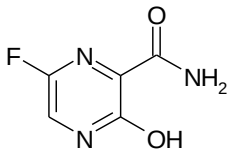
Monographs on Favipiravir and on Favipiravir tablets
International Meeting of World Pharmacopoeias (IMWP)

The pharmacopoeial alert system, established at the 9th IMWP meeting in Da Nang, Vietnam, was convened for the first time in response to the COVID-19 pandemic. The main outcomes of the meetings can be found in the report of the 12th IMWP (see here). They include the development of the IMWP monographs on Favipiravir and on Favipiravir tablets to assist those involved in the fight against falsified and substandard products (such as official control laboratories). IMWP monographs are not legally binding or intended to become official standards (even if they could serve as a basis). They can be used on a voluntary basis and will be made publicly available. The development of these monographs does not imply or confer any demonstrated effectiveness of favipiravir in the treatment of COVID-19, nor does it recommend its therapeutic use.

The IMWP monographs on Favipiravir and on Favipiravir tablets were developed by the Japanese Pharmacopoeia with support from other pharmacopoeias. The reference substances *IMWP RS on Favipiravir* is available from Pharmaceutical and Medical Device Regulatory Science Society of Japan (PMRJ), Pharmaceutical Reference Standards Center, URL: https://www.pmrj-ec.jp/aec/user/?lang=en

Favipiravir
(Favipiravirum)



$C_5H_4FN_3O_2$: 157.10

6-Fluoro-3-hydroxypyrazine-2-carboxamide

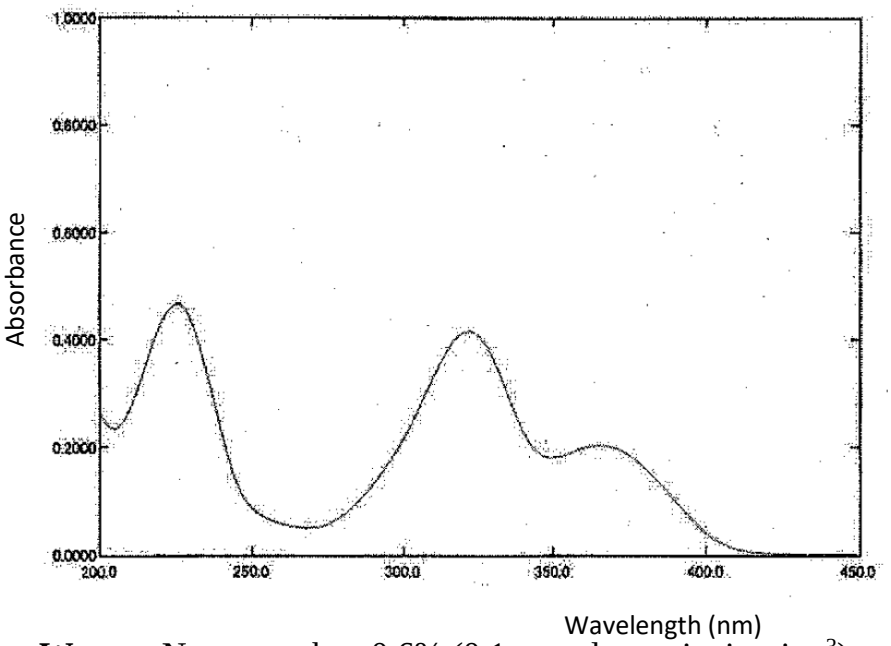
[*259793-96-9*]

Favipiravir contains not less than 98.0% and not more than 102.0% of favipiravir ($C_5H_4FN_3O_2$), calculated on the anhydrous basis.

Identification: Determine the absorption spectrum of a solution of Favipiravir in 0.1 mol/L hydrochloric acid TS (1 in 100000) [1] as directed under Ultraviolet-visible Spectrophotometry[2], and compare the spectrum with the Reference Spectrum: both spectra exhibit similar intensities of absorption at the same wavelengths.

[1] Concentration (g/mL)
[2] Please refer to <*2.24*> Ultraviolet-visible Spectrophotometry (JP17)
https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf

Reference Spectrum



Water: Not more than 0.6% (0.1g, coulometric titration[3]).

Assay: Weigh accurately about 20 mg each of Favipiravir and IMWP RS on Favipiravir (separately determine the water in the Karl-Fisher coulometric titration method[4]), and dissolve each in the diluent to make exactly 50 mL. Pipet 5 mL each of those solutions, add the diluent to make exactly 50 mL, and use those solutions as the sample solution and the standard solution, respectively. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography[5] according to the following conditions, and determine the peak areas of favipiravir, A_T[6] and A_S[7].

Amount (mg) of favipiravir ($C_5H_4FN_3O_2$) = $W_S \times (A_T / A_S)$

*W*s: Amount (mg) of IMWP RS on Favipiravir, calculated on the anhydrous basis

[3] Please refer to <*2.48*> Water Determination (Karl Fischer Method) (JP17)
https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf
[4] Please refer to <*2.48*> Water Determination (Karl Fischer Method) (JP17)
https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf
[5] Please refer to <*2.01*> Liquid Chromatography (JP17)
https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf
[6] A_T: Peak area of favipiravir obtained from the sample solution.
[7] A_S: Peak area of favipiravir obtained from the standard solution.

Diluent: To 0.2 mol/L potassium dihydrogen phosphate[8] add diluted phosphoric acid[9] (137 in 10000)[10] to adjust the pH to 3.0. To 25 mL of this solution, add 100 mL of acetonitrile and 875 mL of water.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

Mobile phase: To 0.2 mol/L potassium dihydrogen phosphate, add diluted phosphoric acid (137 in 10000) to adjust the pH to 3.0. To 100 mL of this solution, add 40 mL of acetonitrile and 860 mL of water.

Flow rate: Adjust so that the retention time of favipiravir is about 13 minutes.

System suitability

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of favipiravir are not less than 8,000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of favipiravir is not more than 1.0%.

[8] Please refer to Potassium dihydrogen phosphate KH_2PO_4 [K 9007,Special class] (JP17)
https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf
[9] Please use HPLC grade.
[10] Concentration (mL/mL)

FAVIPIRAVIR TABLETS (200 mg)
(FAVIPIRAVIRI COMPRESSI)

Favipiravir Tablets contains not less than 95.0% and not more than 105.0% of the labeled amount of favipiravir ($C_5H_4FN_3O_2$: 157.10).

Method of preparation. Prepare as directed under *Tablets*, with favipiravir.

Identification. To a quantity of powdered Favipiravir Tablets, equivalent to 10 mg of favipiravir, add 0.1 mol/L hydrochloric acid TS to make 50 mL, and shake for 20 minutes. Filter this mixture using a membrane filter (pore size: not more than 0.45 μm), discarding first 3 mL. To 1 mL of the filtrate, add 0.1 mol/L hydrochloric acid TS to make 20 mL. Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry[11]: it exhibits maximal absorption between 224 nm and 228 nm, between 320 nm and 324 nm, and between 363 nm and 367 nm.

Assay. Weigh accurately the mass of not less than 20 Favipiravir Tablets. Weigh accurately 5 Favipiravir Tablets, add about 40 mL of acetonitrile and about 40 mL of the diluent, and shake until tablets are disintegrated. Add the diluent to make exactly 200 mL and shake for 20 minutes. Filter this mixture using a membrane filter (pore size: not more than 0.45 μm), discarding first 3 mL. Pipet exactly V_1 mL of the filtrate add the diluent to make exactly V_2 mL, so that each mL contains about 40 μg of favipiravir ($C_5H_4FN_3O_2$), and use this solution as the sample solution. Separately, weigh accurately about 20 mg of IMWP RS on Favipiravir (separately determine the water in the Karl-Fisher coulometric titration method[12]) and dissolved in the diluent to make exactly 50 mL. Pipet 5 mL of this

[11] Please refer to <*2.24*> Ultraviolet-visible Spectrophotometry (JP17)
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[12] Please refer to <*2.48*> Water Determination (Karl Fischer Method) (JP17)
https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf

solution, add the diluent to make exactly 50 mL and use this solution as the standard solution. Perform the test with 20 μL each of the sample solution and standard solution as directed under Liquid Chromatography [13] according to the following conditions and determine the peak areas of favipiravir, A_T[14] and A_S[15].

Amount (mg) of favipiravir ($C_5H_4FN_3O_2$) = $W_S \times (A_T / A_S) \times (M / W_T) \times (V_2 / V_1) \times 2/5$

W_S: Amount (mg) of IMWP RS on Favipiravir, calculated on the anhydrous basis;
M: Average mass (mg) of a Favipiravir tablet obtained from 20 or more Favipiravir tablets;
W_T: Amount (mg) of 5 Favipiravir tablets.

Diluent: To 0.2 mol/L potassium dihydrogen phosphate[16], add diluted phosphoric acid[17] (137 in 10000)[18] to adjust the pH to 3.0. To 25 mL of this solution, add 100 mL of acetonitrile and 875 mL of water.

Operating conditions

Detector: An ultraviolet absorption photometer (wavelength: 225 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35 °C.

[13] Please refer to <*2.01*> Liquid Chromatography (JP17)
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[14] A_T: Peak area of favipiravir obtained from the sample solution.
[15] A_S: Peak area of favipiravir obtained from the standard solution.
[16] Please refer to Potassium dihydrogen phosphate KH_2PO_4 [K 9007,Special class] (JP17)
https://www.mhlw.go.jp/file/06-Seisakujouhou-11120000-Iyakushokuhinkyoku/JP17_REV_1.pdf
[17] Please use HPLC grade.
[18] Concentration (mL/mL)

Mobile phase: To 0.2 mol/L potassium dihydrogen phosphate, add diluted phosphoric acid (137 in 10000) to adjust the pH to 3.0. To 100 mL of this solution, add 40 mL of acetonitrile and 860 mL of water.

Flow rate: Adjust so that the retention time of favipiravir is about 13 minutes.

System suitability

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of favipiravir are not less than 8,000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of favipiravir is not more than 1.0%.

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