DARUNAVIR ORAL SUSPENSION

(DARUNAVIRI SUSPENSIO PERORALUM)

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 (schmidth@who.int), with a copy to Ms Bezawit Kibret (kibretb@who.int))

Comments should be submitted through the online platform by **20 October 2024**. 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 PleaseReviewTM. 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 "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.int and your name will be added to our electronic mailing list and review platform.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/20.848:

DARUNAVIR ORAL SUSPENSION

(DARUNAVIRI SUSPENSIO PERORALUM)

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
Presentation to the 55 th WHO Expert Committee on Specifications for Pharmaceutical Preparations.	October 2020
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 th Meeting of the Expert Committee on Specifications for Pharmaceutical Preparations	October 2024
Further follow-up action as required.	

DARUNAVIR ORAL SUSPENSION 48 (DARUNAVIRI SUSPENSIO PERORALUM) 49 50 51 **Category.** Antiretroviral. Protease inhibitor. **Storage.** Darunavir oral suspension should be kept in tightly closed containers, protected 52 from light at a temperature not exceeding 30 °C. 53 **Additional information.** Strength available: 100 mg of darunavir per mL oral suspension. 54 Samples may contain parahydroxybenzoates. 55 **Labelling.** The designation of the container should state that the active ingredient is 56 Darunavir. Where Darunavir is in the ethanol solvate form, the label so indicates. The 57 quantity should be indicated in terms of darunavir or the equivalent amount of darunavir. 58 **Requirements** 59 Comply with the monograph on *Liquid preparations for oral use*. 60 **Definition.** Darunavir oral suspension is a suspension of Darunavir, which may be 61 flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of 62 Darunavir ($C_{27}H_{37}N_3O_7S$) stated on the label. 63 **Identity tests** 64 • Either tests A and B or tests B and C may be applied. 65 Carry out the test as described under 1.14.4 High-performance liquid A. 66 chromatography using the conditions given under "Assay". The retention time 67 of the principal peak in the chromatogram obtained with solution (1) corresponds 68 to the retention time of the peak due to darunavir in the chromatogram obtained 69

with solution (2).

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- B. 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 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 A, 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 the 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).
- C. Carry out the test as described under *1.14.1 Thin-layer chromatography*, 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 $10~\mu L$ of each of the following solutions in methanol R. For solution (A), add 20~mL of methanol R to a quantity of oral solution, nominally containing 100~mg of darunavir, shake and filter. For solution (B), use 5 mg of darunavir RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in a current of air. Examine the chromatogram in ultraviolet light (254 nm). The principal spot obtained with solution (A) corresponds in position, appearance and intensity to the spot due to darunavir in the chromatogram obtained with solution (B).
- Dissolution. Carry out the test as described under <u>5.5 Dissolution test for oral dosage</u> forms using as the dissolution medium 900 mL of a solution of 0.2% sodium laurilsulfate in sodium dihydrogen phosphate buffer, pH 6.8, TS and rotating the paddle at 75 revolutions per minute.

- 98 Shake the container of the oral suspension to re-suspend any settled material. Withdraw
- 99 2.0 mL of the oral suspension and rapidly deliver the sample below the medium surface
- with the paddle in motion.
- 101 At 30 minutes, withdraw a sample of 10 mL of the medium through an in-line filter.
- Dilute 5.0 mL of the filtrate to 20.0 mL with dissolution medium.
- Determine the content as described under 1.14.4 High-performance liquid
- 104 *chromatography* using the conditions given under "Assay".
- For the reference solution, weigh and transfer 55.0 mg of darunavir RS into a 100.0 mL
- volumetric flask and add 80 mL of dissolution medium. Sonicate the flask for 10
- minutes and dilute to volume. Dilute 10.0 mL of this solution to 100.0 mL with
- 108 dissolution medium.
- 109 Measure the areas of the peaks corresponding to darunavir obtained in the
- chromatograms of the sample and reference solution. For each of the samples tested,
- calculate the total amount of darunavir ($C_{27}H_{37}N_3O_7S$) in the medium using the declared
- 112 content of darunavir (C₂₇H₃₇N₃O₇S) in darunavir RS.
- Evaluate the results as described under 5.5 Dissolution test for oral dosage forms,
- 114 Acceptance criteria. The amount of darunavir released is not less than 75% (Q) of the
- amount declared on the label.
- Related substances. Carry out the test as described under <u>1.14.4 High-performance</u>
- 117 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 μm).¹
- 120 Use the following conditions for gradient elution:

¹A Zorbax-SB-C18 column has been found suitable.

121	Mobile phase A	a mixture o	f 90 volun	nes of (0.01	M pota	assiu	m dihydrog	gen
122		phosphate	(~1.361	g/L)	TS	and	10	volumes	of
123		acetonitrile	R.						
124	Mobile phase B	a mixture o	f 30 volun	nes of (0.01	M pota	assiu	m dihydrog	gen
125		phosphate	(~1.361	g/L)	TS	and	70	volumes	of
126		acetonitrile	R.						

Use the following gradient:

Time (minutes)	Mobile phase A (% V/V)	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 at 35 °C.

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), shake the container of the oral suspension to re-suspend any settled material. Transfer a quantity of the oral suspension, nominally containing 100.0 mg of darunavir into a 200 mL volumetric flask. Add 100 mL and shake for 10 minutes. Dilute to volume and shake vigorously. For solution (2), dilute 1.0 mL of solution (1) to 100.0 mL. For solution (3), dilute 5.0 mL of solution (2) to 50.0 mL. For solution (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. For solution (5) dissolve a suitable amount of each of the excipients stated on the label or in

- the accompanying leaflet in 10 mL of a suitable solvent and dilute to 100 mL with
- the mobile phase.
- Inject 75 μ L each of solutions (1), (2), (3), (4) and (5).
- 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
- 147 A, C, E, F and D.
- 148 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.
- 157 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
- 165 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 a retention time similar to any of the peaks in the chromatogram obtained with solution (5), 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> <u>chromatography</u>, 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 μm).²
- 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.

²A Zorbax-SB-C8 column has been found suitable.

193	Prepare the following solutions using a mixture of 50 volumes of water R and 50
194	volumes of acetonitrile R as a diluent. For solution (1), shake the container of the oral
195	suspension to re-suspend any settled material. Transfer a quantity of the oral
196	suspension, nominally containing 100.0 mg of darunavir into a 200 mL volumetric
197	flask. Add 100 mL and shake for 10 minutes. Dilute to volume and shake vigorously.
198	Dilute 10.0 mL of this solution to 100.0 mL and filter. For solution (2), dissolve 50.0
199	mg of darunavir RS in 100.0 mL. Dilute 10.0 mL to 100.0 mL.

- 200 Inject 10 μL of solutions (1) and (2) and record the chromatograms for 22 minutes.
- The retention time of darunavir is about 6 minutes.
- 202 Measure the areas of the peaks corresponding to darunavir obtained in the
- 203 chromatograms of solutions (1) and (2). Calculate the percentage content of darunavir
- 204 (C₂₇H₃₇N₃O₇S) in the oral suspension using the declared content of darunavir
- 205 $(C_{27}H_{37}N_3O_7S)$ in darunavir RS.

Impurities

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- The impurities limited by the requirements of this monograph include those listed in the monograph on Darunavir.
- 209 Reference substances to be established.
- Darunavir for peak identification RS (containing darunavir and the impurities A,
- 211 C, E, F and D)
- ICRS to be established
- 213 Darunavir RS
- ICRS to be established.

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