Favipiravir for the prevention and management of COVID# 19: evidence review of the clinical benefit and harm

South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: FAVIPIRAVIR FOR THE PREVENTION AND MANAGEMENT OF COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 25 June 2020

Key findings

- We conducted a rapid review of available published clinical evidence regarding the use of favipiravir, with or without other medicines, for patients with COVID-19.
- We found three trials from China evaluating favipiravir therapy in adult COVID-19 patients.
- It is unclear whether the use of favipiravir as part of the treatment of COVID-19 has any effect on outcomes critical for decision-making (e.g. mortality or decreased need for mechanical ventilation).
- Use of favipiravir did not show better conversion to SARS-CoV-2 virus negative serostatus or clinical benefits, but the certainty of the available evidence was low.
- Adverse effects caused by favipiravir were mild and manageable.
- No studies evaluating favipiravir as a prophylactic agent were retrieved.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
Type of recommendation		X			

Recommendation: Favipiravir should only be used for the treatment of COVID-19 in the context of an approved clinical trial.
Rationale: There is insufficient evidence of the balance of benefits and harms at this time. Favipiravir has not been registered by any mature regulatory authority, and is not yet registered by SAHPRA.
Level of Evidence: RCTs of low methodological quality (of which study results of 2 are published in preprints)

(Refer to appendix 2 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish (Chair), Helen Rees, Gary Reubenson (Vice-chair).

Note: Due to the continuous emergence of new evidence, this rapid review will be updated if and when more relevant evidence becomes available.

BACKGROUND

Effective therapeutic options to manage hospitalised patients with COVID-19 need to be identified urgently.

Favipiravir, an antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase, is being studied for the treatment of COVID-19.[1] It has broad antiviral activity including activity against influenza A and B, viral haemorrhagic fevers like Ebola and SARS-CoV-2 *in vitro*.[2–4]

Favipiravir has been suggested as an option for treating COVID-19. We reviewed current evidence for efficacy and harms of favipiravir in the treatment and prevention of COVID-19.

METHODS

On 20 June we conducted a rapid review of the evidence including systematic searching on three electronic databases: Epistemonikos (https://www.epistemonikos.org/en/), Network Meta-analysis website (www.covid-nma.com) and the Cochrane Library (https://www.cochranelibrary.com/). A further search on PubMed (https://www.pubmed.gov) and the preprint database MedRxiv (https://www.medrxiv.org) was conducted.

ST summarised the included studies and extracted the data from the studies into a narrative table; the second reviewer (AG) checked the search and evidence synthesis for due diligence, with editorial review. JN then did a final editorial review with a final check of the facts. The search strategy is shown in **Appendix 1**.

Eligibility criteria for review

A: FAVIPIRAVIR AS A THERAPEUTIC AGENT:

Population:

- *SARS-CoV-2 infected:*
    - *Ambulatory (mild disease not requiring hospitalisation or supplementary oxygen)*
    - *Hospitalised with no oxygen support or low-flow nasal oxygen*
    - *Hospitalised and requiring intensive oxygen therapy (i.e. high-flow nasal oxygen, continuous positive airway pressure or invasive mechanical ventilation)*

Intervention:

- Favipiravir either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparator:

- Any (standard of care/placebo/no intervention or active comparator).

Outcomes:

- These are listed per population group:

Population 1 – *Ambulatory patients***:** Ambulant patients with confirmed COVID-19, no restriction to age but disease sufficiently mild that management outside hospital is feasible.
Outcomes: Mortality; progression to hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; adverse events, adverse drug reactions.

Population 2 – *hospitalised with no oxygen support or with low-flow nasal oxygen*: Patients with confirmed COVID-19, no restriction to age but disease severity such that hospitalisation required.
Outcomes: Mortality; duration of hospitalisation; proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time point(s) post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; progression to ICU admission; progression to oxygen support; duration of ICU stay; duration of oxygen support; adverse events, adverse drug reactions.

Population 3 – *hospitalised and requiring more intensive oxygen therapy (i.e. high-flow nasal oxygen, continuous positive airway pressure or invasive mechanical ventilation):* Patients with confirmed COVID-19, no restriction to age but severe disease requiring more intensive oxygen support or ventilatory assistance.
Outcomes: Mortality; duration of ventilatory support; progression to mechanical ventilation; duration of ICU stay; duration of mechanical ventilation; adverse events, adverse drug reactions.

B: FAVIPIRAVIR AS A PROPHYLACTIC AGENT:

Population: SARS-CoV uninfected, but at risk of COVID-19. No limitations on age or occupational status (may separately look at health workers and general public populations).

Intervention: Favipiravir either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparator: Any (standard of care/placebo/no intervention or active comparator).

Outcomes: Development of COVID-19 with positive SARS-CoV-2 PCR; duration of symptoms; proportion requiring hospitalisation; adverse events, adverse drug reactions.

RESULTS

Results of search: We searched on 20 June 2020 and three network meta-analyses including favipiravir comparisons were found from the Network Meta-analysis website (www.covid-nma.com).[5] The reviews included two intervention trials in the preprint database MedRxiv (https://www.medrxiv.org).[6,7] A further search on PubMed (https://www.pubmed.gov) revealed an additional study by Cai et al.[8] Searches in the Cochrane Library (https://www.cochranelibrary.com/) and Epistemonikos (https://www.epistemonikos.org/en/) did not reveal new studies relevant to the PICO. The three network meta-analyses were excluded in the final synthesis as they made rather broader and indirect comparisons of favipiravir with many other antiviral agents. We report below findings from the three identified trials. In clinicaltrials.gov we identified 25 ongoing trials.

Included studies: The three trials examining favipiravir (Luo et al, 2020, Chen et al, 2020 and Cai et al, 2020) were conducted in China. Data in **Table 1** report the main characteristics and outcomes of the trials.

Effects of the intervention:
Favipiravir as a therapeutic agent: In a three-arm exploratory trial among hospitalized COVID-19 patients, adding favipiravir or baloxavir marboxil to an antiviral treatment regimen comprising inhaled interferon-α plus lopinavir/r or darunavir/cobicistat plus umifenovir did not provide additional clinical benefit.[6] Outcomes evaluated were conversion to SARS-CoV-2 virus negative serostatus, time to clinical improvement, incidence of mechanical ventilation, incidence of transfer to ICU and duration of oxygen support. Adverse events were generally mild and moderate with no differences in frequency or severity among the three groups. **Table 1** details these findings. The authors point out that potential suboptimal concentrations of favipiravir and delay between infection and treatment initiation may have blunted any response of the intervention. The major concern is that these patients were already on other antivirals before randomization and the treatment scheme and medication times were also different making it difficult to have standardized comparisons. The sample size was rather small, out of 30 recruited, 29 were analysed. This is reflected in the wide 95% confidence intervals of the effect estimates.

Chen et al enrolled 240 COVID-19 patients in to an open-label multicenter trial, where patients were randomly assigned to receive umifenovir or favipiravir. For important clinical outcomes such as clinical recovery rate, auxiliary oxygen therapy, noninvasive mechanical ventilation rate, overall respiratory failure rate, ICU admission or all-cause mortality, there was no difference between the intervention arms. Adverse events related to antiviral use were mild and the frequency was largely similar. See **Table 1**. In an analysis restricted to "moderate" patients, the favipiravir arm had better clinical recovery than the umifenovir arm (Risk Difference 15.6%; 95%CI 2.7% – 28.4%). However, the findings of this subgroup analysis should be interpreted with caution: these stratifications were not pre-specified in the protocol nor was this "moderate" group clinically defined and lastly it is unclear whether clinical criteria rather

than PCR seropositivity were used for COVID-19 diagnosis. In addition, all patients in both arms were also treated with a range of other therapeutic agents, including traditional Chinese herbal medicine, antibiotics, additional antiviral treatment, immunomodulatory drugs and corticosteroids, but not consistently. Attributing any differences to one additional antiviral agent is therefore questionable.

In a quasi-experimental comparative study of cases defined to be of moderate disease severity reported by Cia et al, those treated with favipiravir appeared to have faster viral clearance and better chest imaging change than patients treated with lopinavir/ritonavir.[8] More adverse events occurred in the control arm than in the favipiravir arm. The study design however limits the validity of these findings for treatment decisions. As a non-randomized study that made comparisons with historical controls, imbalances in both measured and unmeasured prognostic factors in the groups are potentially introduced and these cannot be entirely removed by multivariate analysis. Also, historical controls were treated before the study started. See Table 1 for the full risk of bias assessment.

Favipiravir as a prophylactic agent: No studies were retrieved in all databases searched.

CONCLUSION

There is currently insufficient evidence to support the inclusion of favipiravir in treatment guidelines for COVID-19 in South Africa until further evaluations are conducted and reported. There are currently at least 25 registered RCTs on this topic, some of which are already recruiting patients (https://clinicaltrials.gov/).

Reviewers: Simbarashe Takuva, Jeremy Nel and Andy Gray

Declaration of interests: ST (University of the Witwatersrand), JN (University of the Witwatersrand) and AG (University of KwaZulu-Natal) have no interests to declare in respect of favipiravir.

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Table 1. Characteristics of included studies

Citation	Study design	Population (n)	Treatment	Main findings	Comments
Luo et al [6] Full-text journal pre-print. Not peer-reviewed	Exploratory single center, open-label, randomized, controlled trial	China N = 30 Age 18-85 years (mean 52.5 years); Males = 72.4% Days from symptom onset to randomization (mean 11.7 days) All hospitalised, SAR-CoV-2 PCR positive. Respiratory rate >24/min (3.4%), fever (20.7%), NEWS2 score (median 4) Comorbidities: Diabetes (6.9%), hypertension (20.7%), hyperlipidaemia (3.4%) and cardiovascular disease (13.8%) Excluded: critical illness (respiratory failure and mechanical ventilation; shock; other organ failure requiring ICU monitoring and treatment), weight < 40kg, patients with liver and/or renal impairment	All had the following existing antiviral treatment: Interferon-α inhalation (100,000 iu, tid or qid) in combination with lopinavir/ritonavir (400mg/100mg, bid, po.) or darunavir/cobicistat (800mg/150mg, qd, po.) and umifenovir (200mg, tid, po.) **Interventions** **Baloxavir marboxil arm**: 80 mg days 1, 4 and 7 + existing antiviral treatment **Favipiravir arm**: 1600 mg or 2200mg orally, followed by 600 mg tid for 14 days + existing antiviral treatment **Control arm:** existing antiviral treatment	Baloxavir marboxil vs. Favipiravir vs. Control arm: **Primary endpoints** *Viral negative Day 14*: 70%, 77%, 100% *Time to clinical improvement (days)*: 14 (IQR 6-49), 14 (IQR 6-38), 15 (IQR 6-24) (defined as the time from randomization to an improvement of two points on a seven-category ordinal scale* or live discharge from the hospital, whichever came first) * The seven-category ordinal scale consisted of the following categories: 1, not hospitalized with resumption of normal activities; 2, not hospitalized, but unable to resume normal activities; 3, hospitalized, not requiring supplemental oxygen; 4, hospitalized, requiring supplemental oxygen; 5, hospitalized, requiring nasal high-flow oxygen therapy, noninvasive mechanical ventilation, or both; 6, hospitalized, requiring ECMO, invasive mechanical ventilation, or both; and 7, death. **Secondary endpoints** *Viral negative by Day 7*: 60%, 44%, 50% *Mechanical ventilation by Day 14*: 10%, 0%, 0% *ICU admission by Day 14*: 10%, 22%, 0% *Duration of oxygen support, median days (IQR*): 13 (3-41), 13 (3-37), 12 (5-23) *All-cause mortality by Day14*: No mortality in study *Adverse events by Day 14*: n=69; n= 54; n=64 The adverse events occurring in the study population were generally mild, moderate and similar among all groups.	**Issues of concern:** -Main issue is that the participants were all already under treatment with other medication and following different dosing times. Each experimental arm included multiple antivirals and the specific antiviral of interest. -Very small sample size -Unequal baseline characteristics i.e. favipiravir group showed oldest average age and shortest time from symptom onset to randomization **Overall judgement with regards to risk of bias judged as "*HIGH RISK*":** **-Random sequence generation (selection bias)**: Patients were randomized. **LOW RISK**. **-Allocation concealment (selection bias)**: Allocation was not concealed. **HIGH RISK.** **-Blinding of participants and personnel (performance bias)**: There was no blinding. **HIGH RISK.** **-Blinding of outcome assessment (detection bias) (patient-reported clinical improvement outcomes)**: There was no blinding. **HIGH RISK.** **-Blinding of outcome assessment (detection bias) (most outcomes)**: Obtained from medical records. **LOW RISK**. **-Incomplete outcome data addressed (attrition bias)**: 30 randomized, 29 analysed - high for this small sample size. **MODERATE RISK**. **-Selective reporting (reporting bias)**: no protocol or pre-specified analyses plan available. **HIGH RISK**.
Chen et al[7] Full-text journal pre-print. Not peer-reviewed	Randomized, controlled, open-label multicenter trial	China, 3 centres N = 240 Age >= 18 years, Males (46.6%), initial symptoms were within 12 days, critical (1.2%), fever (53%), dyspneoa (5.5%)	All received standard care which could comprise traditional Chinese herbal medicine, antibiotics, additional antiviral treatment, immunomodulatory drugs, corticosteroids	Favipiravir vs. Umifenovir: **Primary endpoints** *Clinical recovery rate at 7 days*: Clinical recovery was defined as continuous (>72 hours) recovery of temperature ≤36.6°C; respiratory frequency ≤24 times/min; Oxygen saturation ≥98% without oxygen inhalation; mild or no cough	**Issues of concern:** -All participants received standard care which could comprise traditional Chinese herbal medicine, antibiotics, additional antiviral treatment, immunomodulatory drugs, corticosteroids, therefore making interpretation of the effects of the intervention very difficult. In

Citation	Study design	Population (n)	Treatment	Main findings	Comments
		Clinical COVID-19 pneumonia diagnosis (without need for a positive SARS-CoV-2 PCR), Participants with moderate, severe or critical types of COVID-19 Comorbidities: Hypertension (30%), diabetes (11.4%) Excluded: chronic liver disease, severe/critical patients whose expected survival time were <48 hours, female in pregnancy, HIV infection;	**Intervention:** Favipiravir (1600mg, bd first day followed by 600mg, bd daily, plus standard care **Comparison:** Umifenovir (200mg, three times daily) plus standard care for 7 days	Overall: RD 9.5% (95%CI -3.1% - 22.1%) Moderate disease: RD 15.6% (2.7% - 28.4%) Severe/critical illness: RD 5.6% (95%CI -5.0% - 16.1%) **Secondary endpoint** *Rate of auxiliary oxygen therapy or non-mechanical ventilation:* RR -4.4% (95%CI -14.6% - -5.9%) *All-cause mortality*: No deaths reported *Rate of respiratory failure* (defined as SPO2 ≤90% without oxygen inhalation or PaO2/FiO2 <300mmHg, requires oxygen therapy or additional respiratory support): 0.9% vs. 3.3% (p=0.37) *Rate of patients needed to receive intensive care in ICU*: estimates not reported in paper. Authors state there was no difference. *Adverse events (antiviral-associated adverse effects)*: 21.9% vs. 33.3% (p=0.141). All AEs were grade 1.	addition, a clinical diagnosis was relied upon, not a positive SARS-CoV-2 PCR result -increased ratio of severe to critical patients in the favipiravir group (16 (severe)+2 (critical)) compared to umifenovir group (8+1) -the finding that moderate participants in the favipiravir had better recovery at day 7 (risk difference of 15.6%): this subgroup analysis where severely ill participants were excluded was not pre-specified in the protocol or trial registry so should be interpreted with caution -details of the randomization procedure were lacking, and there was no allocation concealment in this non-blinded study. -estimates for the ICU admission endpoint are not reported in the paper. **Overall judgement with regards to risk of bias judged as "*HIGH RISK*":** **-Random sequence generation (selection bias)**: details not clear. **HIGH RISK.** **-Allocation concealment (selection bias)**: Allocation was not concealed. **HIGH RISK.** **-Blinding of participants and personnel (performance bias)**: There was no blinding. **HIGH RISK.** **-Blinding of outcome assessment (detection bias) (patient-reported clinical improvement outcomes)**: There was no blinding. **HIGH RISK.** **-Blinding of outcome assessment (detection bias)**: four participants excluded from study after randomization. Larger proportion in umifenovir arm received antivirals and glucocorticoids than favipiravir arm. **MODERATE RISK**. **-Incomplete outcome data addressed (attrition bias)**: missing outcome data: 240 randomized and 236 analyzed. **LOW RISK**. **-Selective reporting (reporting bias)**: subgroup analysis not part of protocol / methods section. **HIGH RISK**.
Cai et al, 2020	Non-randomized open label,	China N=80	Both arms were co-treated with inhaled interferon-α1b 60 μg twice daily and therapy was continued until	Favipiravir vs. Lopinavir/ritonavir *Time to viral clearance, median (IQR)*: 4 days (2.5-9) vs. 11 days (8-13), p<0.001 (**Unadjusted analysis**)	**Issues of concern** -treatment assignment was not randomized, hence very high likelihood of uneven distribution of prognostic confounders

Citation	Study design	Population (n)	Treatment	Main findings	Comments
	before-after study	Age 16–75 years; median age of 47 years (IQR = 35.8–61); 13.7% were ≥65 years old PCR positive; duration from disease onset to enrolment was less than 7 d; willing to take contraception during the study and within 7 d after treatment; and no difficulty in swallowing the pills Moderate COVID-19 patients were enrolled within 7 days from disease onset Comorbidities: Excluded: ≥75 years old, with severe or critical disease, chronic liver disease or end-stage renal disease	viral clearance, up to a maximum of 14 days. **Intervention**: favipiravir 1600 mg orally twice daily on day 1 followed by 600 mg orally twice daily on days 2–14 **Comparison**: lopinavir/ritonavir 400 mg/RTV 100 mg twice daily up to 14 days	*Chest CT changes*: adjusted OR 3.19, 95% CI 1.05 – 12.44 Viral clearance: adjusted HR 3.43, 95% CI 1.16 – 10.15 *Adverse events*: 11.4% vs. 55.6%, p<0.001	-this is a before-after study where controls are historical, they completed treatment before the study began. Comparisons were not done in parallel -analysis approach used to evaluate chest CT clearance has limitations of overestimating the risk ratio as this outcome is large (i.e. for outcomes >10%, logistic regression may not be appropriate to estimate risk) **Overall judgement with regards to risk of bias judged as "*HIGH RISK*":** **-Random sequence generation (selection bias)**: Patients were not randomized. **HIGH RISK.** **-Allocation concealment (selection bias)**: Allocation was not concealed. **HIGH RISK.** **-Blinding of participants and personnel (performance bias)**: There was no blinding. **HIGH RISK.** **-Blinding of outcome assessment (detection bias) (patient-reported clinical improvement outcomes)**: There was no blinding. **HIGH RISK.** **-Blinding of outcome assessment (detection bias) (most outcomes)**: One of the outcomes was subjective. **MODERATE RISK**. **-Incomplete outcome data addressed (attrition bias)**: All data analysed. **LOW RISK**. **-Selective reporting (reporting bias)**: no protocol or pre-specified analyses plan available. Subgroup analysis not pre-specified. **HIGH RISK**.

Appendix 1: Search strategy

Epistemonikos and Network Meta-analysis website
Manual search for comparisons of “favipiravir OR avigan OR favipivavir OR t 705 OR t705” versus any therapeutic agent or placebo on the website

PubMed (adapted for Cochrane Library search)

1. coronavir* OR coronovirus* OR "corona virus" OR "virus corona" OR "corono virus" OR "virus corono" OR hcov* OR "covid-19" OR covid19* OR "covid 19" OR "2019-nCoV" OR cv19* OR "cv-19" OR "cv 19" OR "n-cov" OR ncov* OR "sars-cov-2" OR (wuhan* AND (virus OR viruses OR viral) OR coronav*) OR (covid* AND (virus OR viruses OR viral)) OR "sars-cov" OR "sars cov" OR "sars-coronavirus" OR "severe acute respiratory syndrome"
2. favipiravir OR avigan OR favipivavir OR t 705 OR t705
3. randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh: noexp] OR randomly [tiab] OR trial [ti] OR systematic review) NOT (animals [mh] NOT humans [mh])
4. **1** AND **2** AND **3**

MedRxiv
Advanced search option for terms “favipiravir OR avigan OR favipivavir OR t 705 OR t705” and full text or abstract or title (match whole any) and posted between "01 Jan, 2020 and 20 Jun, 2020"

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ X *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Two preprints and one poorly controlled study published in an engineering journal
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☐ None ☐ Uncertain ☒ X	No estimate of effect size or direction can be made with any confidence
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ X *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Short-term studies with very complex treatment regimens make attribution of any adverse effects difficult to interpret.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☐ None ☐ Uncertain ☒ X	No confident estimate of the extent or clinical relevance of harms can be made on the basis of the available evidence.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control *or* Uncertain ☒ X	Cannot be gauged at this time, on the basis of this evidence.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☐ No ☒ X Uncertain ☐	At present, favipiravir is not registered by SAHPRA, so use under clinical trial conditions only is appropriate.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☒ X	Cost of medicines/ month: **Medicine** | **Cost (ZAR)** Favipiravir | No pricing data available at present.

Version	Date	Reviewer(s)	Recommendation and Rationale
First	25 June 2020	ST, AG, JN	Favipiravir should only be used in the context of an approved clinical trial, as not currently SAHPRA registered; and there is insufficient evidence to assess benefit vs harms.