Review Article

Critical Review and Analysis of Approval of Favipiravir for Restricted Emergency Use in Mild-to-Moderate COVID-19

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Abstract

The Central Drugs Standard Control Organization, the Indian drug regulatory agency, granted accelerated approval to Glenmark Pharmaceuticals to market favipiravir in mild-to-moderate COVID-19 on June 19, 2020, for restricted use. The patients should sign informed consent before receiving favipiravir. Subsequently, Glenmark Pharmaceuticals issued a press release on June 20, 2020, stating that it was a landmark development for COVID-19 patients in India and the approval was backed by strong clinical evidence supporting the use of favipiravir in COVID-19. The authors carefully reviewed the press release issued by Glenmark Pharmaceuticals, product information, and informed consent form available with FabiFlu® (Glenmark's favipiravir brand) and public notice issued by the Drugs Controller General of India. They have gone through the regulatory requirements of emergency approvals in India and the USA, WHO's clinical trial synopsis for assessing efficacy of anti-COVID drugs and emergency use authorization granted to remdesivir in the USA. They critically analyzed the efficacy data presented in favor of favipiravir in this due process. Based on the review and analysis, the authors consider that the two crucial publications quoted in the product information, Chen *et al*. (2020) and Cai *et al*. (2020), do not provide convincing evidence for the efficacy of favipiravir. The entire clinical data presented in the press release and product information do not offer undisputed support for the efficacy of favipiravir in mild-to-moderate COVID-19. Moreover, it is the right time to take policy decision and frame guidelines on how to handle emergency approvals for medicinal products in grave situations such as the COVID-19 pandemic, in India.

Keywords: COVID-19, FabiFlu, favipiravir, Glenmark

Introduction

Glenmark Pharmaceuticals Ltd. issued a press release on June 20, 2020, claiming that it was the first pharmaceutical company in India to receive approval to market favipiravir in the treatment of mild-to-moderate COVID-19. It created sensation in the media and among the public and health-care workers as it boosts confidence in their minds that finally a medication has arrived for COVID-19. The press release stated that the approval was based on an accelerated review considering the current COVID-19 situation in the country and that the company is marketing the drug under the brand name FabiFlu®.[1]

The purpose of this manuscript is to review the relevant documents and data available in the public domain with regard to the approval granted to Glenmark Pharmaceuticals to market favipiravir by the Central Drugs Standard Control Organization (CDSCO), the apex drug regulatory body in India, and further to critically analyze whether the data submitted in favor of favipiravir fully justify the emergency approval.

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The authors of this article have taken the following documents or details for review and analyzed the circumstances, facts, and data.

1. Press release issued by Glenmark Pharmaceuticals
2. Product information available with FabiFlu® marketed pack
3. Public notice issued by the Drugs Controller General of India
4. Relevant legal aspects of emergency approvals in India and the USA

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5. Informed consent form given with FabiFlu® marketed pack
6. Clinical data needed to establish drug efficacy in COVID-19
7. Emergency Use Authorization (EUA) granted for remdesivir in the USA.

Press release issued by Glenmark pharmaceuticals

The press release of Glenmark said the approval granted to favipiravir was a landmark development for COVID-19 patients in India and the approval was backed by strong clinical evidence showing favorable results of efficacy in mild-to-moderate COVID-19. It further noted that the approval was for restricted use and every patient should sign informed consent before starting treatment with favipiravir.[1]

The press note especially highlighted the following two points in support of the efficacy of favipiravir:

a. "Favipiravir shows clinical improvements of up to 88% in COVID-19, with rapid reduction in viral load by 4 days" and
b. "Clinical improvement was noted across age groups 20 to >90 years, including in patients with comorbid conditions such as diabetes and heart disease, who were suffering from mild-to-moderate COVID-19."[1]

It does not specifically state whether the key highlights quoted were derived from the clinical trials currently ongoing in India with favipiravir sponsored by Glenmark or from other studies conducted elsewhere by different stakeholders. This doubt arises as there are five references quoted in support of the efficacy of favipiravir, and none of them seem to be from the data generated in India. The authors of this manuscript reviewed the five references and present the following observations or comments.

The first reference is related to the approval of Avifavir in the treatment of COVID-19 by the Russian Ministry of Health.[2] It was a press release or news available in the website of the Russian Direct Investment Fund (RDIF), Russia's sovereign wealth fund. It stated that the joint venture between RDIF and ChemRar, a company involved in the Research and Development of innovative pharmaceuticals, has shown the efficacy of Avifavir in COVID-19. A simple literature search indicates that Avifavir is the Russian domestic version of favipiravir. Some of the efficacy claims attributed for favipiravir in the press note of Glenmark were from the press release of RDIF and not from any peer-reviewed research articles.

The second reference is a review article published in 2013 in the "Antiviral Research Journal," and it is related to the antiviral activity of favipiravir against RNA viruses and its efficacy against various viral infections caused by influenza viruses, arenaviruses, phleboviruses, hantaviruses, flaviviruses, enteroviruses, alphavirus, Western equine encephalitis virus, respiratory syncytial virus, and norovirus.[3] This article shows the broad-spectrum antiviral activity of favipiravir, and it does not refer to the antiviral activity of favipiravir against COVID-19 virus, as the disease-causing virus was not known at that point in time, 2013.

The third reference is the preliminary report of the Japanese observational study of favipiravir, dated May 15, 2020. This study collected the data of clinical outcomes from hospitalized patients who received favipiravir on a compassionate use basis. The clinical outcomes were measured on days 7 and 14 and approximately after 1 month. The 7th day data were available for 1713 patients and 14th day data for 1282 patients. The clinical improvement rate was 79% at day 7 and 92.4% at day 14 after starting treatment in the patients with the age of <59 years. Though the results seem to be promising in favor of favipiravir, the study is more like a survey and does not have control group and has lot of other variables including concomitant medications affecting the study outcomes. Moreover, the report itself concluded that the efficacy of favipiravir based on this data should be interpreted with caution.[4]

The fourth reference is the publication of Cai *et al*., and it reports rapid reduction of viral load and improvement in radiological findings in COVID-19 patients upon administration of favipiravir. This was based on the clinical study conducted in National Clinical Research Center for Infectious Diseases (The Third People's Hospital of Shenzhen), Shenzhen, China. It was an open-label, nonrandomized, before-after controlled study comparing the efficacy of favipiravir and lopinavir/ritonavir. All the participants received interferon-a1b, 60 μg twice daily by aerosol inhalation in addition to favipiravir or lopinavir/ritonavir.[5]

The study[5] did not generate data for the efficacy and safety of the treatments in parallel allocation of favipiravir and lopinavir/ritonavir. Instead, the data of patients who previously received lopinavir/ritonavir were used to compare the data of favipiravir, and such studies would have serious design issues and confounding variables influencing the study outcomes.

The efficacy of treatment was assessed by the time of viral clearance and improvement in chest computed tomography (CT) scan findings. The study showed that favipiravir had rapid viral clearance compared to lopinavir/ritonavir as indicated by the median time for viral clearance at 4 days in the favipiravir group against 11 days in the lopinavir/ritonavir group. Similarly, favipiravir was associated with 91.43% improvement in chest CT scan findings compared to 62.22% with lopinavir/ritonavir.[5] However, this study does not detail the improvement in clinical symptoms among the patients enrolled in both treatment groups and relied on viral clearance and imaging findings. The influence of the other medication, interferon-a1b, co-administered with favipiravir and lopinavir/ritonavir, has to be taken into consideration when the efficacy demonstrated in this study is accounted.

Moreover, we do not know why Cai *et al*. published this study of evaluation of treatment effects in COVID-19 in the *Journal of Engineering*. It is the *Journal of Chinese Academy*

of Engineering, which aims to provide a "high-level platform where cutting-edge advancements in engineering R and D, current major research outputs, and key achievements can be disseminated and shared." This actually questions the credibility of the journal for accepting a manuscript not relevant to its specialty and the authors who chose to publish the medical article in an engineering journal.

The fifth reference quoted for the efficacy of favipiravir is a publication related to the randomized controlled trial of favipiravir and Arbidol. Arbidol is the brand name of umifenovir, one of the antiviral drugs currently evaluated for COVID-19. The study was a prospective, randomized, controlled, open-label multicentric trial conducted on 240 patients, with 120 patients receiving favipiravir (1600 mg two times for the 1st day followed by 600 mg two times a day) for 10 days and 120 patients receiving Arbidol, 200 mg, three times a day for 10 days. The patients were enrolled within 12 days of the onset of the disease symptoms and all of them were having viral pneumonia. The primary efficacy outcome was clinical recovery, which was defined by continuous (>72 h) recovery of body temperature, respiratory rate, oxygen saturation, and cough relief after 7 days of treatment. The study showed that favipiravir and Arbidol have similar clinical recovery rates, though favipiravir had better results for relief from pyrexia and cough.[6]

This study[6] is comparing the efficacy of two drugs that were not approved for their efficacy in COVID-19, namely favipiravir and Arbidol (umifenovir). This raises the question whether the effects attributed to the treatments are actually due to the medication effect or the patients themselves recovered due to their natural immunity and other supportive medications. This question could have been avoided if the study had a placebo arm and the outcomes were compared to the clinical recovery in the placebo group. It is a routine method in clinical drug development of new drug candidates that the efficacy outcomes of a new drug should be generated in a placebo-controlled study when there is no approved medication for the disease. The new drug should demonstrate superiority over placebo arm in order to avoid approval of a drug, which has the efficacy similar to only placebo.

The critical analysis of the efficacy claims in the press release of Glenmark shows that it was based on a press/news release by RDIF, a clinical survey conducted with the compassionate use of favipiravir without any control, a nonrandomized clinical study with no clinical outcome as a measure of efficacy, and a randomized controlled study having clinical recovery as a measure of efficacy without a valid control.

Product information available with FabiFlu® marketed pack

The authors have browsed the website of Glenmark Pharmaceuticals and online search engines to look into the product information and informed consent form supplied along with FabiFlu®. However, both the documents are not available in the public domain. The product information is a scientific document that gives key information on the drug including its safety and efficacy. It is also called drug label or prescribing information in the USA or summary of product characteristics in European countries. This is the absolute and binding document, which the medical practitioners usually refer to have clarity on drug-related information, and is approved by the Drug Regulatory Agency. It will be usually available in the public domain especially in the website of the company marketing the respective drug. The authors of the manuscript have obtained these documents from a retail pharmacy selling FabiFlu®, reviewed, and analyzed.

The product information of FabiFlu® is restricted for the use of a registered medical practitioner or hospital or laboratory. It provides information related to the pharmaceutical, pharmacological, clinical, and nonclinical details of favipiravir including the adverse events. It also quotes two clinical studies in support of the efficacy of favipiravir in COVID-19. These studies were from the publications of Chen *et al*.[6] and Cai *et al*.[5] and were already reviewed in this manuscript and their limitations were also discussed.

The product information quotes Chen *et al*.[6] and states that favipiravir showed 71.43% clinical recovery and the control drug showed 55.86% recovery in "ordinary COVID-19 patients," with $P = 0.0199$, which is highly statistically significant for favipiravir. However, it does not mention the name of the control drug, Arbidol (umifenovir) for reasons not known.

The authors are surprised to see the claim that favipiravir was more effective than control in "ordinary COVID-19" patients. The severity of COVID-19 is not usually graded as "ordinary" or otherwise, and there are clear severity classifications given by different regulatory agencies in India and abroad. According to the revised guidelines on the clinical management of COVID-19 in India (dated March 31, 2020), the patients are classified into six categories, having (i) uncomplicated illness, (ii) mild pneumonia, (iii) severe pneumonia, (iv) acute respiratory distress syndrome, (v) sepsis, and (vi) septic shock.[7] Similarly, the interim guidance on the clinical management of COVID-19 released by the World Health Organization (WHO) dated May 27, 2020, classifies the patients into mild, moderate, severe, and critical (with acute respiratory distress syndrome/sepsis/septic shock).[8]

When the authors carefully carried out web search to find out what is actually given in the publication of Chen *et al*. (2020), three different publications were retrieved, first was dated March 20, 2020, second dated April 8, 2020, and the third, April 15, 2020. All the three are having the same title, same authors, and same clinical trial registration number (ChiCTR2000030254), and they are all preprint versions without any peer review. These publications are available with medRxiv with the preprint doi: https://doi.org/10.1101/2020.03.17.20037432.

The preprint manuscript published on March 20, 2020, has classified the patients into "ordinary" and "critical"

and concluded that favipiravir was superior to the control drug Arbidol in ordinary COVID-19, and it was taken and mentioned by Glenmark in the product information. However, the manuscripts published on April 8, 2020, and April 15, 2020, for the same study, concluded that favipiravir was not superior to Arbidol in improving the clinical recovery. Moreover, the classification of severity into "ordinary and critical" was also removed or modified. The clinical recovery was 51.67% in the Arbidol group and 61.21% in the favipiravir group after 7 days of treatment, with $P = 0.1396$, which is not statistically significant. However Chen *et al*. (2020) performed *post hoc* analysis in the subgroup of moderate COVID-19 patients and reported that the clinical recovery on day 7 was 55.86% in the Arbidol group and 71.43% in the favipiravir group ($P = 0.0199$). This is not factually presented in the product information.

The product information also gives two more studies described as Phase III, placebo-controlled studies in Type A and B influenza patients, with the primary outcome being the time required for alleviation of influenza symptoms. The data table presented for these two studies was titled "Results of primary analysis (ITT Population)." However, the data provided were related to the number of events and confidence interval. It is not clear what these data offer in support of the efficacy of favipiravir in COVID-19 as the data are not from COVID-19 patients and the data presented do not communicate its efficacy even in Type A and B influenza. There could be some error in the transcription of data, and this could not be verified, as these studies do not have references.

The authors are not fully convinced that the clinical data presented are adequate and satisfactory to support the use of favipiravir in mild-to-moderate COVID-19. The two studies quoted in the product information are not credible as one was published in an irrelevant journal, having design issues,[5] and the other one was not peer reviewed and is only a preprint version having a controversial reporting pattern.[6] The product information does not give any details from the Indian favipiravir study under progress, which is sponsored by Glenmark. Though the Indian study is not completed, for the sake of transparency, interim data could have been presented or Glenmark could have indicated that the drug is under trial in India at various sites and the outcomes would be updated in the product information.

Moreover, the product information is not dated and does not indicate that:

a. The product information was approved by the CDSCO
b. The drug was approved for emergency and restricted use
c. Informed consent should be obtained from the patients before prescription.

Public notice issued by the Drugs Controller General of India

A public notice dated June 21, 2020, is available in the CDSCO website under the title "Approval of Favipiravir Tablets to Glenmark Pharmaceuticals and Remdesivir Injection to Cipla Ltd and Hetero Drugs."[9] It states "Considering the emergency and unmet medical need for COVID-19 disease, CDSCO has approved Restricted Emergency Use of Remdesivir Injectable Formulations for treatment of patients with severe COVID-19 infection and Favipiravir Tablets for mild to moderate COVID-19 infection subject to various conditions and restrictions." It further says, "Favipiravir Tablet has been approved for manufacture and marketing on 19.6.2020."[9] The public notice lays down the following two conditions.

a. Favipiravir tablets should be sold only under the prescription of a registered medical practitioner
b. Informed consent should be obtained from the patients or their relatives before initiating treatment.

The other terms, conditions, and restrictions for the use of favipiravir were not provided in the notice, and it is not known whether there are any further terms, conditions, and restrictions imposed on the marketing company "Glenmark Pharmaceuticals."

The Notice refers "emergency and unmet medical need" for granting approval to favipiravir in India. However, there is no information provided on the evidences and/or clinical trial data submitted by Glenmark along with the application for marketing authorization of favipiravir and the details of the review process and observations made by the reviewers before approval was granted. Though a public notice is not expected to have too many technical details, comments on the relevant aspects of the quality of the data based on which approval was granted would instill confidence in the stakeholders.

Further, it is not known whether the approval granted for marketing favipiravir is a "Routine and full approval of a new drug for marketing" or "EUA pending full and complete approval of the new drug for marketing."

Relevant legal aspects of emergency approvals in India and the USA

In India, the Drugs and Cosmetics Act 1940 and Rules 1945 (As amended up to December 31, 2016) govern the approval of drugs. This has the special provision to expedite the approval of a new drug in the public interest to handle emergency health conditions arising out of epidemic diseases or natural calamities by notification in the official gazette.[10] We do not know whether favipiravir is approved in the public interest to handle emergency through a gazette notification as defined in the Drugs and Cosmetics Act or through the public notice or by an office order. However, there are no additional details provided in the Act that are relevant to the submission of application and review and approval process for such emergency approvals. Hence, we have to assume that the approval granted for favipiravir is close to full and complete approval as we do not have any further information either in the CDSCO website or Glenmark website.

Here, it is important to analyze the procedures followed in the USA for granting approvals for medical products for emergency use as it has well-evolved rules and guidelines

in the Code of Federal Regulations and US Food and Drugs Administration (FDA) guidance documents. The FDA has provided a guidance document for industries and stakeholders titled "EUA of Medical Products and Related Authorities."[11] The document gives FDA's general recommendations and procedures applicable for EUA of medical products including drugs, biologics, and devices under sections 564, 564A, and 564B of the Federal Food, Drug, and Cosmetic Act (FD and C Act). The EUA can be accorded for a medical product, which is unapproved, or an unapproved indication for an approved medical product. The decision to accord EUA will depend on the following four statutory criteria, which the medical product must fulfill.

a. Serious or life-threatening disease or condition
b. Evidence of effectiveness
c. Risk–benefit analysis
d. No alternatives.

The relevant acts and guidelines state that a EUA for a medical product will be granted by the FDA based on the declaration by the Secretary of Health and Human Services (HHS) and whose declaration should be based on the determinations of situation by any one of:

a. The Secretary of Homeland Security that there is a domestic emergency
b. The Secretary of Defence that there is a military emergency
c. The Secretary of HHS that there is a public health emergency
d. Identification of a material threat, by the Secretary of Homeland Security.

The Secretary of HHS further discusses with other officials and issues "EUA declaration," and then the Commissioner of FDA authorizes "the emergency use of an unapproved product or an unapproved use of an approved product, provided that other statutory criteria are met."

The Secretary of HHS based on the subsequent prevailing situation may terminate the EUA declaration. In that scenario, the EUAs accorded for the medical products based on the declaration will no longer be effective. EUA declaration will be terminated if the circumstances that precipitated the declaration have ceased and/or the unapproved medical products/unapproved indications that were accorded EUA are approved in the regular and due administrative process of FDA. Based on these procedures, several medical products including diagnostics, devices, and medications such as remdesivir were given authorizations in the USA. Compared to the detailed and transparent guidelines prevailing in the USA, we do not have such guidelines or rules to regulate the emergency approvals of medications. Due to the lack of such guiding mechanisms, the stakeholders involved in health care and research such as doctors, patients, hospitals, and pharmaceutical companies are not able to make their own judgments on the merits and demerits of such approvals.

If we evaluate the four statutory criteria applied for EUA by the US FDA to the "restricted emergency use approval" granted to favipiravir in India, the notice issued in the CDSCO website does not have sufficient information on the Evidence of Effectiveness and Risk-Benefit Analysis, though there cannot be any dispute that the COVID-19 situation is a public health emergency and there is no alternate treatment available currently.

Informed consent form given with FabiFlu® marketed pack

Generally, the informed consent form has two components: patient information sheet and declaration by the patient. The form annexed with FabiFlu® has only the declaration component and the patient information sheet is not available. Overall, it has five generic statements such as "My treating doctor has explained to me…" and "I have been explained about the possible benefits as well as risks…". It has a statement that the patient read or was explained about the product information leaflet or sheet.

The product information leaflet inserted with the product pack is a technical document meant for medical practitioners and not for patients, as the patients usually do not understand it. The usual procedure is that the marketing company shall prepare the patient information sheet in a language understandable by the common public and attach with the declaration form. This crucial document is missing in the informed consent form. Moreover, the information sheet and declaration form, both, have to be made available in the vernacular language and presently the consent form is available only in English.

Clinical data needed to establish drug efficacy in COVID-19

It is pertinent to review the type of clinical data needed to establish the efficacy of a drug potentially useful in COVID-19. The WHO has released a clinical trial synopsis for COVID-19 to help scientists, doctors, and pharmaceutical companies to design a sound clinical trial for the evaluation of drug efficacy in COVID-19. It recommends that the primary end point should be a composite measure of clinical improvement and/or survival, assessed at a prespecified time post randomization. The synopsis also gives an 8-point ordinal scale for assessing clinical improvement in patients with COVID-19. The other efficacy measures such as viral clearance, all-cause mortality, biomarkers, and imaging studies are in fact secondary end points.[12] Similarly, a 7-point ordinal scale has been designed with clinical parameters for assessing the efficacy of drugs in COVID-19, and it was used in the randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection.[13]

From this, we can imply that the efficacy of drugs in COVID-19 is not solely based on viral clearance or changes in biomarkers or findings of imaging studies, but on composite clinical improvement. Hypothetically, a drug having excellent viral clearance if not offering improvement in clinical measures, may not be approved for COVID-19. However, upon review of the three clinical trials, presently conducted in India to evaluate the efficacy of favipiravir, we could note that two trials have the primary efficacy outcome as viral clearance and the third one has clinical cure as the primary outcome.

The trial with the registration number CTRI/2020/05/025114 was registered on May 12, 2020, and the recruitment has been completed. Glenmark sponsors the trial, which compares the efficacy and safety of favipiravir added to standard treatment in comparison with standard treatment alone as control in mild-to-moderate COVID-19. It is an open-label, randomized, multicentric, Phase III trial with 12 centers including the All India Institute of Medical sciences, Delhi. The enrollment was started on May 20, 2020, and completed on June 15, 2020. The primary outcome of the trial was viral clearance in the nasopharyngeal swab test and the secondary outcomes were clinical cure, clinical worsening, and serious adverse events.[14] The details of standard care have not been provided, and it is a possibility that the standard care provided might not be uniform at all centers. We can also assume that Glenmark may shortly publish the efficacy data from this study in support of the emergency approval granted to its FabiFlu®, but we need to see the clinical cure rather than viral clearance as the outcome of efficacy.

Cipla Ltd. sponsors a similar trial of favipiravir (CTRI Reg No. CTRI/2020/06/025799), which was registered on June 10, 2020.[15] The study design is very close to the Glenmark study[14] and has viral clearance based on reverse transcription-polymerase chain reaction assay as the primary efficacy outcome, and the other outcomes including the clinical cure are only the secondary outcome measures.

Glenmark has registered one more study (CTRI/2020/06/025957), and it intends to evaluate the efficacy and safety of combination of favipiravir and umifenovir in comparison with favipiravir alone in moderate COVID-19. Seventeen sites across India participated in the study. The study was registered on June 17, 2020, and it is a Phase III, open-label, randomized controlled study involving 158 patients, having clinical cure as the primary efficacy measure.[16]

We do not know the reason for the companies choosing viral clearance as the primary efficacy measure over the WHO-recommended composite clinical measures. Especially, the sponsor of two studies, Glenmark, has chosen viral clearance as the primary efficacy measure for the favipiravir trial and clinical cure for the other trial of combination of favipiravir and umifenovir.

Emergency Use Authorization granted for remdesivir in the USA

While we reviewed the clinical data submitted for favipiravir in support of its efficacy in India, we also reviewed the EUA granted for remdesivir by the US FDA. The EUA document of remdesivir available in the public domain is a 35-page document divided into two components. The first component is the fact sheet for health-care providers consisting of instructions related to the administration of remdesivir, instructions for health-care providers, and mandatory requirements for the administration of remdesivir under EUA. It also gives information on the authority under which EUA was granted and it categorically states that remdesivir is an unapproved drug product accorded EUA to handle the COVID-19 pandemic. The second component is the full EUA prescribing information providing pharmacological, pharmaceutical, and clinical and nonclinical information of remdesivir.[17]

It says that the health-care providers shall communicate to the patients or their relatives all the necessary information prior to the administration of remdesivir to the patients and should document in the case sheet or case record that they have:

a. "Given the fact sheet for patients and parents/caregivers
b. Informed of alternatives to receiving remdesivir, and
c. Informed that remdesivir is an unapproved drug that is authorized for use under EUA."[17]

The EUA granted for remdesivir does not have any instruction that informed consent should be obtained from the patients before they receive the medication. Of course, it should not be interpreted that informed consent is not needed for remdesivir administration just because it is not mentioned in the EUA. We, as authors, understand and relate that informed consent is routine and mandatory, and the health-care workers must be obtaining informed consent like in any other clinical situation for administration of remdesivir as well, even without much emphasis in EUA. We only see that the mandate of properly informing the patients about the facts and circumstances under which remdesivir is administered lies with the health-care providers, and there is no additional obligation from patients specifically for receiving remdesivir or favipiravir, other than what is usually their responsibility as patients in any other clinical situation.

However, the approval granted to favipiravir in India, does not specify the obligations of health-care providers in properly communicating these aspects and recording the relevant details in the case notes. Instead, it solely fixes all these aspects on the informed consent form. Moreover, the informed consent form comes with FabiFlu® does not have the information but only the declaration as mentioned previously.

Further, the review of full prescribing information shows that the clinical data submitted in favor of remdesivir was based on two trials conducted by the sponsor, Gilead Life Sciences, and not based on literature data. One trial was a randomized, double-blind, placebo-controlled clinical study that evaluated its effect in mild/moderate and severe COVID-19. The other trial was an open-label, multicentric, randomized trial in severe COVID-19. The primary outcome measure for efficacy in both the studies was clinical recovery and not viral clearance.[17]

Summary and Conclusion

The authors of the manuscript have carefully reviewed and analyzed the data and documents related to the approval of favipiravir by the CDSCO and the EUA granted to remdesivir in the USA and based on the analysis, the authors make the following conclusions, observations, and comments.

a. The entire clinical efficacy data presented in the form of key highlights in the press release of Glenmark do not offer undisputed support for the efficacy of favipiravir in mild-to-moderate COVID-19

b. The two crucial publications quoted in the product information, Chen *et al*. (2020) and Cai *et al*. (2020), do not provide convincing evidence for the efficacy of FabiFlu® in mild-to-moderate COVID-19
c. The informed consent document should have patient information and declaration form and both should be available in English and local vernacular languages
d. The product information and informed consent should state that the drug is granted approval for emergency and restricted use to handle the current pandemic situation
e. The details provided in the product information and informed consent should be reviewed and approved by the CDSCO prior to the release so as to authenticate the claims and the data presented
f. The health-care providers must be accountable for proper communication of the information on the safety and efficacy of favipiravir to the patients and they need to make record of the communications in case sheets/notes
g. The CDSCO may decide on publishing the review reports and observations made on the application submitted by Glenmark in the web portal to ensure transparency in the way such approvals are granted and to improve public confidence on such approvals
h. The CDSCO may take policy decision and frame detailed guidelines on how to handle emergency approvals for medicinal products in grave situations such as the COVID-19 pandemic.

The observations made by the authors are purely academic in nature and in case if Glenmark has alternate views to what is presented in this manuscript, the authors welcome such exchange of ideas and thoughts.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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