World Health Organization

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)
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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 55th 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 58th Meeting of the Expert Committee on Specifications for Pharmaceutical Preparations	October 2024
Further follow-up action as required.	

DARUNAVIR ORAL SUSPENSION

(DARUNAVIRI SUSPENSIO PERORALUM)

Category. Antiretroviral. Protease inhibitor.

Storage. Darunavir oral suspension should be kept in tightly closed containers, protected from light at a temperature not exceeding 30 °C.

Additional information. Strength available: 100 mg of darunavir per mL oral suspension. Samples may contain parahydroxybenzoates.

Labelling. The designation of the container should state that the active ingredient is Darunavir. Where Darunavir is in the ethanol solvate form, the label so indicates. The quantity should be indicated in terms of darunavir or the equivalent amount of darunavir.

Requirements

Comply with the monograph on *Liquid preparations for oral use*.

Definition. Darunavir oral suspension is a suspension of Darunavir, which may be flavoured. It contains not less than 90.0% and not more than 110.0% of the amount of Darunavir ($C_{27}H_{37}N_3O_7S$) stated on the label.

Identity tests

- Either tests A and B or tests B and C may be applied.

A. 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 darunavir in the chromatogram obtained with solution (2).

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 µL 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 *5.5 Dissolution test for oral dosage 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.

Shake the container of the oral suspension to re-suspend any settled material. Withdraw 2.0 mL of the oral suspension and rapidly deliver the sample below the medium surface with the paddle in motion.

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 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 dissolution medium.

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 content of darunavir ($C_{27}H_{37}N_3O_7S$) in darunavir RS.

Evaluate the results as described under *5.5 Dissolution test for oral dosage forms, 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 *1.14.4 High-performance 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]

Use the following conditions for gradient elution:

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

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.

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 µL 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 A, C, E, F and D.

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 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 *1.14.4 High-performance 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).[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.

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

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. Dilute 10.0 mL of this solution to 100.0 mL and filter. For solution (2), dissolve 50.0 mg of darunavir RS in 100.0 mL. Dilute 10.0 mL to 100.0 mL.

Inject 10 µL of solutions (1) and (2) and record the chromatograms for 22 minutes. The retention time of darunavir is about 6 minutes.

Measure the areas of the peaks corresponding to darunavir obtained in the chromatograms of solutions (1) and (2). Calculate the percentage content of darunavir ($C_{27}H_{37}N_3O_7S$) in the oral suspension using the declared content of darunavir ($C_{27}H_{37}N_3O_7S$) in darunavir RS.

Impurities

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

Reference substances to be established.

Darunavir for peak identification RS (containing darunavir and the impurities A, C, E, F and D)

- ICRS to be established

Darunavir RS

- ICRS to be established.

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