### **DARUNAVIR TABLETS**

#### (DARUNAVIRI COMPRESSI)

## Draft proposal for inclusion for The International Pharmacopoeia

(13 August 2024)

### DRAFT FOR COMMENTS

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For any technical questions, you may contact **Dr Herbert Schmidt**, Technical Officer, Norms and Standards for Pharmaceuticals, Technical Standards and Specifications (<a href="mailto:schmidth@who.int">schmidth@who.int</a>), with a copy to Ms Bezawit Kibret (<a href="mailto:kibretb@who.int">kibretb@who.int</a>)

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## SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.830:

# DARUNAVIR TABLETS (DARUNAVIRI COMPRESSI)

Description	Date
Monograph drafted based on information received from manufacturers and on laboratory investigations.	February 2020
Discussion at the consultation on Screening Technologies, Laboratory Tools and Pharmacopoeial Specifications for Medicines.	27-29 April 2020
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications for medicines.	April 2023
Discussion at the Consultation on Quality Control and Pharmacopoeial Specifications for Medicines.	May 2024
Draft monograph sent out for public consultation.	August – October 2024
Presentation at the 58 <sup>th</sup> Meeting of the Expert Committee on Specifications for Pharmaceutical Preparations	October 2024
Further follow-up action as required.	

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- **Category.** Antiretroviral. Protease inhibitor. 53
- **Storage.** Darunavir tablets should be kept in tightly closed containers at a temperature 54

DARUNAVIR TABLETS (DARUNAVIRI COMPRESSI)

- not exceeding 30 °C. 55
- Additional information. Strength in the current WHO Model List of Essential 56
- Medicines (EML): 75 mg, 400 mg, 600 mg and 800 mg of darunavir. Strength in the 57
- current WHO EML for children: 75 mg of darunavir. 58
- **Labelling.** The designation of the container of Darunavir tablets should state that the 59
- active ingredient is Darunavir. Where Darunavir is in the ethanol solvate form, the label 60
- so indicates. The quantity should be indicated in terms of darunavir or the equivalent 61
- amount of darunavir. 62

#### **Requirements** 63

- Comply with the monograph on Tablet 64
- **Definition.** Darunavir tablets contain Darunavir. They contain not less than 90.0% and 65
- not more than 110.0% of the amount of Darunavir (C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>S) stated on the label. 66
- **Identity tests** 67
- Either tests A or tests B and C or tests C and D may be applied. 68
- A. To a quantity of the powdered tablets, nominally containing 25 mg of darunavir, 69
- add 5 mL of dehydrated ethanol R. Shake the suspension and filter. Add 0.2 mL 70
- of the filtrate to 300 mg potassium bromide. Dry the treated potassium bromide in 71
- an oven at 100 °C for 10 minutes. Add again 0.2 mL of the filtrate and dry at 72
- 100 °C for further 60 minutes. Prepare a disc and carry out the test as described 73
- under 1.7 Spectrophotometry in the infrared region. The infrared absorption 74

- spectrum is concordant with the spectrum obtained from darunavir RS similarly treated or with the reference spectrum of darunavir.
- [Note from the Secretariat. Anhydrous darunavir will be used to record the reference spectrum.]
- B. Carry out the test as described under <u>1.14.4 High-performance liquid</u> 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 darunavir in the chromatogram obtained with solution (2).
- C. Use solution (1) as described under "Assay". Dilute 10.0 mL of this solution to 50.0 mL using a mixture of 50 volumes of water R and 50 volumes of acetonitrile R as the diluent (10 μg/mL). Record an absorption spectrum of the solution in the range from 200 nm to 400 nm as described under 1.6 Spectrophotometry in the visible and ultraviolet regions. The spectrum exhibits a maximum at 266 nm.
- Alternatively, in combination with identity test B, where a diode array detector is available, record the UV spectra of the principal peaks in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The retention time and UV spectrum of the principal peak in the chromatogram obtained with solution (1) corresponds to the retention time and the UV spectrum of the peak due to darunavir in the chromatogram obtained with solution (2).
- D. Carry out the test as described under <u>1.14.1 Thin-layer chromatography</u>, using silica gel R2 as the coating substance and a mixture of 48 volumes of dichloromethane R, 25 volumes of methanol R, 22 volumes of ethyl acetate R and 5 volumes of ammonia (~260 g/L) TS as the mobile phase.
- Apply separately to the plate 10 µL of each of the following solutions in methanol

  R. For solution (A), add 5 mL of methanol R to a quantity of the powdered tablets,

  nominally containing 25 mg of darunavir, shake and filter. For solution (B), use a

solution containing 5 mg of darunavir RS per mL. After removing the plate from 102 the chromatographic chamber, allow it to dry in a current of air. Examine the 103 chromatogram in ultraviolet light (254 nm). The principal spot obtained with 104 solution (A) corresponds in position, appearance and intensity to the spot due to 105 darunavir in the chromatogram obtained with solution (B). 106 **Dissolution.** Carry out the test as described under 5.5 Dissolution test for oral dosage 107 forms using as the dissolution medium 900 mL of a solution of 2% sodium laurilsulfate 108 R in sodium dihydrogen phosphate buffer pH 3.0 and rotating the paddle at 75 109 revolutions per minute. 110 Prepare the dihydrogen phosphate buffer pH 3.0 by dissolving 6.90 g sodium 111 dihydrogen phosphate R in about 800 mL of water R, adjusting the pH to 3.0 with 112 Phosphoric acid (105 g/L) TS and diluting to 1000 mL with water R. 113 At 45 minutes, withdraw a sample of 10 mL of the medium through an in-line filter. 114 Dilute to a concentration in the range of 0.04 to 0.07 mg/mL with dissolution medium. 115 Determine the content as described under 1.14.4 High-performance liquid 116 chromatography using the conditions given under "Assay". 117 For the reference solution, weigh and transfer 50.0 mg of darunavir RS into a 100.0 mL 118 volumetric flask and add 80 mL of dissolution medium. Sonicate for 10 minutes and 119 dilute to volume. Dilute 10.0 mL of this solution to 100.0 mL with dissolution medium. 120 Measure the areas of the peaks corresponding to darunavir obtained in the 121 chromatograms of the sample and reference solution. For each of the tablets tested, 122 calculate the total amount of darunavir ( $C_{27}H_{37}N_3O_7S$ ) in the medium using the declared 123 content of darunavir (C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>S) in darunavir RS. 124

Evaluate the results as described under 5.5 Dissolution test for solid oral dosage forms,

126 Acceptance criteria. The amount of darunavir released is

- not less than 80% (Q) for tablets containing 75 mg, 400 mg and 600 mg of Darunavir, or
  - not less than 75% (Q) for tablets containing 800 mg of Darunavir.
- 130 **Related substances**. Carry out the test as described under <u>1.14.4 High-performance</u>
- 131 *liquid chromatography*, using a stainless steel column (25 cm x 4.6 mm) packed with
- particles of silica gel, the surface of which has been modified with chemically-bonded
- octadecylsilyl groups  $(3.5 \mu m)$ .<sup>1</sup>

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- 134 Use the following conditions for gradient elution:
- Mobile phase A: a mixture of 90 volumes of 0.01 M potassium dihydrogen
- phosphate (~1.361 g/L) TS and 10 volumes of acetonitrile R.
- Mobile phase B: a mixture of 30 volumes of 0.01 M potassium dihydrogen
- phosphate (~1.361 g/L) TS and 70 volumes of acetonitrile R.

Time (minutes)	Mobile phase A	Mobile phase B (% V/V)	Comments
0-2	100	0	Isocratic
2–55	100 to 0	0 to 100	Linear gradient
55–55.1	0 to 100	100 to 0	Return to initial composition
55.1–60	100	0	Re-equilibration

- Operate with a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 264 nm. Maintain the column temperature
- 141 at 35 °C.

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- Prepare the following solutions using a mixture of 50 volumes of water R and 50
- volumes of acetonitrile R as a diluent. For solution (1), weigh and powder 20 tablets.

<sup>&</sup>lt;sup>1</sup>A Zorbax-SB-C18 column has been found suitable.

- 144 Transfer a quantity of the powdered tablets, nominally containing 250.0 mg of darunavir,
- into a 500.0 mL volumetric flask and add 300 mL. Sonicate and shake the flask for 10
- minutes. Dilute to volume and filter. For solution (2), dilute 1.0 mL of solution (1) to
- 100.0 mL. For solution (3), dilute 5.0 mL of solution (3) to 50.0 mL. For solution
- 148 (4), prepare a solution containing darunavir for peak identification RS (containing
- darunavir and the impurities A, C, E, F and D) as described in the leaflet of the
- reference substance.
- Inject 75  $\mu$ L each of solutions (1), (2), (3) and (4).
- Use the chromatogram obtained with solution (4) and the chromatogram supplied
- with darunavir for peak identification RS to identify the peaks due to the impurities
- 154 A, C, E, F and D.
- 155 The impurities are eluted, if present, at the following relative retention with
- reference to darunavir (retention time about 36 minutes): impurity M about 0.67;
- impurity A about 0.84; impurity P about 0.98; impurity O about 1.03; impurity C
- about 1.11; impurity E about 1.13; impurity D about 1.15; impurity F about 1.16;
- impurity T about 1.39; impurity G about 1.40; impurity H about 1.43.
- The test is not valid unless, in the chromatogram obtained with solution (4), the
- resolution factor between the peaks due to impurity D and due to impurity F is at least
- 1.0. Also, the test is not valid unless, in the chromatogram obtained with solution (3),
- the peak due to darunavir 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 E is not greater than 0.4 times
- the area of the peak due to darunavir in the chromatogram obtained with
- solution (2) (0.40 %);
- the area of any peak corresponding to impurity C is not greater than 0.3 times
- the area of the peak due to darunavir in the chromatogram obtained with
- solution (2) (0.30 %);

- the area of any peak corresponding to impurity A, when multiplied by a correction factor of 1.27, is not greater than 0.25 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.25 %);
- the area of any peak corresponding to impurity F, when multiplied by a correction factor of 1.64, is not greater than 0.25 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.25 %);
- the area of any peak corresponding to impurity D, when multiplied by a correction factor of 1.35, is not greater than 0.2 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.2 %);
- the area of any other impurity peak is not greater than 0.2 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (0.20 %).
- The sum of the areas of all impurity peaks, including the corrected areas of any peaks corresponding to impurities A, D and F, is not greater than 2 times the area of the peak due to darunavir in the chromatogram obtained with solution (2) (2.0 %). Disregard any peak with an area, or in the case of impurities A, D and F a corrected area, of less than the area of the peak due to darunavir in the chromatogram obtained with solution (3) (0.10%).
- Assay. Carry out the test as described under <u>1.14.4 High-performance liquid</u> chromatography, using a stainless steel column (25 cm x 4.6 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups  $(3.5 \,\mu\text{m})$ .<sup>2</sup>
- As the mobile phase use a mixture of 30 volumes of mobile phase A and 70 volumes of mobile phase B.
- Operate with a flow rate of 1.0 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 264 nm. Maintain the column at a temperature of 35 °C.

<sup>&</sup>lt;sup>2</sup>A Zorbax-SB-C18 column has been found suitable.

- Prepare the following solutions using a mixture of 50 volumes of water R and 50 197 volumes of acetonitrile R as a diluent. For solution (1), weigh and powder 20 tablets. 198 Transfer a quantity of the powdered tablets, nominally containing 250.0 mg of 199 darunavir, into a 500.0 mL volumetric flask and add 300 mL. Sonicate and shake the 200 flask for 10 minutes and dilute to volume. Dilute 10.0 mL of this solution to 100.0 mL 201 and filter. For solution (2), dilute 50.0 mg of darunavir RS in 100.0 mL. Dilute 10.0 202 mL of this solution to 100.0 mL 203 Inject 10 µL each of solution (1) and (2) and record the chromatograms for 22 minutes. 204 The retention time of darunavir is about 6 minutes. 205 Measure the areas of the peaks corresponding to darunavir obtained in the 206 chromatograms of solutions (1) and (2) and calculate the percentage content of 207 darunavir (C<sub>27</sub>H<sub>37</sub>N<sub>3</sub>O<sub>7</sub>S) in the tablets using the declared content of darunavir 208  $(C_{27}H_{37}N_3O_7S)$  in darunavir RS. 209 **Impurities** 210 The impurities limited by the requirements of this monograph include those listed 211 in the monograph on Darunavir. 212 213
- Reference substances to be established. 214
- Darunavir for peak identification RS (containing darunavir and the impurities A, 215

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- C, E, F and D) 216
- ICRS to be established. 217
- Darunavir RS 218
- ICRS to be established. 219