



1 **MOLNUPIRAVIR CAPSULES**
2 **(MOLNUPIRAVIRI CAPSULAE)**

3 **Draft proposal for inclusion in *The International Pharmacopoeia***

4 (14 July 2023)

5 *DRAFT FOR DISCUSSION*

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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.

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12 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.

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30 SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/21.907

31 **MOLNUPIRAVIR CAPSULES (MOLNUPIRAVIRI CAPSULAE)**

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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 56 th meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSP).	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 56 th meeting of the ECSP.	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.	

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

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

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

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

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Draft for comments

48 **MOLNUPIRAVIR CAPSULES (MOLNUPIRAVIRI CAPSULAE)**

49 **Category.** Antiviral.

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

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

55 **Requirements**

56 Complies with the monograph for *Capsules*.

57 **Definition.** Molnupiravir capsules contain Molnupiravir. They contain not less than
58 90.0% and not more than 110.0% of the amount of Molnupiravir ($C_{13}H_{19}N_3O_7$), stated
59 on the label.

60 **Identity tests**

- 61 • Either test A alone or any two of tests B, C and D may be applied
- 62 A. Carry out the test as described under *1.14.1 Chromatography*, High-
63 performance liquid chromatography, using the conditions given under “Assay”,
64 but using, as the detector, a diode array detector to record the UV spectrum of
65 the principal peak in each chromatogram in the range of 200 nm to 400 nm.
66 The retention time and the UV spectrum of the principal peak in the
67 chromatogram obtained with solution (1) correspond to the retention time and
68 the UV spectrum of the peak due to molnupiravir in the chromatogram
69 obtained with solution (2).
- 70 B. Carry out the test as described under *1.14.1 Chromatography*, High-
71 performance liquid chromatography, using the conditions given under “Assay”.

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

75 C. Carry out the test as described under *1.14.1 Chromatography*, Thin layer
76 chromatography, using silica gel R6 as the coating substance and a freshly
77 prepared mixture of ethyl acetate R, methanol R and glacial acetic acid R
78 (90:9:1 V/V/V) as the mobile phase. Apply separately to the plate 2 µL of each
79 of the following two solutions. For solution (A), transfer a quantity of the
80 mixed contents, nominally containing 50 mg of Molnupiravir into a 50 mL
81 volumetric flask. Add about 40 mL of methanol R, sonicate for 10 minutes
82 with intermediate shaking, allow to cool to room temperature and make up to
83 volume with methanol R, mix and filter. For solution (B), use a solution
84 containing 1 mg per mL of molnupiravir RS in methanol R. After removing the
85 plate from the chromatographic chamber, allow it to dry in air or in a current of
86 air. Examine the under ultraviolet light (254 nm). The principal spot in the
87 chromatogram obtained with solution (A) corresponds in position, appearance
88 and intensity with the spot due to molnupiravir in the chromatogram obtained
89 with solution (B).

90 D. Prepare the test solution by diluting 5 mL of solution (1), prepared as described
91 under “Assay”, to 20 mL with the described diluent. The absorption spectrum
92 (*1.6 Spectrophotometry in the visible and ultraviolet regions*) of the test
93 solution, when observed between 200 nm and 400 nm, exhibits two maxima at
94 about 235 nm and 273 nm.

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

- 100 Prepare a buffer solution pH 4.75 by dissolving 3.08 g of ammonium acetate R in
101 water R and diluting to 2000 mL with the same solvent. Adjust the pH to a value
102 between 4.70 and 4.80 using glacial acetic acid R.
- 103 Prepare as the diluent, a mixture of 90 volumes of buffer solution pH 4.75 and 10
104 volumes of methanol R.
- 105 Dilute 5.0 mL of the filtrate to 10.0 mL with the diluent (solution (1). For solution (2),
106 dissolve 20.0 mg of molnupiravir RS in the diluent and dilute to 100.0 mL with the
107 same solvent.
- 108 Carry out the determination as described under *1.14.1 Chromatography*, High-
109 performance liquid chromatography, using the conditions given under “Assay”.
- 110 Measure the areas of the peaks corresponding to molnupiravir, obtained in the
111 chromatograms of solutions (1) and (2), and corresponding to impurity A, obtained in
112 the chromatogram of solution (1). Multiply the area of the peak corresponding to
113 impurity A with a correction factor of 0.84.
- 114 For each of the capsules tested, calculate the total amount of Molnupiravir
115 ($C_{13}H_{19}N_3O_7$) dissolved in the medium, using the sum of the area of the peak
116 corresponding to molnupiravir and the corrected area of the peak corresponding to
117 impurity A. Use the declared content of ($C_{13}H_{19}N_3O_7$) in molnupiravir RS to calculate
118 the concentration of molnupiravir in solution (2).
- 119 Evaluate the results as described under *5.5 Dissolution test for solid oral dosage*
120 *forms*, Acceptance criteria. The amount of Molnupiravir released is not less than 80%
121 (Q) of the amount declared on the label.
- 122 **Related substances.** Carry out the test as described under *1.14.1 Chromatography*,
123 High-performance liquid chromatography, using a stainless-steel column (4.6 mm

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

126 Use the following conditions for gradient elution:

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

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

133 Prepare as the solvent mixture, a mixture of 30 volumes of methanol R and 70
134 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.

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

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

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

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

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

155 The test is not valid unless, in the chromatogram obtained with solution (4), the peak-
156 to-valley ratio (H_p/H_v) is at least 3.0, where H_p is the height above the baseline of the
157 peak due to impurity I and H_v is the height above the baseline of the lowest point of
158 the curve separating the peak due to molnupiravir from the peak due to impurity I.

159 Also, the test is not valid unless, in the chromatogram obtained with solution (3), the
160 peak due to molnupiravir is obtained with a signal-to-noise ratio of at least 20. In the
161 chromatogram obtained with solution (1):

- 162 • the area of any peak corresponding to impurity A is not greater than three
163 times the area of the peak due to molnupiravir in the chromatogram
164 obtained with solution (2) (3.0 %);
- 165 • the area of any peak corresponding to impurity B is not greater than 0.22
166 times the area of the peak due to molnupiravir in the chromatogram
167 obtained with solution (2) (0.22 %);
- 168 • the area of any other impurity peak is not greater than 0.15 times the area of
169 the peak due to molnupiravir in the chromatogram obtained with solution
170 (2) (0.15 %);
- 171 • the area of any peak corresponding to impurity F, recorded at 260 nm, when
172 multiplied with a correction factor of 0.7, is not greater than 0.15 times the
173 area of the peak due to molnupiravir in the chromatogram obtained with
174 solution (2), recorded at 260 nm (0.15 %).
- 175 • Determine the sum of the areas of all impurity peaks recorded at 230 nm,
176 excluding the area of any peak corresponding to impurity F. Disregard any
177 peaks with an area of less than the area of the peak due to molnupiravir in
178 the chromatogram obtained with solution (3), recorded at 230 nm (0.05%).
179 Calculate the percentage content of all impurities using the area of the peak
180 due to molnupiravir in the chromatogram obtained with solution (2),
181 recorded at 230 nm, as a reference.
- 182 • Determine the corrected area of any peak corresponding to impurity F,
183 recorded at 260 nm, and calculate its percentage content using the area of
184 the peak due to molnupiravir in the chromatogram obtained with solution
185 (2), recorded at 260 nm, as a reference. Disregard any peak with an area of
186 less than the area of the peak due to molnupiravir in the chromatogram
187 obtained with solution (3), recorded at 260 nm (0.05%).
- 188 • The sum of the percentage content of all impurities, recorded at 230 nm,
189 and the percentage content of impurity F, recorded at 260 nm, is not greater
190 than 3.5 %.

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

195 Use the following conditions for gradient elution:

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

198 Prepare the ammonium dihydrogen phosphate solution by dissolving 5.75 g of
199 ammonium dihydrogen phosphate R in water R and diluting to 1000 mL with the
200 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

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

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

² A Kinetex Biphenyl column has been found suitable.

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

209 Prepare the following solutions. For solution (1), weigh and powder the contents of
210 20 capsules. Transfer a quantity of the mixed contents, nominally containing 300.0
211 mg of Molnupiravir into a 250 mL volumetric flask. Add about 200 mL, sonicate for
212 10 minutes with intermediate shaking, allow to cool to room temperature, make up to
213 volume, mix and filter. Dilute 5.0 mL of this solution to 50.0 mL. For solution (2),
214 weigh 60.0 mg of molnupiravir RS into a 50 mL volumetric flask. Add 30 mL,
215 sonicate to dissolve, and make up to volume. Dilute 5.0 mL of this solution to 50.0
216 mL.

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

218 Measure the areas of the peaks corresponding to molnupiravir obtained in the
219 chromatograms of solutions (1) and (2) and calculate the percentage content of
220 Molnupiravir (C₁₃H₁₉N₃O₇) in the capsules, using the declared content of
221 C₁₃H₁₉N₃O₇ in molnupiravir RS.

222 **Impurities**

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

225 ***Reference substances to be established***

226 *Molnupiravir RS*

- 227 • *International Chemical Reference Substance to be established.*

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

- 229 • *International Chemical Reference Substance to be established.*

Draft for comments