Draft Proposal for Comments and Inclusion in The Indian Pharmacopoeia

Molnupiravir Capsules

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This draft proposal contains monograph text for inclusion in the Indian Pharmacopoeia (IP). The content of this draft document is not final, and the text may be subject to revisions before publication in the IP. This draft does not necessarily represent the decisions or the stated policy of the IP or Indian Pharmacopoeia Commission (IPC).

Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Manufacturers are also invited to submit samples of their products to the IPC to ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.

Document History and Schedule for the Adoption Process

Description	Details
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Further follow-up action as required.	

Molnupiravir Capsules

Molnupiravir Capsules contain not less than 90.0 per cent and not more than 110.0 per cent of the stated amount of molnupiravir, $C_{13}H_{19}N_3O_7$.

Usual strengths. 200 mg; 400 mg.

Identification

In the Assay, the principal peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

Tests

NOTE- Prepare the solutions immediately before use.

Dissolution (2.5.2).
Apparatus No. 2 (Paddle),
Medium. 500 ml of *0.1 M hydrochloric acid,*
Speed and time. 50 rpm and 60 minutes.

Withdraw a suitable volume of the medium and filter.

Determine by liquid chromatography (2.4.14).

Solvent mixture. 90 volumes of a buffer solution prepared by dissolving 1.54 g of *ammonium acetate* in 1000 ml of *water*, adjusted to pH 4.75 with *glacial acetic acid* and 10 volumes of *methanol*.

Test solution. Use the filtrate, dilute, if necessary, with the dissolution medium.

Reference solution. Dissolve 20 mg of *molnupiravir IPRS* in the solvent mixture and dilute to 25.0 ml with the solvent mixture. Dilute 5.0 ml of the solution to 10.0 ml with the dissolution medium.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (5 µm) (Such as inertsil, ODS-3V),
- sample temperature: 5º,
- mobile phase: a mixture of 83 volumes of 0.1 per cent v/v solution of *trifluoroacetic acid* and 17 volumes of *acetonitrile*,
- flow rate: 1 ml per minute,
- spectrophotometer set at 270 nm,
- Injection volume: 5 µl.

Inject the reference solution. The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{19}N_3O_7$ in the medium.

Q. Not less than 80 per cent of the stated amounts of $C_{13}H_{19}N_3O_7$.

Related substances. Determine by liquid chromatography (2.4.14).

NOTE- Prepare the solutions immediately before use.

Solvent mixture. 90 volumes of *water* and 10 volumes of *methanol*.

Test solution. Disperse a quantity of mixed contents of capsules containing 0.1 g of Molnupiravir with 180 ml of the solvent mixture, with the aid of ultrasound for 20 minutes and dilute to 250.0 ml with the solvent mixture.

Reference solution (a). A 0.0004 per cent w/v solution of *molnupiravir IPRS* in the solvent mixture.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 50.0 ml with the solvent mixture.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (2.7 µm) (Such as Supelco Ascentis Express 90Aº C18),
- sample temperature: 5º,
- mobile phase: A. 0.1 per cent v/v solution of *trifluoroacetic acid* in *water*,
  B. *methanol*,
- a gradient programme using the conditions given below,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 275 nm,
- injection volume: 5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	95	5
2	95	5
15	70	30
20	65	35
30	30	70
40	30	70
42	95	5
50	95	5

Name	Relative retention time	Correction factor
Molnupiravir impurity A[1]	0.2	0.7
Molnupiravir	1.0	--
MOL-Hydroxylamine[2,*]	1.7	--

*Process impurity controlled in drug substance and no need to report in drug product,
[1]1-((2R,3R,4S,5R)-3,4-dihydroxy-5-(hydroxymethyl)tetrahydrofuran-2-yl)-4-(hydroxyamino)pyrimidin-2(1H)-one,
[2]((3aR,4R,6R,6aR)-6-(4-(hydroxyamino)-2-oxopyrimidin-1(2H)-yl)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)methyl isobutyrate.

Inject reference solution (a) and (b). The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 5.0 per cent in the chromatogram obtained with reference solution (a) and the signal-to-noise ratio is not less than 10 in the chromatogram obtained with reference solution (b).

Inject reference solution (a) and the test solution. In the chromatogram obtained with the test solution, the area of any peak corresponding to molnupiravir impurity A is not more than 3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.0 per cent), the area of any other secondary peak is not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 3.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (3.5 per cent). Ignore any peak with an area less than 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

Microbial contamination (2.2.9). Total aerobic viable count is not more than 10^3 CFU per g and total fungal count is not more than10^2 CFU per g. 1 g is free from *Escherichia coli.*

Other tests. Comply with the tests stated under Capsules.

Assay. Determine by liquid chromatography (2.4.14).

Buffer solution. Dissolve 1.54 g of *ammonium acetate* in 1000 ml of *water,* adjusted to pH 4.75 with *glacial acetic acid.*

Solvent mixture. 90 volumes of the buffer solution and 10 volumes of *methanol*.

Test solution. Weigh and mix the contents of 20 capsules. Disperse a quantity of the mixed content containing 0.1 g of Molnupiravir in the solvent mixture, with the aid of ultrasound for 15 minutes with intermitted shaking and dilute to 200.0 ml with the solvent mixture. Centrifuge a portion of the solution at 5000 rpm for 10 minutes, filter.

Reference solution. A 0.05 per cent w/v solution of *molnupiravir IPRS* in the solvent mixture.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilane bonded to porous silica (2.7 µm) (Such as Ascentis Express C18),
- column temperature: 45°,
- sample temperature: 8º,
- mobile phase: A. a mixture of 98 volumes of 0.1 per cent v/v solution of *formic acid* in *water* and 20 volumes of *acetonitrile,*
  B. *acetonitrile,*
- a gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 260 nm,
- injection volume: 5 µl.

Time (in min.)	Mobile phase A (per cent v/v)	Mobile phase B (per cent v/v)
0	100	0
8	65	35
12	45	55
13	100	0
16	100	0

Inject the reference solution. The test is not valid unless the tailing factor is not more than 2.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent.

Inject the reference solution and the test solution.

Calculate the content of $C_{13}H_{19}N_3O_7$ in the capsules.

Storage. Store protected from moisture, at a temperature not exceeding 30°.