**Favipiravir Information for healthcare providers**

Favipiravir is a purine nucleoside analogue, which acts as a competitive inhibitor of RNA-dependant RNA polymerase.[1] It has *in vitro* activity against influenza A, several agents of viral hemorrhagic fever, and SARS-CoV-2.[1-3] Favipiravir was approved for novel influenza strains unresponsive to standard antiviral therapies in Japan in 2004, under the trade name Avigan®. It is manufactured by Toyama Chemical Co., Ltd.

**Evidence for Favipiravir and COVID-19**

Favipiravir has *in vitro* activity against SARS-CoV-2.[2] Early clinical experience with favipiravir for COVID-19 is promising. In a non-randomized open-label trial of favipiravir in China, there was a significant reduction in the median time to viral clearance with favipiravir (4 days; IQR 2.5-9) as compared to historical controls treated with lopinavir/ritonavir (11 days; IQR 8-13) $p < 0.001$.[4] In an open-label trial in China, 240 patients with COVID-19 were randomized to favipiravir or arbidol.[5] The rate of clinical recovery by day 7 of treatment was higher amongst patients receiving favipiravir, albeit not statistically significant (61% v. 52%, p=0.1).

Given the demonstrated in-vitro activity and signals of benefit in preliminary clinical experience, it is critical to now evaluate the efficacy of favipiravir as chemoprophylaxis against COVID-19 using a placebo-controlled randomized trial.

**Dosing and Administration of Favipiravir**

Favipiravir is provided as 200 mg tablets and dosed orally. In this study, favipiravir is used for both treatment and prophylaxis. For treatment, the does of favipiravir is 2000 mg (10x 200 mg tablets) orally twice daily on day 1, and 1000 mg (5 x 200 mg tablets) orally twice daily for 13 additional days. The dose for favipiravir for prophylaxis is 1600 mg (8 x 200 mg tablets) orally twice daily on day 1 followed by 800 mg (4 x 200 mg tablets) orally twice daily for 24 additional days.

Favipiravir is rapidly and completely absorbed after oral administration of the 200 mg immediate release tablets. Favipiravir can be taken with or without food. Compounding services at the distributing pharmacy can prepare suspensions for study participants who are not able to swallow tablets.

**Potential Risks of Favipiravir**

Favipiravir is considered a safe drug. No related serious adverse events occurred in licencing studies; more than 40 clinical studies have been conducted with favipiravir. Favipiravir has been well tolerated in elderly subjects with uncomplicated influenza.

A consistent safety profile with infrequent mild to moderate primarily gastrointestinal adverse events has been observed. Mild transient, asymptomatic elevations in serum uric acid and mild to moderate diarrhea are the two most common adverse events known to occur with favipiravir (diarrhea 2.3%, nausea 2.1%).

Favipiravir is contraindicated in nursing mothers and pregnant women due to its potential teratogenicity; this potential for teratogenicity is not of significant relevance to LTCH residents. No dosing modifications are required for renal dysfunction or age. Higher drug levels occur in patients with cirrhosis, and we have thus excluded patients known to have cirrhosis.

Overall, the safety of favipiravir suggests that the potential benefit to human participants exposed to a confirmed case of COVID-19 outweighs potential risks.

**Drug-Drug Interactions**

Though an inhibitor of CYP 2C8 and aldehyde oxidase, few drugs are contra-indicated. Only three relevant drug-drug interactions are noted for this trial of favipiravir:

1) **Acetaminophen must be limited to ≤ 3000 mg per day**

- Favipiravir may increase acetaminophen levels

2) **Hydralazine** is contra-indicated (may increase risk of hypotension)
- All other anti-hypertensive agents are permitted

3) **Pyrazinamide** is contra-indicated (may increase favipiravir levels)

**References**

1. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral Res*. 2013;100(2):446-454.
2. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269-271.
3. Shiraki K, Daikoku T. Favipiravir, an anti-influenza drug against life-threatening RNA virus infections. *Pharmacol Ther*. 2020:107512.
4. Kai Q, Yang M, Liu D, et al. Experimental treatment with favipiravir for COVID-19: an open-label control study. *Engineering.* 2020.
5. Chen C, huang J, cheng Z, et al. Favipiravir versus arbidol for COVID-19: A randomized clinical trial. medRxiv. 2020. [preprint, doi:10.1101/2020.03.17.20037432]. .