World Health Organization

MOLNUPIRAVIR CAPSULES

(MOLNUPIRAVIRI CAPSULAE)

Draft proposal for inclusion in *The International Pharmacopoeia*

(14 July 2023)

DRAFT FOR DISCUSSION

Please submit your comments through the online platform, PleaseReview™ (https://who.pleasereview.net/Main/Default.aspx?action=loaddocument&reviewid=188) If not registered or included in our mailing list, kindly submit your request with your full name, email address and organization/affiliation to jonessi@who.int, nsp@who.int.

For any technical queries, please contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (schmidth@who.int), with a copy to Ms Sinéad Jones (jonessi@who.int, nsp@who.int).

Comments should be submitted through the online platform on or by **17 September 2023**. Please note that only comments received by this deadline will be considered for the preparation of this document.

Our working documents are sent out electronically and uploaded into PleaseReview™. The working documents are also placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/working-documents-public-consultation) under the "Working documents in public consultation". If you wish to receive all our draft guidelines during the course of the year, please send your full name, organization/ affiliation, and email address to jonessi@who.int, nsp@who.intand your name will be added to our electronic mailing list and review platform.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/21.907

MOLNUPIRAVIR CAPSULES (MOLNUPIRAVIRI CAPSULAE)

Description	Date
Drafting of the monograph based on information received from manufacturers.	December 2021
Draft revision sent out for public consultation.	January – February 2022
Presentation to the 56th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).	April 2022
Laboratory investigations to verify the analytical provision.	May – August 2022
Preparation of Revision 1 based on the results of the laboratory investigations and the discussion at the 56th meeting of the ECSPP.	September 2022
Revision 1 sent out for public consultation.	September – November 2022
Updated version 1A prepared based on feedback received.	November 2022
Discussion of the comments received during the second public consultation with Experts and agreement on Revision 2.	April 2023
Discussion at the WHO Consultation on Quality Control and Pharmacopoeial Specifications for Medicines	April 2023
Public consultation of Rev. 2 as agreed upon at the a.m. consultation	July – August 2023
Further follow-up action as required.	

*[**Note from the Secretariat.** The monograph on Molnupiravir capsules is proposed for inclusion in* The International Pharmacopoeia.

Being the first public standard on Molnupiravir capsules, this monograph is expected to play an important role in ensuring access to safe, effective and quality assured molnupiravir-containing medicines.

The monograph is based on information received from manufacturers and on the testing of products from the market. Manufacturers, regulatory authorities, procurement agencies and other stakeholders are invited to provide their comments on the draft monograph to the Secretariat of The International Pharmacopoeia.

Should manufacturers propose to widen limits set in the monograph, the information which regulatory authority has approved such limits should be included in the request.]

MOLNUPIRAVIR CAPSULES (MOLNUPIRAVIRI CAPSULAE)

Category. Antiviral.

Storage. Molnupiravir capsules should be kept in a tightly closed container, protected from moisture.

Additional information. Molnupiravir 200 mg capsules are listed on the 8th Invitation to Manufacturers of therapeutics against COVID-19 to submit an Expression of Interest (EOI) for Product Evaluation to the WHO Prequalification Unit.

Requirements

Complies with the monograph for *Capsules*.

Definition. Molnupiravir capsules contain Molnupiravir. They contain not less than 90.0% and not more than 110.0% of the amount of Molnupiravir ($C_{13}H_{19}N_3O_7$), stated on the label.

Identity tests

- Either test A alone or any two of tests B, C and D may be applied

A. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under "Assay", but using, as the detector, a diode array detector to record the UV spectrum of the principal peak in each chromatogram in the range of 200 nm to 400 nm. The retention time and the UV spectrum of the principal peak in the chromatogram obtained with solution (1) correspond to the retention time and the UV spectrum of the peak due to molnupiravir in the chromatogram obtained with solution (2).

B. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under "Assay".

The retention time of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time of the peak due to molnupiravir in the chromatogram obtained with solution (2).

C. Carry out the test as described under *1.14.1 Chromatography*, Thin layer chromatography, using silica gel R6 as the coating substance and a freshly prepared mixture of ethyl acetate R, methanol R and glacial acetic acid R (90:9:1 *V/V/V*) as the mobile phase. Apply separately to the plate 2 µL of each of the following two solutions. For solution (A), transfer a quantity of the mixed contents, nominally containing 50 mg of Molnupiravir into a 50 mL volumetric flask. Add about 40 mL of methanol R, sonicate for 10 minutes with intermediate shaking, allow to cool to room temperature and make up to volume with methanol R, mix and filter. For solution (B), use a solution containing 1 mg per mL of molnupiravir RS in methanol R. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of air. Examine the under ultraviolet light (254 nm). The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to molnupiravir in the chromatogram obtained with solution (B).

D. Prepare the test solution by diluting 5 mL of solution (1), prepared as described under “Assay”, to 20 mL with the described diluent. The absorption spectrum (*1.6 Spectrophotometry in the visible and ultraviolet regions*) of the test solution, when observed between 200 nm and 400 nm, exhibits two maxima at about 235 nm and 273 nm.

Dissolution.Carry out the test described under *5.5 Dissolution test for oral dosage forms*, using as the dissolution medium 500 mL of hydrochloric acid (~3.65 g/L) TS and rotating the paddle at 50 revolutions per minute. Use sinkers to prevent floating of the capsules, as necessary. At 30 minutes, withdraw a sample of 10 mL of the medium through an in-line filter. Allow the filtered sample to cool to room temperature.

Prepare a buffer solution pH 4.75 by dissolving 3.08 g of ammonium acetate R in water R and diluting to 2000 mL with the same solvent. Adjust the pH to a value between 4.70 and 4.80 using glacial acetic acid R.

Prepare as the diluent, a mixture of 90 volumes of buffer solution pH 4.75 and 10 volumes of methanol R.

Dilute 5.0 mL of the filtrate to 10.0 mL with the diluent (solution (1). For solution (2), dissolve 20.0 mg of molnupiravir RS in the diluent and dilute to 100.0 mL with the same solvent.

Carry out the determination as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using the conditions given under "Assay".

Measure the areas of the peaks corresponding to molnupiravir, obtained in the chromatograms of solutions (1) and (2), and corresponding to impurity A, obtained in the chromatogram of solution (1). Multiply the area of the peak corresponding to impurity A with a correction factor of 0.84.

For each of the capsules tested, calculate the total amount of Molnupiravir ($C_{13}H_{19}N_3O_7$) dissolved in the medium, using the sum of the area of the peak corresponding to molnupiravir and the corrected area of the peak corresponding to impurity A. Use the declared content of ($C_{13}H_{19}N_3O_7$) in molnupiravir RS to calculate the concentration of molnupiravir in solution (2).

Evaluate the results as described under *5.5 Dissolution test for solid oral dosage forms*, Acceptance criteria. The amount of Molnupiravir released is not less than 80% (Q) of the amount declared on the label.

Related substances. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless-steel column (4.6 mm

x 25 cm) packed with particles of silica gel, the surface of which has been modified with chemically bonded phenyl groups (5 µm).[1]

Use the following conditions for gradient elution:

- mobile phase A: pH 2.3 buffer solution;
- mobile phase B: mixture of 20 volumes of water R and 80 volumes of the solvent mixture.

Prepare the pH 2.3 buffer solution by dissolving 3.4 g of potassium dihydrogen phosphate R in water R and diluting to 1000 mL with the same solvent. Carefully adjust the pH to 2.30 with phosphoric acid (~105 g/L) TS.

Prepare as the solvent mixture, a mixture of 30 volumes of methanol R and 70 volumes of acetonitrile for chromatography R.

Time (minutes)	**Mobile phase A (% v/v)**	**Mobile phase B (% v/v)**	**Comments**
0–5	100	0	Isocratic
5–20	100 to 80	0 to 20	Linear gradient
20–40	80 to 75	20 to 25	Linear gradient
40–55	75 to 40	25 to 60	Linear gradient
55–65	40 to 0	60 to 100	Linear gradient
65–73	0	100	Isocratic
73–74	0 to 100	100 to 0	Return to initial composition
74–85	100	0	Re-equilibration

[1] A Kromasil 100-5 Phenyl column has been found suitable.

Operate with a flow rate of 0.9 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 230 nm and for impurity F at 260 nm. Maintain the column temperature at 25 °C.

Prepare the following solutions freshy and perform the analysis without delay. Use water R as a diluent. For solution (1), transfer a quantity of the mixed contents, nominally containing 120 mg of Molnupiravir into a 100 mL volumetric flask. Add about 60 mL, sonicate for 10 minutes with intermediate shaking, allow to cool to room temperature, make up to volume, mix and filter. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3), dilute 1.0 mL of solution (2) to 20.0 mL. For solution (4), dissolve and dilute molnupiravir for system suitability RS (containing molnupiravir and impurity I) as described in the leaflet of the reference substance.

Inject 20 µL each of solutions (1), (2), (3) and (4).

Use the chromatogram obtained with solution (4) and the chromatogram supplied with molnupiravir for system suitability RS to identify impurity I.

The impurities are eluted, if present, at the following relative retentions with reference to molnupiravir (retention time about 23 minutes): impurity D about 0.19; impurity A about 0.23; impurity E about 0.45; impurity L about 0.82; impurity I about 1.03, impurity F about 1.14; impurity G about 1.70 and 1.72, impurity B about 1.83 and impurity H about 2.04.

The test is not valid unless, in the chromatogram obtained with solution (4), the peak-to-valley ratio (Hp/Hv) is at least 3.0, where Hp is the height above the baseline of the peak due to impurity I and Hv is the height above the baseline of the lowest point of the curve separating the peak due to molnupiravir from the peak due to impurity I. Also, the test is not valid unless, in the chromatogram obtained with solution (3), the peak due to molnupiravir is obtained with a signal-to-noise ratio of at least 20.In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity A is not greater than three times the area of the peak due to molnupiravir in the chromatogram obtained with solution (2) (3.0 %);
- the area of any peak corresponding to impurity B is not greater than 0.22 times the area of the peak due to molnupiravir in the chromatogram obtained with solution (2) (0.22 %);
- the area of any other impurity peak is not greater than 0.15 times the area of the peak due to molnupiravir in the chromatogram obtained with solution (2) (0.15 %);
- the area of any peak corresponding to impurity F, recorded at 260 nm, when multiplied with a correction factor of 0.7, is not greater than 0.15 times the area of the peak due to molnupiravir in the chromatogram obtained with solution (2), recorded at 260 nm (0.15 %).
- Determine the sum of the areas of all impurity peaks recorded at 230 nm, excluding the area of any peak corresponding to impurity F. Disregard any peaks with an area of less than the area of the peak due to molnupiravir in the chromatogram obtained with solution (3), recorded at 230 nm (0.05%). Calculate the percentage content of all impurities using the area of the peak due to molnupiravir in the chromatogram obtained with solution (2), recorded at 230 nm, as a reference.
- Determine the corrected area of any peak corresponding to impurity F, recorded at 260 nm, and calculate its percentage content using the area of the peak due to molnupiravir in the chromatogram obtained with solution (2), recorded at 260 nm, as a reference. Disregard any peak with an area of less than the area of the peak due to molnupiravir in the chromatogram obtained with solution (3), recorded at 260 nm (0.05%).
- The sum of the percentage content of all impurities, recorded at 230 nm, and the percentage content of impurity F, recorded at 260 nm, is not greater than 3.5 %.

Assay. Carry out the test as described under *1.14.1 Chromatography*, High-performance liquid chromatography, using a stainless steel column (4.6 mm x 15 cm) packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded phenyl groups (2.6 µm).[2]

Use the following conditions for gradient elution:

- mobile phase A: ammonium dihydrogen phosphate solution;
- mobile phase B: acetonitrile for chromatography R.

Prepare the ammonium dihydrogen phosphate solution by dissolving 5.75 g of ammonium dihydrogen phosphate R in water R and diluting to 1000 mL with the same solvent.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–15	90	10	Isocratic
15–16	90 to 35	10 to 65	Linear gradient
16–22	35	65	Isocratic
22–23	35 to 90	65 to 10	Return to initial composition
23–30	90	10	Re-equilibration

Operate with a flow rate of 0.7 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 260 nm. Maintain the column temperature at 40 °C.

Prepare a buffer solution pH 4.75 by dissolving 3.08 g of ammonium acetate R in water R and diluting to 2000 mL with the same solvent. Adjust the pH to a value between 4.70 and 4.80 using glacial acetic acid R.

[2] A Kinetex Biphenyl column has been found suitable.

Prepare as the diluent, a mixture of 90 volumes of buffer solution pH 4.75 and 10 volumes of methanol R.

Prepare the following solutions. For solution (1), weigh and powder the contents of 20 capsules. Transfer a quantity of the mixed contents, nominally containing 300.0 mg of Molnupiravir into a 250 mL volumetric flask. Add about 200 mL, sonicate for 10 minutes with intermediate shaking, allow to cool to room temperature, make up to volume, mix and filter. Dilute 5.0 mL of this solution to 50.0 mL. For solution (2), weigh 60.0 mg of molnupiravir RS into a 50 mL volumetric flask. Add 30 mL, sonicate to dissolve, and make up to volume. Dilute 5.0 mL of this solution to 50.0 mL.

Inject 10 µL each of solutions (1) and (2) and record the chromatograms.

Measure the areas of the peaks corresponding to molnupiravir obtained in the chromatograms of solutions (1) and (2) and calculate the percentage content of Molnupiravir ($C_{13}H_{19}N_3O_7$) in the capsules, using the declared content of $C_{13}H_{19}N_3O_7$ in molnupiravir RS.

Impurities

The impurities limited by the requirements of this monograph include those listed in the monograph on Molnupiravir.

Reference substances to be established

Molnupiravir RS

- *International Chemical Reference Substance to be established.*

Molnupiravir for system suitability RS (containing molnupiravir and impurity I)

- *International Chemical Reference Substance to be established.*

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