MOLNUPIRAVIR CAPSULES
(MOLNUPIRAVIRI CAPSULAE)

Draft proposal for inclusion in The International Pharmacopoeia

(9 September 2022)

DRAFT FOR DISCUSSION

Please send any comments you may have on this draft working document to Dr Herbert Schmidt, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (email: schmidt@who.int), with a copy to Ms Sinéad Jones (email: jonessi@who.int) by 05 November 2022.

Our working documents are sent out electronically and they will be placed on the WHO Medicines website (https://www.who.int/teams/health-product-and-policy-standards/standards-and-specifications/pharmaceuticals/current-projects) for comments under the “Working documents in public consultation” link. If you wish to receive our draft guidelines, please send your e-mail address to

© World Health Organization 2022

All rights reserved.

This is a draft. The content of this document is not final, and the text may be subject to revisions before publication. The document may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means without the permission of the World Health Organization.

Please send any request for permission to:

Ms Sinéad Jones, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications, Department of Health Products Policy and Standards, World Health Organization, CH-1211 Geneva 27, Switzerland, email: jonessi@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers’ products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft.

However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.
SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/21.907Rev1

MOLNUPIRAVIR CAPSULES

(MOLNUPIRAVIRI CAPSULAE)

<table>
<thead>
<tr>
<th>Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drafting of the monograph based on information received from manufacturers</td>
<td>December 2021</td>
</tr>
<tr>
<td>Draft revision sent out for public consultation.</td>
<td>January – February 2022</td>
</tr>
<tr>
<td>Presentation to the 56th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).</td>
<td>April 2022</td>
</tr>
<tr>
<td>Laboratory investigations to verify the analytical provision</td>
<td>May – August 2022</td>
</tr>
<tr>
<td>Preparation of Revision 1 based on the results of the laboratory investigations and the discussion at the 56th meeting of the ECSPP.</td>
<td>September 2022</td>
</tr>
<tr>
<td>Revision 1 sent out for public consultation.</td>
<td>September – November 2022</td>
</tr>
<tr>
<td>Discussion with Experts</td>
<td>TBD</td>
</tr>
<tr>
<td>Further follow-up action as required.</td>
<td></td>
</tr>
</tbody>
</table>

[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, the monograph is expected to play an important role in ensuring access to safe, effective and quality assured molnupiravir containing medicines. Manufacturers, regulatory authorities, procurement agencies and other stakeholders are therefore invited to provide their feedback to the Secretariat of The International Pharmacopoeia.
Manufacturers that have not submitted samples for the elaboration of the monograph are also invited to test their products according the proposed monograph and to submit their results. They will thereby help ensure that the proposed monograph adequately controls the quality of the product(s) they manufacture. For further information, please contact Dr Herbert Schmidt at schmidt@who.int.
MOLNUPIRAVIR CAPSULES (MOLNUPIRAVIRI CAPSULAE)

Category. Antiviral.

Storage. Molnupiravir capsules should be kept in 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_{3}O_{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 1.14.4 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 1.14.4 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 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 chromatogram 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 a mixture of 20 volumes of acetonitrile R and 80 volumes of water R. 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 236 nm and 272 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. Dilute 5.0 mL of the filtrate to 10.0 mL with a mixture of 20 volumes of acetonitrile R and 80 volumes of water R (solution (1)). For solution (2), dissolve 20.0 mg of molnupiravir
RS Prepare in a mixture of 20 volumes of acetonitrile R and 80 volumes of water R and dilute to 100.0 mL with the same solvent.

Carry out the determination as described under 1.14.04 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 0.7.

For each of the capsules tested, calculate the total amount of Molnupiravir \((C_{13}H_{19}N_{3}O_{7})\) 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 \((C_{13}H_{19}N_{3}O_{7})\) 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 1.14.4 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 (3 \(\mu\)m).\(^1\)

Use the following conditions for gradient elution:

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

---

\(^1\) A Kromasil 100-5 Phenyl column has been found suitable.
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 R.

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

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 and the autosampler temperature at 6 °C.

Prepare the following solutions freshy and perform the analysis without delay. Use water 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 15 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), transfer 1.2 mg of molnupiravir impurity I into a 10 mL volumetric flask. Add 1 ml of acetonitrile R and sonicate to dissolve. Dilute to
volume. Transfer 1.0 mL of this solution to a 10 mL volumetric flask and make up to volume with solution (1).

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

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 K about 0.67; 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 this chromatogram obtained with solution (4), the peak-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 peak corresponding to impurity F, recorded at 260 nm, when multiplied with a correction factor of 0.7, is not greater than 0.13 times the area of the peak due to molnupiravir in the chromatogram obtained with solution (2), recorded at 260 nm (0.13 %);
- the area of any other impurity peak is not greater than 0.13 times the area of the peak due to molnupiravir in the chromatogram obtained with solution (2) (0.13 %).
Determine the areas of all impurity peaks recorded at 230 nm, including the corrected areas of any peak corresponding to impurity A. 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 concentration of the 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 concentration 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 230 nm (0.05%).

The sum of the percentage areas of all impurities, recorded at 230 nm, and the percentage area of impurity F, recorded at 260 nm, is not greater than 3.5%.

**Assay.** Carry out the test as described under *1.14.4 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.

---

² A Kinetex Biphenyl column has been found suitable.
<table>
<thead>
<tr>
<th>Time (minutes)</th>
<th>Mobile phase A (% v/v)</th>
<th>Mobile phase B (% v/v)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–15</td>
<td>90</td>
<td>10</td>
<td>Isocratic</td>
</tr>
<tr>
<td>15–16</td>
<td>90 to 35</td>
<td>10 to 65</td>
<td>Linear gradient</td>
</tr>
<tr>
<td>16–22</td>
<td>35</td>
<td>65</td>
<td>Isocratic</td>
</tr>
<tr>
<td>22–23</td>
<td>35 to 90</td>
<td>65 to 10</td>
<td>Return to initial composition</td>
</tr>
<tr>
<td>23–30</td>
<td>90</td>
<td>10</td>
<td>Re-equilibration</td>
</tr>
</tbody>
</table>

Operate with a flow rate of 1.0 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 as the diluent A a mixture of 50 volumes of acetonitrile R and 50 volumes of water R. Prepare as the diluent B a mixture of 20 volumes of acetonitrile R and 80 volumes of water 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 of diluent A, sonicate for 15 minutes with intermediate shaking, allow to cool to room temperature and make up to volume with diluent A, mix and filter. Dilute 5.0 mL of this solution to 50.0 mL with the diluent B. For solution (2), weigh 60.0 mg of molnupiravir RS into a 50 mL volumetric flask. Add 30 mL of diluent A, sonicate to dissolve and make up to volume with the diluent A. Dilute 5.0 mL of this solution to 50.0 mL with the diluent B. 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_{3}O_{7}) in the capsules, using the declared content of C_{13}H_{19}N_{3}O_{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.