SUMMARY OF EVIDENCE

Favipiravir

Section 1.

General information of the proposed health technology

Product name	Avigan
Generic name	Favipiravir
FDA approved indication	Not Philippine FDA-registered
Indication/s	Treatment of influenza
Proposed indication:	Treatment of COVID-19
Dosage formulation/ strength	200 mg film-coated tablet
Route of administration	Oral
Dosage regimen	• For influenza: 1600 mg for day 1 twice daily and 600 mg twice daily for days 2 through 5 • For COVID-19: 1600 mg twice daily for day 1 and 600 mg twice daily for days 2 through 10
Therapeutic class	Anti-viral
Anatomical Therapeutic Chemical (ATC) classification	J05AX27
Pharmacological action	Selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses.

Section 2.
Context of the health technology

Background

The World Health Organization (WHO) declared the novel coronavirus disease (COVID-19) caused by severe acute coronavirus 2 (SARS-COV-2) a global pandemic. The most common symptoms are fever, sore throat, malaise and dry cough. The symptoms are usually mild and begin gradually. It can spread from person-to-person through small droplets when coughing or sneezing. As of 12 April 2020, it has affected 160 countries with at least 4,171,859 cases and 285,690 deaths worldwide [1]. Locally, there are 11,086 COVID-19 cases with 726 deaths and a case fatality rate of 6.5% [2].

Currently, the WHO, US Centers for Disease Control and Prevention (CDC) and US Food and Drug Administration have not yet listed any intervention that has been proven effective against COVID-19. As a response to the increasing number of COVID-19 cases, the WHO announced a global testing of effective treatments across several countries called the "SOLIDARITY Trial," however, favipiravir is not included in this trial. Globally, there have been separate studies and trials on the treatment for COVID-19 using the existing drugs in the market such as those medicines used in the treatment of influenza.

Locally, by virtue of Department Memorandum (DM) No. 2020-0108, the Department of Health endorsed the treatment guidelines for COVID-19 issued by the Philippine Society of Microbiology and Infectious Diseases (PSMID) on 31 March 2020. The guidelines listed the following drugs that may be used in hospitalized, probable or confirmed COVID-19 cases with moderate to high-risk pneumonia:

1) **off-label use of hydroxychloroquine, chloroquine, lopinavir/ritonavir and tocilizumab**
2) **compassionate use of remdesivir**

Favipiravir is a prodrug antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase (RdRp) of RNA viruses. It is registered in Japan, however, it can only be manufactured and distributed upon the request of the government for use during an outbreak of a new influenza virus, provided that other influenza antiviral drugs are ineffective or not sufficiently effective, and in whom the efficacy of favipiravir can be expected (Inagaki, 2020; Pharmaceuticals and Medical Devices Agency, 2014). It was investigated before as a potential intervention for Ebola virus during the outbreak in 2014; however, no or unclear benefit was observed, and as such, it was no longer investigated for the said indication. To date, there is no conclusive guidance on the use of favipiravir for the treatment of COVID-19

[1]Johns Hopkins University, *COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University*, https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6 (accessed on 12 May 2020)
[2]Department of Health. (2020), *COVID-19 Tracker*, https://www.doh.gov.ph/covid19tracker (accessed on 12 May 2020)

Policy

Should the Philippine government introduce favipiravir as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31?*

Research Questions:

1. What are the current country TGs or CPGs which recommend the use of favipiravir in treating patients with COVID-19?

2. What is the clinical efficacy/ effectiveness and safety of favipiravir as an add-on to the DOH-PSMID-recommended treatment regimens for patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31?*

3. Does favipiravir as an add-on to the DOH-PSMID-recommended treatment regimens represent value for money for the treatment of patients with COVID-19 *versus the DOH-PSMID recommended guidelines as of March 31?*

Section 3.

Details of supporting evidence on the use of the proposed HT

3.1. Clinical evidence

Favipiravir is included in the treatment/ clinical practice guidelines of Japan (off-label use while clinical trials are ongoing) and Turkey (as compassionate use) for the treatment of COVID-19 among adults. Several clinical trials are also being conducted in different countries such as Italy, Thailand and US through compassionate use, and China and Japan through off-label use.

The salient points of the evidence found for the clinical efficacy and safety of favipiravir for COVID-19 are tabulated below:

Cai et al., 2020	• In an open-label non-randomized controlled trial (N=80), favipiravir (N=35) was compared with the combination drug lopinavir/ritonavir (N=45). The reported observed outcomes [i.e., faster viral clearance (median: 4 versus 11 days, p<0.001), improvement on chest CT scan imaging after 14 days [91.4% (32/35) versus 62.2% (28/80) of patients, p=0.004], and fewer adverse reactions [11.43% (4/35) versus 55.56% (25/45) of patients, p<0.001] favored favipiravir. • While they concluded favorable treatment effect of favipiravir, our critical appraisal shows low validity of the

	study due to high risk of selection bias, performance bias and detection bias.
Chen et al., 2020	• In an open-label randomized controlled trial (N=236), favipiravir (N=116) was compared with arbidol (N=120) as add-on therapy to conventional routine therapy. T The reported observed outcomes [i.e., clinical recovery rate at day 7 in mild cases [71.43% (70/98) vs 55.86% (62/111) of recovered patients, p=0.02], favored favipiravir. However, its benefit is inconclusive for critical COVID-19 cases and COVID-19 patients with hypertension and/or diabetes. In terms of adverse events, it was observed that elevated serum uric acid is more common among patients in the favipiravir group than those in the control arm. • Upon the completion of the rapid review, the publisher has withdrawn the paper at the request of the authors. • While they concluded favorable treatment effect of favipiravir, our critical appraisal shows low validity of the study due to high risk of selection bias, performance bias and detection bias.
Rapid review published by Singapore's HTA organization Ministry of Health - Agency for Care Effectiveness (MOH-ACE)	• Their rapid review which was based on the same studies mentioned above concluded that further investigation is needed to conclude the safety and efficacy of favipiravir against COVID-19.
On-going clinical trials	• Our search detected seven ongoing clinical trials on favipiravir for COVID-19 treatment.

As such, there is limited evidence, to date, to establish the clinical efficacy and safety of favipiravir in the treatment of COVID-19. The results of the ongoing trials are anticipated to further conclude the value of favipiravir for COVID-19.

3.2. Economic Evaluation

There is no existing evidence on the cost-effectiveness of favipiravir for COVID-19.

The Chinese distributor of Fujifilm Toyama Chemical Co., Ltd., which produces favipiravir (Avigan®), provided a cost of USD 3 or PHP 153.13 per 200-mg tablet (where USD 1 = PHP 51.0440 as per Bangko Sentral ng Pilipinas April 1, 2020 conversion rate). Using the treatment regimen by Chen et. al. (2020), the full treatment course (i.e., 10 days) will require a total of 70 tablets per patient (16 tablets for Day 1 then 6 tablets per day for Days 2-10) amounting to a total treatment cost of PHP 10,719.34 or USD 210 per patient.

There is limited evidence, to date, to establish the value for money of using favipiravir for the treatment of patients with COVID-19.

Section 4.

Ethical, Legal, Social, and Health System Impact

No evidence available.

Section 5.

Recommendation

Given that favipiravir is not locally registered, the HTAC assumed that it will be intended for compassionate use in the management and treatment of COVID-19. The HTAC deemed that compassionate use is acceptable as long as the following conditions are followed:

1. There is a reasonable basis for its use (e.g., early trials show promise, no other drug is available).
2. A valid informed consent shall be obtained from the patients or their legally appointed representatives. The process shall be free of undue influence and coercive presence and the risks are well described and understood.
3. The clinical data and course must follow a systematic protocol which shall be the basis of subsequent reports to the DOH and FDA as required.
4. The health providers involved shall exercise due diligence in furthering its use in a clinical trial when sufficient amount of medicines (needed in the clinical trial) will be provided by the donor.

It is also in this context that the **HTAC supports the decision of the Philippine government to join a multi-country clinical trial** for favipiravir.

For inquiries, you may contact the HTA Unit:

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