WHO Drug Information

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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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Contents

Consultation Documents

ATC/DDD Classification

International Nonproprietary Names (INN)

Abbreviations and websites

CHMP	Committee for Medicinal Products for Human Use (EMA)
EMA	European Medicines Agency (www.ema.europa.eu)
EU	European Union
FDA	U.S. Food and Drug Administration (www.fda.gov)
Health Canada	Federal department responsible for health product regulation in Canada (www.hc-sc.gc.ca)
HPRA	Health Products Regulatory Authority, Ireland(www.hpra.ie)
HSA	Health Sciences Authority, Singapore (www.hsa.gov.sg)
ICDRA	International Conference of Drug Regulatory Authorities
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (www.ich.org)
IGDRP	International Generic Drug Regulators Programme (https://www.igdrp.com)
INN	International Nonproprietary Names
MHLW	Ministry of Health, Labour and Welfare, Japan
MHRA	Medicines and Healthcare Products Regulatory Agency, United Kingdom (www.mhra.gov.uk)
Medsafe	New Zealand Medicines and Medical Devices Safety Authority (www.medsafe.govt.nz)
Ph. Int	*The International Pharmacopoeia* (http://apps.who.int/phint/)
PMDA	Pharmaceuticals and Medical Devices Agency, Japan (www.pmda.go.jp/english/index.htm)
Swissmedic	Swiss Agency for Therapeutic Products(www.swissmedic.ch)
TGA	Therapeutic Goods Administration, Australia (www.tga.gov.au)
WHO	World Health Organization (www.who.int)
WHO MHP	WHO Access to Medicines and Health Products Division (https://www.who.int/our-work/access-to-medicines-and-health-products)
WHO RPQ	WHO Regulation and Prequalification Department (https://www.who.int/teams/regulation-prequalification)
WHO PQT	WHO Prequalification Unit (https://extranet.who.int/pqweb)
WHO HPS	WHO Health Product Policy and Standards Department (https://www.who.int/teams/health-product-policy-and-standards)

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

Comments on this draft working document are to be sent 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 **15 July 2022**.

Working documents are sent out electronically and 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.

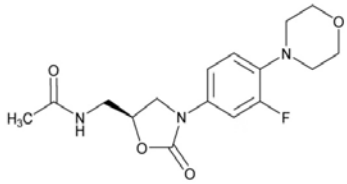
*[**Note from the Secretariat.** The draft proposal is based on information submitted by manufacturers and found in other pharmacopoeias and in the scientific literature.*

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.]*

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, slightly soluble in dehydrated ethanol R.

Category. Antituberculosis.

Storage. Linezolid should be kept in an airtight 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% of $C_{16}H_{20}FN_3O_4$, calculated with reference to the anhydrous substance.

Identity tests

- Either test A alone, or any two of tests B, C or 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 dehydrated ethanol R at a temperature of about 50 to 60 °C. Evaporate the solvent using a rotary evaporator. 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 "Related substances". Prepare the following solutions in a mixture of 20 volumes of acetonitrile R and 80 volumes of 1.36 g/L potassium dihydrogen phosphate in water. For solution (1), dissolve 10 mg of the test substance in 50 mL. For solution (2), dissolve 10 mg of linezolid RS in 50 mL.
Inject 10 µl each of solutions (1) and (2). The retention time of the principal peak obtained with solution (1) corresponds to the retention time 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). 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.
Alternatively, in combination with identity test B, where a diode-array detector is available, record the UV spectrum of the principal peak in the chromatograms with a diode array detector in the range of 200 nm to 400 nm. The UV spectrum of the principal peak in the chromatogram obtained with solution (1) corresponds to the UV spectrum of the peak due to linezolid in the chromatogram obtained with solution (2).

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 5.0 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 5. Determine the heavy metals content according to Method C; 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.

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

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 (15 cm x 4.6 mm), packed with end-capped particles of silica gel, the surface of which has been modified with chemically-bonded octylsilyl groups (3.5 µm)[2].

Use the following conditions for gradient elution:

- mobile phase A: 90 volumes of phosphate buffer and 10 volumes of methanol R .
- mobile phase B: 30 volumes of phosphate buffer, 50 volumes of acetonitrile R and 20 volumes of methanol R.

Prepare the phosphate buffer by dissolving 1.36 g of potassium dihydrogen phosphate R in 1000 mL of water R.

Time (minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comments
0–2	100	0	Isocratic
2–10	100 to 75	0 to 25	Linear gradient
10–15	75	25	Isocratic
15–30	75 to 20	25 to 80	Linear gradient
30–35	20	80	Isocratic
35–36	20 to 100	80 to 0	Return to initial composition
36–40	100	0	Re-equilibration