP) pertinent to the manufacturing, packaging, and holding of drug products [34]. Although this can help meet the increased demand for these drugs, there is a concern that harmful and poor-quality products with possible toxic impurities might be reaching the market [33]. A similar observation was seen with remdesivir. The available supplies of the drug were limited, because it was not intended for high-demand use in response to a pandemic, making global and equitable distribution of the drug difficult [35].

Data from EAPs is not usually included within the regulatory review of drugs when submitting an NDA [36]. This is partly because real-world data cannot be easily collected from these programs [37]. Given that RCTs are associated with increased costs and decreased efficiency and possible delays, real-world data might soon become a required component of an NDA. This calls for major reforms in the way that EAPs in the USA obtain and use clinical data and in how these programs are developed. It would appear that, for the future, the FDA should consider requiring and funding costs of data entry into registries to collect and scrutinize all clinical data associated with EA and EUA approved therapeutics. This would be a faster and far less expensive approach to tracking clinical outcomes and unanticipated complications and adverse effects.

Clinical effectiveness of COVID-19 therapeutics granted EAs or EUAs

EAPs were developed for various drugs, and EUAs have authorized the use of hydroxychloroquine and chloroquine, convalescent plasma, remdesivir, Fresenius Propoven (propofol) 2%, bamlanivimab, baricitinib, and casirivimab plus imdevimab for the management of COVID-19 [38]. Incyte Corporation has also started an emergency EAP in the USA for its drug ruxolitinib [39,40]. The scope of authorization of these therapies is summarized in Table 2.

Hydroxychloroquine and chloroquine

EUA for hydroxychloroquine and chloroquine donated to the Strategic National Stockpile was issued on March 28, 2020, and later revoked on June 15, 2020 [41]. The decision to rescind the EUA was grounded on new studies and re-evaluation of data showing that these drugs are unlikely to be effective in the treatment of COVID-19 and have not demonstrated superiority over placebo in several respected studies [41]. In addition, life-threatening arrhythmias and serious cardiac events, particularly at higher doses, and several newly reported cases of methemoglobinemia secondary to the use of these drugs were described [41]. The RECOVERY trial revealed that hydroxychloroquine did not provide a significant difference in the primary endpoint of 28-day mortality; 25.7% in those treated with hydroxychloroquine and 23.5% in the usual-care arm (HR 1.11, 95% CI 0.98–1.26, $P = 0.10$) [42]. Moreover, there was no evidence of beneficial effects on duration of hospitalization or the need for mechanical ventilation. These findings are congruent with the ORCHID study, which was halted by the NIH because of the lack of evidence of efficacy [43]. Interim analysis of the double-blind, randomized Phase IIb Brazilian study by Borba *et al.*, which evaluated the efficacy and safety of two different chloroquine dosages as adjunctive therapy in hospitalized patients with severe COVID-19, showed that the high-dose regimen was associated with more cardiac toxic effects (QTc > 500 ms, 18.9% versus 11.1%) and death (39% versus 15%) [44].

Convalescent plasma

The Mayo Clinic-sponsored EAP for convalescent plasma started on April 3, 2020, allowing physicians to request this treatment through a single-patient eIND application [45]. On August 23, 2020, the FDA issued an EUA that allows use of convalescent for the management of patients hospitalized with COVID-19 [46], based on data from previous outbreaks (SARS, Ebola, H1N1, and MERS) [41], preclinical evidence, small-scale COVID-19 studies, and the national EAP for COVID-19 convalescent plasma showing that the known and potential benefits of this therapy outweigh the known and potential risks [46].

The National EAP was initially designed to expand access to plasma for those unable to participate in clinical trials and to evaluate the safety of convalescent plasma [47]. This open-label study (i.e., neither randomized nor placebo controlled) was crucial to the August 23, 2020 EUA of convalescent plasma. Their initial goal had been to enroll 5000 patients. However, this was expanded between April 4, 2020 and July 4, 2020, and a total of 47 047 patients were enrolled as part of the EA protocol; of these, 36 226 were transfused, and 35 322 patients had adequate data to be included in the analysis. The analysis split patients into groups based on when they were transfused. This was done to account for changes in patient characteristics or concurrent management strategies as the pandemic progressed. In total, 3082 patients transfused with a single unit of plasma for which antibody levels were known were included in the final analysis. By splitting the patients into three windows during the early phases of the pandemic, there were certain differences that were observed between the severity of illness and concurrent therapies between the groups. Specifically, patients enrolled early on were more likely to be critically ill and receive concurrent therapy with hydroxychloroquine and azithromycin, compared with patients later in the analysis, who were more likely to receive concurrent remdesivir and less likely to be critically ill.

With regards to early administration, it was observed that patients who received plasma transfusions within 3 days of diagnosis had lower mortality rates at both 7 and 30 days, compared with those who received transfusions after more than 3 days from diagnosis. The time to transfusion was measured from the time of diagnosis to transfusion, not the time from symptom onset to transfusion. One plausible explanation for the finding that early infusion improved outcomes is that transfusing earlier in the course of illness allows for transfer of effective antibodies to those who had not yet seroconverted. This trend regarding mortality and the timing of infusion held true for each of the three periods in the study when broken down by month. With regards to antibody levels, lower rates of 7- and 30-day mortality were observed with the administration of plasma with higher levels of antibody. This also held true when accounting for time to transfusion. Specifically, the greatest benefit was observed in those who received high antibody plasma less than 3 days from diagnosis to transfusion.

TABLE 2

Scope of authorization of EUAs granted by FDA

Treatment	FDA Scope of Authorization
Remdesivir	Distribution of the authorized Veklury will be controlled by the U.S. Government for use consistent with the terms and conditions of the EUA. Gilead will supply Veklury to authorized distributors, or directly to a U.S. government agency, who will distribute to hospitals and other healthcare facilities as directed by the U.S. Government, in collaboration with state and local government authorities, as needed. Veklury covered by this authorization will be used only to treat adults and children with suspected or laboratory confirmed COVID-19 administered in an in-patient hospital setting via IV infusion by a healthcare provider. The use of Veklury covered by this authorization should be in accordance with the dosing regimens as detailed in the authorized Facts Sheets.
Convalescent plasma	The scope of the authorization is limited to the use of the authorized COVID-19 convalescent plasma for the treatment of hospitalized patients with COVID-19. The emergency use of the authorized COVID-19 convalescent plasma under the EUA must be consistent with, and may not exceed, the terms of the letter of authorization, including the scope and the conditions of authorization set by the letter.
Fresenius Propoven 2% Emulsion	Fresenius Propoven 2% Emulsion will be used only to maintain sedation via continuous infusion in patients greater than 16 years old who require mechanical ventilation. Fresenius Propoven 2% Emulsion will be administered only by a licensed healthcare provider in an ICU setting. Fresenius Propoven 2% Emulsion will NOT be administered to pregnant women, unless there are no FDA-approved products available to maintain sedation for these patients should they require mechanical ventilation in an ICU setting. Fresenius Propoven 2% Emulsion will be used only in accordance with the dosing regimens as detailed in the authorized Fact Sheets.
Hydroxychloroquine (REVOKED)	FDA-approved hydroxychloroquine sulfate that is approved by FDA for other uses and accompanied by its FDA-approved labeling and authorized Fact Sheets. The hydroxychloroquine sulfate must be administered by a healthcare provider pursuant to a valid prescription of a licensed practitioner. The hydroxychloroquine sulfate may only be used to treat adult and adolescent patients who weigh 50 kg or more, hospitalized with COVID-19 for whom a clinical trial is not available, or participation is not feasible.
Bamlanivimab	Distribution of the authorized bamlanivimab will be controlled by the U.S. Government for use consistent with the terms and conditions of the EUA. Lilly will supply bamlanivimab to authorized distributors, who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities. The bamlanivimab covered by this authorization will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients with positive results of direct SARS-CoV-2 viral testing who are 12 years of age and older weighing at least 40 kg, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Bamlanivimab is not authorized for use in the following patient populations: Adults or pediatric patients who are hospitalized due to COVID-19, adults or pediatric patients who require oxygen therapy due to COVID19, adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity. Bamlanivimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the EMS, as necessary. The use of bamlanivimab must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.
Baricitinib	The baricitinib covered by the authorization will be used only by healthcare providers, in combination with remdesivir, to treat suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients 2 years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or ECMO. The use of baricitinib covered by this authorization must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.
Casirivimab and Imdevimab	Distribution of the authorized casirivimab and imdevimab will be controlled by the U.S. Government for use consistent with the terms and conditions of the EUA. Regeneron will supply casirivimab and imdevimab to authorized distributor (s), who will distribute to healthcare facilities or healthcare providers as directed by the U.S. Government, in collaboration with state and local government authorities, as needed. The casirivimab and imdevimab will be used only by healthcare providers to treat mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progressing to severe COVID-19 and/or hospitalization. Casirivimab and imdevimab may only be administered together. Casirivimab and imdevimab is not authorized for use in the following patient populations: adults or pediatric patients who are hospitalized due to COVID-19, adults or pediatric patients who require oxygen therapy due to COVID19, adults or pediatric patients who require an increase in baseline oxygen flow rate due to COVID-19 in those patients on chronic oxygen therapy due to underlying non-COVID-19-related comorbidity. Casirivimab and imdevimab may only be administered in settings in which health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary. The use of casirivimab and imdevimab must be in accordance with the dosing regimens as detailed in the authorized Fact Sheets.

TABLE 3

Summary of therapeutic agents granted EA and/or EUA for the management of COVID-19[a]

Treatments with Expanded Access	Sponsor	Dosing regimen	Route of administration	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Remdesivir	Gilead Sciences	EUA for hospitalized adults and children weighing 40 kg or more: Loading dose of 200 mg by IV infusion on day 1, followed by a maintenance dose of 100 mg by IV infusion once daily from day 2 for 5–10 days. EUA for hospitalized children weighing 3.5 to less than 40 kg (lyophilized powder formulation only): Loading dose of 5 mg/kg by IV infusion on day 1, followed by maintenance doses of 2.5 mg/kg by IV infusion once daily from day 2 for 5–10 days.	IV	RNA replicase inhibitor	Infusion-related reaction, increased transaminases, nausea, headache, rash	Known hypersensitivity to any ingredient of remdesivir	Substrate for CYP2C8, CYP2D6, CYP3A4, OATP1B1, P-gp. Inhibitor of CYP3A4, OATP1B1, OATP1B3, BSEP, MRP4, NTCP. Coadministration of remdesivir and hydroxychloroquine or chloroquine may result in reduced antiviral activity of remdesivir.	Use during pregnancy and breastfeeding only if potential benefits outweigh potential risks. Use appropriate caution and monitoring in elderly. Not recommended in adults and pediatrics with eGFR <30 mL/min. Use in patients with hepatic impairment only if potential benefits outweigh potential risks.
Convalescent plasma	Collaboration between industry, academic and government partners, Mayo Clinic, Lead Institution	Initiate therapy with one unit (i.e. 200 mL) of COVID-19 convalescent plasma. One or two infusions.	IV	Neutralizing antibodies provide short-term passive immunity	Inadvertent transmission of infectious agents, allergic reactions, thrombotic complications, transfusion-associated circulatory overload, transfusion-related acute lung injury	Allergy to human plasma, sodium citrate, methylene blue IgA-deficient patients with antibodies to IgA and a history of hypersensitivity	None	Not recommended in patients with heart failure, chronic kidney failure in the dialysis phase, and organ transplant
Ruxolitinib	Incyte Corporation	5 mg bid	PO	JAK/JAK2 inhibitor	Thrombocytopenia, neutropenia, anemia, infections, edema, headache, dizziness	None	CYP3A4 substrate. Serum roxulitinib levels may increase when used with CYP3A4 inhibitors (i.e. ritonavir)	Use in pregnant and lactating women is not recommended. May require starting dose reduction in hepatic and renal impairment.
Fresenius Propoven 2% Emulsion	Fresenius Kabi USA, LLC.	0.3-0.4 mg/kg/hr	Infusion only	Activation of GABA receptors	Hypotension, respiratory depression, apnea, increased triglycerides, myoclonus	Hypersensitivity to peanut or soy	CYP3A4 inhibitor. Metabolized by CYP2B6. Fentanyl, cyclosporine, valproate	Caution should be taken when treating patients with mitochondrial disease, epilepsy, and disorders of fat metabolism. Do not use in pregnant women unless no other medications to maintain sedation.

TABLE 3 (*Continued*)

Treatments with Expanded Access	Sponsor	Dosing regimen	Route of administration	Mode of action	Common adverse events	Contraindications (US labeling)	Major drug interactions	Use in specific populations
Hydroxychloroquine (REVOKED)	Supplied from Strategic National Stockpile	400 mg bid on day 1, then 200 mg bid on days 2–5; 400 mg od for 5 days; 200 mg tid for 10 days; 100–200 mg bid for 5–14 days	PO	Anti-inflammatory and immunomodulatory effects	QTc prolongation, abdominal pain, decreased appetite, diarrhea, nausea, vomiting, hemolysis in G-6-PD deficiency, hypoglycemia, retinopathy, nervous system disorders, psychiatric disorders	Known hypersensitivity to hydroxychloroquine, 4-aminoquinoline derivatives, or any component of the formulation	CYP2D6, CYP2C8, CYP3A4, CYP3A5	Caution should be exercised when administering to pregnant and nursing mothers
Bamlanivimab	Eli Lilly	700 mg as single infusion over 60 mins	IV	Neutralizing IgG_1 monoclonal antibody	Dizziness, headache, pruritis, immediate nonserious hypersensitivity	None	None	Use during pregnancy only if the potential benefit outweighs the potential risk for the mother and fetus. Data are unknown regarding presence in human or animal milk, effects on breastfed infants, or effects on milk production.
Baricitinib	Eli Lilly	4 mg for 14 days	PO	JAK/JAK2 inhibitor	Upper respiratory tract infections, nausea, herpes simplex, herpes zoster	None	Substrate of BCRP/ABCG2, CYP3A4, OAT1/3, P-gp/ABCB1. Avoid use with strong OAT3 inhibitors	Not studied in pregnant or lactating women with COVID-19. Dose adjustment for patients with eGFR <60. No dose adjustment required for patient with mild or moderate hepatic impairment.
Casirivimab and Imdevimab	Regeneron	1,200 mg of casirivimab and 1,200 mg of imdevimab administered together as a single infusion	IV	Combination of two recombinant neutralizing IgG1 monoclonal antibodies	Anaphylaxis and infusion-related reactions, fever, chills, hives, itching, flushing	None	None	No dose adjustment is recommended in pregnant or lactating women. Not recommended for pediatric patients weighing less than 40 kg or those less than 12 years of age.

[a] Abbreviations: bid, twice daily; COVID-19, coronavirus disease 2019; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; EUA, emergency use authorization; G-6-PD, glucose-6-phosphate dehydrogenase; IgA, immunoglobulin A; IV, intravenous; JAK, Janus kinase; OAT, organic anion transporter; od, once daily; P-gp, P-glycoprotein; PO, oral; tid, three times daily.

The National EAP study is the largest study of its kind regarding the use of convalescent plasma therapy in patients with COVID-19 to date and continues to add to the evidence regarding early transfusion and higher antibody levels. The study also adds to the knowledge of potential adverse effects of convalescent plasma. Fewer than 1% of patients manifested SAEs [i.e., transfusion-associated circulatory overload, transfusion-related acute lung injury (TRALI), severe allergic transfusion reaction] in the first 4 h after transfusion, there was a 0.3% mortality rate, and only 13 out of 146 of these events were clinically judged as certainly associated with the transfusion. Notably, the lack of a control group and randomization limits our ability to draw significant conclusions with regards to the overall efficacy of convalescent therapy in the treatment of COVID-19.

Remdesivir

Remdesivir received an EUA in the USA on May 1, 2020 following data from three RCTs showing improved clinical outcomes in patients with moderate or severe COVID-19 [48]. EAPs evaluated the safety and efficacy of remdesivir in adults, pediatrics, and pregnant and postpartum women. Patients enrolled in these programs had a confirmed SARS-CoV-2 infection and were receiving supplemental oxygen or had an oxygen saturation of =<94% on room air [49–51].

Preliminary data reported for 53 adults with COVID-19 who received compassionate use remdesivir showed a 68% overall clinical improvement rate after a median follow-up of 18 days [49]. Additionally, compassionate-use remdesivir was well tolerated in pregnant and postpartum women with COVID-19, and no major adverse events were reported [50]. For pregnant women, preliminary data indicated an improvement in oxygen support of 96% and a clinical recovery rate of 93%; for postpartum women, the respective rates were 89% for both outcomes. Given that compassionate-use studies do not provide enough information to confirm efficacy and safety, remdesivir should be avoided in pregnant women unless the physician recommends otherwise. Pediatric patients with severe COVID-19 treated with compassionate-use remdesivir showed a clinical improvement rate of 88% at day 28 [51]. Ongoing clinical trials (NCT04431453) and compassionate-use programs are evaluating the safety and efficacy of remdesivir in pediatrics.

Propoven

Propoven 2% (propofol 20 mg/mL) emulsion was granted an EUA from the FDA on May 8, 2020 [52]. Unlike Diprivan 1% (propofol 10 mg/mL), which contains half the concentration of propofol, Propoven 2% is not approved by the FDA [53]. The EUA was in response to the propofol shortages, and the growing demand for propofol to maintain sedation in patients with COVID-19 16 years and older who require mechanical ventilation in an ICU.

Ruxolitinib

Ruxolitinib (Jakafi®), a potent and selective oral inhibitor of both JAK1 and JAK2 protein kinases, could combat cytokine release syndrome (CRS) in patients severely ill with COVID-19 [40]. While Phase III RCTs are evaluating the efficacy and safety of ruxolitinib plus standard of care, open-label emergency EAPs for patients with severe or very severe COVID-19 illness (NCT04337359) and patients with COVID-19-associated CRS (NCT04355793) were started by Incyte. The program will include patients who meet eligibility criteria but are not able to be hospitalized or who are hospitalized with a clinical diagnosis and/or positive SARS-CoV-2 test. See Table 3 for a summary of these agents. On November 19, 2020, the FDA issued an EUA for baricitinib, another JAK inhibitor, in combination with remdesivir in hospitalized adults and children aged ≥2 years with COVID-19 who require supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) [54].

Bamlanivimab

Bamlanivimab is a recombinant neutralizing IgG1 monoclonal antibody that specifically binds to an epitope on the S protein of SARS-CoV-2 overlapping the ACE2 binding site [55]. The FDA issued an EUA for bamlanivimab on November 9, 2020 that permits use of the drug for the treatment of mild to moderate COVID-19 in adults and pediatric pts ≥12 years of age weighing at least 40 kg with positive results of direct SARSCoV-2 viral testing who are outpatients, and are at high risk for progressing to severe COVID-19 and/or hospitalization [56]. The decision was based on an interim analysis of an ongoing randomized, double-blind, placebo-controlled, phase 2 trial of bamlanivimab monotherapy in non-hospitalized patients with mild to moderate COVID-19. On November 21, 2020, the FDA issued an EUA for REGN-COV2, which combines monoclonal antibodies casirivimab and imdevimab, for treatment of mild to moderate COVID-19 in adults and pediatric patients ≥12 years of age weighing ≥40 kg with positive results of direct SARSCoV-2 viral testing who are outpatients and are at high risk for progressing to severe COVID-19 and/or hospitalization [57].

Concluding remarks

Drug approval is a lengthy and cumbersome process not suited to address the emergent needs of a pandemic. The current pandemic has forced us to recognize the weaknesses of our current EAPs and has stimulated reconsideration of possible ways in which such programs could be better designed and implemented. EAPs can be a challenge for regulatory bodies, physicians, and patients. There are many regulatory and ethical issues surrounding these programs, as well as issues related to the health outcomes, health equity, and costs incurred. EA program candidates are often patients who have tried and failed several lines of therapies and have no other options for their life-threatening disease(s). These programs allow patients to access these potentially life-saving drugs outside of clinical trials. Many of these agents are approved for other indications and are undergoing evaluation in EA programs or clinical trials. Ongoing efforts are focusing on accelerating EA procedures to serve the best interest of patients severely ill with COVID-19, while still monitoring safety and efficacy as closely as possible. The safety and efficacy of these therapies are not well established, although their EA use in fact facilitated development of rapidly deployed clinical investigations to better assess these factors.

The issuance of diagnostic EUAs during the COVID-19 pandemic has set a precedent to issue additional EUAs for therapeutics. A framework for reporting safety outcomes represents a

much-needed resource for therapies granted an EUA. Seven aforementioned therapies have been granted EUAs, with the one for hydroxychloroquine later rescinded. With the exception of the impact of remdesivir on length of hospitalization, none of the agents have yet been shown to be clearly effective for COVID-19. With other novel targeted therapies in the pipeline, more options might hopefully soon become available for treatment of COVID-19. RCTs remain the gold standard for safety and effectiveness assessments, but EAPs and EUAs can help provide timely and prompt answers.

Declaration of interests

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References

1 Le, T.T. *et al.* (2020) Evolution of the COVID-19 vaccine development landscape. *Nat. Revi. Drug Discovery* 19, 667–668

2 FDA. How FDA Is Responding to COVID-19 Pandemic. www.fda.gov/media/140595/download. [Accessed 23 November 2020].

3 Jarow, J.P. *et al.* (2017) Overview of FDA's Expanded Access Program for Investigational Drugs. *Ther. Innovation Regul. Sci.* 51, 177–179

4 Fountzilas, E. *et al.* (2018) Expanded access to investigational drugs: balancing patient safety with potential therapeutic benefits. *Expert Opin. Invest. Drugs* 27, 155–162

5 Iudicello, A. *et al.* (2016) Expanded Access Programme: looking for a common definition. *Trials* 17, 21

6 Polak, T.B. *et al.* (2020) Expanded Access as a source of real-world data: An overview of FDA and EMA approvals. *Br. J. Clin. Pharmacol.* 86, 1819–1826

7 Rozenberg, O. and Greenbaum, D. (2020) Making it count: extracting real world data from compassionate use and expanded access programs. *Am. J. Bioethics* 20, 89–92

8 Baumfeld Andre, E. *et al.* (2020) Trial designs using real-world data: the changing landscape of the regulatory approval process. *Pharmacoepidemiol. Drug Saf.* 29, 1201–1212

9 McKee, A.E. *et al.* (2017) How often are drugs made available under the Food and Drug Administration's Expanded Access Process approved? *J. Clin. Pharmacol.* 57 (Suppl. 10), S136–S142

10 Gilead. Emergency access to remdesivir outside of clinical trials. https://www.gilead.com/news-and-press/company-statements/gilead-sciences-statement-on-access-to-remdesivir-outside-of-clinical-trials. [Accessed 23 November 2020].

11 Expanded Access to Convalescent Plasma for the Treatment of Patients with COVID-19. Comparing EAP vs. EUA: What You Need to Know. www.uscovidplasma.org/-/media/kcms/gbs/patient-consumer/documents/2020/08/23/18/22/eap-vs-eua.pdf. [Accessed 23 November 2020].

12 FDA. Emergency Use Authorization. www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization. [Accessed 23 November 2020].

13 FDA. Expanded access to investigational drugs for treatment use – questions and answers. www.fda.gov/media/85675/download. [Accessed 23 November 2020].

14 Van Norman, G.A. (2018) Expanding patient access to Investigational Drugs: single patient Investigational New Drug and the 'right to try'. *JACC. Basic Transl. Sci.* 3, 280–293

15 Klopfenstein, M. *et al.* (2015) Expanded Access Programs: ethical and practical considerations for biopharmaceutical sponsors. *Ther. Innov. Regul. Sci.* 49, 352–358

16 Halimi, V. *et al.* (2020) Current regulatory approaches for accessing potential COVID-19 therapies. *J. Pharm. Policy Pract.* 13, 16

17 Tunis, S.R. and Pearson, S.D. (2006) Coverage options for promising technologies: Medicare's 'coverage with evidence development'. *Health Affairs* 25, 1218–1230

18 Jarow, J.P. *et al.* (2016) Expanded access of investigational drugs: the experience of the center of drug evaluation and research over a 10-year period. *Ther. Innovation Regul. Sci.* 50, 705–709

19 Speers, M.A. (2019) Providing patients with critical or life-threatening illnesses access to experimental drug therapy: a guide to clinical Trials and the US FDA Expanded Access Program. *Pharm. Med.* 33, 89–98

20 Van Norman, G.A. (2018) Expanding patient access to Investigational New Drugs: overview of intermediate and widespread treatment Investigational New Drugs, and Emergency Authorization in public health emergencies. *JACC. Basic Transl. Sci.* 3, 403–414

21 FDA. Recommendations for Investigational COVID-19 Convalescent Plasma. www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma. [Accessed 23 November 2020].

22 FDA. Expanded Access Categories for Drugs (Including Biologics). www.fda.gov/news-events/expanded-access/expanded-access-categories-drugs-including-biologics [Accessed 23 November 2020].

23 FDA, and HHS, (2009) Expanded access to investigational drugs for treatment use. Final rule. *Fed. Regist.* 74, 40900–40945

24 Gilead. Gilead's Investigational Antiviral Remdesivir Receives US Food and Drug Administration Emergency Use Authorization for the Treatment of COVID-19. www.gilead.com/news-and-press/press-room/press-releases/2020/5/gileads-investigational-antiviral-remdesivir-receives-us-food-and-drug-administration-emergency-use-authorization-for-the-treatment-of-covid19. [Accessed 23 November 23, 2020].

25 FDA. Request for Emergency Use Authorization for Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied from the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease. www.fda.gov/media/136534/download. [Accessed 23 November 2020].

26 Sarpatwari, A. *et al.* (2020) Missed opportunities on emergency remdesivir use. *JAMA* 324, 331–332

27 Rome, B.N. and Avorn, J. (2020) Drug evaluation during the Covid-19 pandemic. *N. Engl. J. Med.* 382, 2282–2284

28 Bollyky, T.J. *et al.* (2020) The equitable distribution of COVID-19 therapeutics and vaccines. *JAMA* 323, 2462–2463

29 Chapman, C.R. *et al.* (2019) What compassionate use means for gene therapies. *Nat. Biotechnol.* 37, 352–355

30 FDA. Frequently Asked Questions on the Emergency Use Authorization for Veklury (remdesivir) for Hospitalized COVID-19 Patients. www.fda.gov/media/137574/download. [Accessed 23 November 2020].

31 Cohen, P.A. (2014) Hazards of hindsight–monitoring the safety of nutritional supplements. *N. Engl. J. Med.* 370, 1277–1280

32 Sarpatwari, A. and Curfman, G. (2019) Mitigating health risks of prescription drugs: lessons from FDA oversight of opioid products. *JAMA* 321, 651–653

33 Piszczatoski, C.R. and Powell, J. (2020) Emergency authorization of chloroquine and hydroxychloroquine for treatment of COVID-19. *Ann. Pharmacother.* 54, 827–831

34 Hinton, D.M. Letter to: Rick Bright, Director, US Department of Health and Human Services. www.fda.gov/media/136534/download. [Accessed 28 April 2020].

35 Rozenberg, O. and Greenbaum, D. (2020) Making it count: extracting real world data from compassionate use and expanded access programs. *Am. J. Bioethics* 20, 89–92

36 Kalil, A.C. (2020) Treating COVID-19-off-label drug use, compassionate use, and randomized clinical trials during pandemics. *JAMA* 323, 1897–1898

37 FDA. FDA Combating COVID-19 with Therapeutics. www.fda.gov/media/136832/download. [Accessed 23 November 2020].

38 Van Norman, G.A. (2020) Update to drugs, devices, and the FDA: how recent legislative changes have impacted approval of new therapies. *JACC. Basic Transl. Sci.* 5, 831–839

39 Incyte. Incyte Announces Initiation of Phase 3 RUXCOVID Study Evaluating Ruxolitinib (Jakafi®) as a Treatment for Patients with COVID-19 Associated

Cytokine Storm. https://investor.incyte.com/press-releases/press-releases/2020/Incyte-Announces-Initiation-of-Phase-3-RUXCOVID-Study-Evaluating-Ruxolitinib-Jakafi-as-a-Treatment-for-Patients-with-COVID-19-Associated-Cytokine-Storm/default.aspx. [Accessed 23 November 2020].
40 Rizk, J.G. *et al.* (2020) Pharmaco-immunomodulatory therapy in COVID-19. *Drugs* 80, 1267–1292
41 FDA. Letter Revoking EUA for Chloroquine Phosphate and Hydroxychloroquine Sulfate. www.fda.gov/media/138945/download. [Accessed 23 November 2020].
42 Recovery. Low-Cost Dexamethasone Reduces Death by up to One Third in Hospitalised Patients with Severe Respiratory Complications of COVID-19. www.recoverytrial.net/news/low-cost-dexamethasone-reduces-death-by-up-to-one-third-in-hospitalised-patients-with-severe-respiratory-complications-of-covid-19. [Accessed 23 November 2020].
43 NIH (2020) *NIH Halts Clinical Trial of Hydroxychloroquine*. 2020 [Accessed 23 November 2020]www.nih.gov/news-events/news-releases/nih-halts-clinical-trial-hydroxychloroquine
44 Borba, M. *et al.* (2020) Effect of high vs low doses of chloroquine diphosphate as adjunctive therapy for patients hospitalized with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection: a randomized clinical trial. *JAMA Network Open* 3, e208857
45 FDA. Investigational COVID-19 Convalescent Plasma - Emergency INDs. www.fda.gov/media/136470/download. [Accessed 23 November 2020].
46 FDA. Emergency Use Authorization (EUA) of COVID-19 Convalescent Plasma for treatment of COVID-19 in Hospitalized Patients. www.fda.gov/media/141479/download. [Accessed 23 November 2020].
47 Joyner, M.J. *et al.* (2020) Effect of convalescent plasma on mortality among hospitalized patients with COVID-19: initial three-month experience. *medRxiv* . http://dx.doi.org/10.1101/2020.08.12.20169359 Published online August 12, 2020
48 Lamb, Y.N. (2020) Remdesivir: first approval. *Drugs* 80, 1355–1363
49 Grein, J. *et al.* (2020) Compassionate use of remdesivir for patients with severe Covid-19. *N. Engl. J. Med.* 382, 2327–2336
50 Burwick, R. *et al.* (2020) Compassionate use of remdesivir in pregnant women with severe COVID-19. *Clin. Infect. Dis.* . http://dx.doi.org/10.1093/cid/ciaa1466 Published online October 8, 2020
51 Chiotos, K. *et al.* (2020) Compassionate use of remdesivir in children with severe COVID-19. *AIDS 2020: COVID-19 Conference Proceedings abstr no. 3946* [Accessed 23 November 2020] In: https://cattendee.abstractsonline.com/meeting/9307/Presentation/3946
52 FDA. Fresenius Kabi Propoven Emergency Use Letter of Authorization. www.fda.gov/media/137888/download. [Accessed 23 November 2020].
53 FDA. Emergency Use Authorization (EUA) of Fresenius Propoven 2% Emulsion. www.fda.gov/media/137889/download. [Accessed 23 November 2020].
54 Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization (EUA) of baricitinib. 2020. Available at: https://www.fda.gov/media/143823/download. [Accessed 18 January 2021].
55 Lilly announces proof of concept data for neutralizing antibody LY-CoV555 in the COVID-19 outpatient setting. Press release. 2020 Sep 16. Available at https://investor.lilly.com/newsreleases/news-release-details/lilly-announces-proof-concept-data-neutralizing-antibody-ly
56 US Food and Drug Administration. Letter of authorization: Emergency use authorization for use of bamlanivimab for the treatment of mild to moderate coronavirus disease 2019 (COVID-19). 2020 Nov 9. From FDA website. (https://www.fda.gov/media/143602/download).
57 US Food and Drug Administration. Fact sheet for health care providers: Emergency use authorization (EUA) of casirivimab and imdevimab. 2020 Dec. From FDA website. (https://www.fda.gov/media/143892/download).