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International Nonproprietary Names for Pharmaceutical Substances

World Health Organization

WHO Drug Information

WHO Drug Information provides an overview of topics relating to medicines development, regulation, quality and safety. The journal also publishes and reports on guidance documents and includes lists of International Nonproprietary Names for Pharmaceutical Substances (INN), ATC/DDD classification and monographs for The International Pharmacopoeia. It presents and describes WHO policies and activities while reflecting on technical and pharmaceutical topics of international and regional interest.

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Extraordinary (virtual) International Conference of Drug Regulatory Authorities (ICDRA)
20 to 24 September 2021

World Health Organization is pleased to announce the organization of an extraordinary International Conference of Drug Regulatory Authorities (ICDRA) in September 2021. This virtual conference will give the opportunity to the global regulatory community and other key stakeholders to exchange information, best practices and collaborative approaches related to regulation of medical products, especially important during the current challenging times of the COVID-19 pandemic.
The decision for the extraordinary ICDRA was taken as the planned 2020 ICDRA which should have taken place in India had to be cancelled due to COVID-19 pandemic. The conference is intended to bridge to the 19th ICDRA, which will be organised in India in 2022, when situation permits.

The theme of the extraordinary Conference planned for September is "Smart Regulation: Timely Delivery of Quality Assured Medical Products for All during the Global Pandemic". The Conference will be held virtually with daily sessions of two hours from 13:00 to 15:00 (CET) from Monday 20 to Friday 24 September 2021. Information regarding the registration process and the programme will be released in the coming weeks. WHO is looking forward to welcoming all to this extraordinary ICDRA 2021 Conference.

Link to WHO ICDRA site:
https://www.who.int/teams/regulation-prequalification/regulation-and-safety/regulatory-convergence-networks/icdra

Note: The online version of this issue is available at:
https://www.who.int/our-work/access-to-medicines-and-health-products/who-drug-information

LINEZOLID

(*LINEZOLIDUM*)

DRAFT FOR COMMENTS

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: schmidth@who.int), with a copy to Ms Sinéad Jones (email: jonessi@who.int) by **31 July 2021**.

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 jonessi@who.int and your name will be added to our electronic mailing list.

*[**Note from the Secretariat.** The draft proposal is based on information submitted by manufacturers and found in other pharmacopoeias and in the scientific literature.*

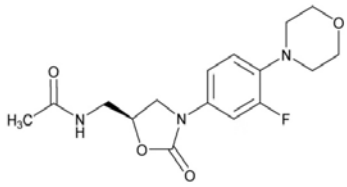
All stakeholders, in particular manufacturers of this product, regulatory authorities, quality control laboratories and procurement agencies, are invited to provide their feedback to the Secretariat of The International Pharmacopoeia. *Your support will help ensure that the proposed monograph adequately controls the quality of Linezolid active pharmaceutical ingredient on the market.*

Comments are in particular sought on the values used for the correction factors for impurities I and J.]

LINEZOLID

(*LINEZOLIDUM*)

Graphic formula



Molecular formula. $C_{16}H_{20}FN_3O_4$

Relative molecular mass. 337.4

Chemical name. *N*-[[(*S*)-3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl] methyl] acetamide; CAS Reg. No. 165800-03-3.

Description. A white to off-white powder.

Solubility. Sparingly soluble in methanol R; soluble in dichloromethane R.

Category. Antituberculosis.

Storage. Linezolid should be kept in a tight container, protected from light and moisture.

Additional information. Linezolid may exhibit polymorphism.

Requirements

Manufacture. The production method is validated to demonstrate that genotoxic impurities are adequately controlled in the final product.

Definition. Linezolid contains not less than 99.0% and not more than 101.0% ("Assay", Method A) and not less than 98.0% and not more than 102.0% ("Assay", Method B) of $C_{16}H_{20}FN_3O_4$, calculated with reference to the anhydrous substance.

Identity tests

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

A. Carry out the examination as described under *1.7 Spectrophotometry in the infrared region*. The infrared absorption spectrum is concordant with the spectrum obtained from linezolid RS.
If the spectra thus obtained are not concordant, repeat the test using the residues obtained by separately dissolving the test substance and linezolid RS in a small amount of ethanol R and evaporating to dryness. The infrared absorption spectrum of the test substance is concordant with the spectrum obtained from linezolid RS.

B. Carry out the test as described under *1.14.4 High-performance liquid chromatography* using the conditions given under "Assay". Record the UV spectrum of the principle peak 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) correspond to the retention time and UV spectrum of the peak due to linezolid 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 acetone R, toluene R and glacial acetic acid R (45:45:10 V/V/V) as the mobile phase. Apply separately to the plate 2 µL of each of the following 2 solutions in methanol R containing (A) 5 mg of the test substance per mL and (b) 5 mg of linezolid RS per mL. After removing the plate from the chromatographic chamber, allow it to dry in air or in a current of air. Examine the plate under ultraviolet light (254 nm). Spray the plate with potassium permanganate, basic (~5 g/L) TS and examine the plate in daylight. The principal spot in the chromatogram obtained with solution (A) corresponds in position, appearance and intensity with the spot due to linezolid in the chromatogram obtained with solution (B).

D. Dissolve 20 mg of the test substance in methanol R and dilute to 100 mL with the same solvent. Dilute 1 mL of this solution to 20 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 258 nm.

Water. Determine as described under *2.8 Determination of water by the Karl Fischer method*, Method A. Use 0.300 g of the test substance. The water content is not more than 5 mg/g.

Sulfated ash (*2.3*). Not more than 2.0 mg/g

Heavy metals. Use 2.0 g of the test substance for the preparation of the test solution as described under *2.2.3 Limit test for heavy metals*, Procedure 3. Determine the heavy metals content according to Method A; not more than 10 µg/g.

Impurity E (Linezolid *R*-isomer). Carry out the test as described under *1.14.4 High-performance liquid chromatography* using a stainless-steel column (15 cm x 4.6 mm) packed with silica particles, the surface of which has been modified with chemically-bonded amylose tris-3,5-dimethylphenylcarbamate, (5 µm)[1].

As mobile phase, use a mixture of 960 volumes acetonitrile R, 40 volumes of dehydrated ethanol R, 1 volume of n-butylamine R and 1.6 volumes of trifluoroacetic acid R. Operate at a flow rate of 0.8 mL per minute. As a detector, use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Maintain the column temperature at 40 °C. Use a mixture of 960 volumes of acetonitrile R and 40 volumes of dehydrated ethanol R as diluent. For solution (1), dissolve 25.0 mg of the test substance and dilute to 50.0 mL. For solution (2) dilute 1.0 mL of solution (1) to 100.0 mL. Dilute 1.0 mL of this solution to 10.0 mL. For solution (3), dissolve 5.0 mg each of linezolid RS and linezolid impurity E RS and dilute to 200.0 mL.

Inject 5 µL each of solutions (1), (2) and (3). Record the chromatograms for about two times the retention time of linezolid.

In the chromatogram obtained with solution (3), impurity E is eluted with a relative retention of about 0.39 with reference to linezolid. The test is not valid unless in the chromatogram obtained with solution (3) the resolution between the peak of impurity E and the peak of linezolid is greater than 10. The test is also not valid unless in the chromatogram obtained with solution (2) the peak due to linezolid is detected with a signal-to-noise ratio of at least 10. In the chromatogram obtained with solution (1):

- the area of any peak corresponding to impurity E is not greater than 3 times the area of the peak due to linezolid in the chromatogram obtained with solution (2) (0.3%).

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 end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm)[2].

[1] Phenomenex Lux Amylose-1 or Chiralpak IA column was found suitable.

[2] An Inertsil ODS-3V column was found suitable.

Use the following conditions for gradient elution:

- mobile phase A: potassium dihydrogen phosphate (6.8 g/L) TS.
- mobile phase B: methanol R.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–5	65	35	Isocratic
5–25	65 to 35	35 to 65	Linear gradient
25–30	35	65	Isocratic
30–31	35 to 65	65 to 35	Return to initial composition
31–40	65	35	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 251 nm. Maintain the column temperature at 50 °C. Prepare the following solutions in a mixture of 30 volumes of methanol R and 70 volumes of water R. For solution (1), dissolve 40.0 mg of the test substance in 50.0 mL. 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 10.0 mL. For solution (4) dissolve 5.0 mg each of linezolid RS and linezolid impurity D RS in 100.0 mL.

Inject 10 µL each of solutions (1), (2), (3) and (4).

Use the chromatogram obtained with solution (4) to identify the peaks due to linezolid and impurity D in the chromatogram obtained with solution (1). The impurity peaks, if present, are eluted at the following relative retention times with reference to linezolid (retention time about 13.6 minutes): impurity G about 0.28; impurity C about 0.38; impurity F about 0.69; impurity H about 0.73, impurity D about 1.08; impurity J about 1.46; impurity B about 1.57; impurity A about 1.62; impurity I about 1.95