COVER PAGE

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LUPIN	**FINISHED PRODUCT STANDARD TEST PROCEDURE FOR DRUG PRODUCT**

NAME: LINEZOLID TABLET 600 MG
CODE: 316367

01. Description: Take 20 tablets at random in a petri dish and check for defects like surface finish, crumbling, mottling, chipping, capping, swelling, powder on the tablets, embossing (if any), stickiness and variation in colour.

Acceptance criteria: The appearance of the tablet should comply with that mentioned in the individual specification.

02. Identification:

1) By HPLC

The retention time of the Linezolid peak in the chromatogram of the test preparation corresponds to that of standard preparation as obtained in the assay.

2) By UV

Diluent preparation: Dissolve 6.8g of potassium dihydrogen ortho phosphate and 0.89 gm of sodium hydroxide pellets in 1000 ml of water and adjust pH 6.8±0.05 with sodium hydroxide solution or Orthophosphoric acid and mix.

Standard preparation: Weigh and transfer 48.0 mg of Linezolid working standard into 200 ml of volumetric flask add 100 ml of diluent and sonicate to dissolve in cool water with intermediate shaking and make up the volume with diluent and mix. Further dilute 5 ml of this solution to 100 ml with diluent and mix.

Test preparation: Crush not less than 20 tablets into fine powder. Weigh and transfer powder sample equivalent to 600.0 mg of Linezolid into 500 ml volumetric flasks, add 300 ml of diluent and sonicate for 15 minutes in cool water with intermediate shaking. Make up volume with diluent. Centrifuge at 5000 rpm for 10 minutes. Further dilute 5 ml of supernatant solution to 500 ml with diluent and mix.

Procedure: Filter the blank, standard and test preparation through 0.45µ nylon filter. Scan the diluent as a blank, standard and test preparation in the range of 200-400 nm wavelength on UV spectrophotometer.

Observation: The Test preparation should exhibit the maxima at the same wavelength as that obtained in the standard preparation.

03. Colour identification test for titanium dioxide:

Reagents required:

1. Concentrated Sulfuric acid.
2. Strong Hydrogen Peroxide.
3. Purified Water**.**

Test Preparation:
Randomly select 5 tablets, Peel out coating without losing tablet material. Transfer the coating material to silica crucible. Ignite the material in a muffle furnace at 800°C for 3 hours to convert it to ash. Remove and cool the crucible to room temperature in desiccator. Add 15 ml of concentrate sulfuric acid and boil the solution on hot plate for 2 hours. Cool the solution at room temperature. Transfer the solution in glass tube. Add 0.5 ml of water and mix. Further add 0.5 ml of strong hydrogen peroxide solution.

Note: Do not allow the crucible to dry, if required add little more amount of concentrated sulfuric acid.
Observation: An orange red colour is produced in the test Preparation.

04. Average weight: Weigh individually 20 tablets selected at random and calculate the average weight as follows:

$$\text{Average weight} = \frac{\text{Weight of 20 tablets}}{20}$$

05. Uniformity of dosage units: (By mass variation)
Proceed as directed ph. Eur. Method 2.9.40
Accurately weigh 10 tablets individually, taking care to preserve the identity of each tablet. Calculate the drug substance content expressed as % of label claim of each tablet from the weight of the individual tablet and the result of the assay. Calculate the acceptance value.

Calculation of acceptance value: Calculate the individual estimated contents of the unit tested x_i (x_1, x_2, …….. x_n) as below $x_i = w_i \times A / w$

Where,
$W_i = w_1, w_2$ ……w_n (individual weight of the unit tested),

A = Content of drug substance (% of label claim) determined as described in the assay and
$\bar{W}$ = mean of the individual weights (w_1, w_2 , …… w_n)

Reference Value (M): Calculate the average value (x) of the 10 individual results and the sample standard deviation (s):

If 98.5 ≤$\bar{X}$ ≤ 101.5	M = $\bar{X}$
If $\bar{X}$ < 98.5	M = 98.5
If $\bar{X}$ > 101.5	M = 101.5

$$s = \left[\frac{\sum_{i=1}^{n} \left(x_i - \bar{x} \right)^2}{n-1} \right]^{1/2}$$

Acceptance Value (AV): Calculate the acceptance value using the following expression:

$$AV = \left| M - \bar{X} \right| + ks \qquad k = 2.4$$

Requirements: The requirements for dosage uniformity are met if the acceptance value of the first 10 dosage units is less than or equal to L1% (AV≤15.0). If the acceptance value is greater than L1%, test another 20 tablets.

Reference and Acceptance values (10 + 20 tablets): Calculate the average value and standard deviation for the 30 tablets. Establish the new reference value (M) following the same criteria than before.

Calculate the new acceptance value:

$$AV = \left| M - \bar{X} \right| + ks \qquad k = 2.0$$

Requirements (10 + 20 tablets): The requirements are met if the final acceptance value of the 30 dosage units is less than or equal to L1% and no individual content of any dosage unit is less than [1-(0.01) (L2)] M nor more than [1+ (0.01)(L2)]M. The value of L1 is 15.0 and L2 is 25.0. Report the acceptance value

06. Water Content (% w/w): By Karl Fischer Titrimetric (Method 1): Add about 20 ml of dehydrated methanol to the titration vessel and titrate to the electrometric end point with the KF reagent. Transfer quickly about 1.0 g of the test sample, accurately weighed, to the titration vessel. Stir for 1 minute and titrate again to the electrometric end point using the KF reagent. The water content of the sample, in mg is given by the expression S×F, in which S is the volume, in ml of the KF reagent used to titrate the sample and F is the water equivalent factor. Calculate the content of water in % w/w by the expression S×F / W x 100, where S×F is the water content of the sample in mg and W is the weight of the test sample in mg.

07. Dissolution: (By HPLC Method):
Dissolution Parameters:

Apparatus	:	USP apparatus No. II (paddle)
RPM	:	50 rpm.
Time	:	30 min
Volume Withdrawn	:	20 ml.
Dissolution Medium	:	900 ml, pH 6.8 phosphate buffer
Temperature	:	37 ±0.5°c

NOTE: For mobile phase, chromatographic conditions refer assay method. Solution stability of standard and sample solution is 48 hrs at 25°c

Preparation of 6.8 pH phosphate buffer: Dissolve 68 g potassium Dihydrogen phosphate in 10 liters of purified water add 9 g of sodium hydroxide and adjust pH 6.8±0.05 with dilute sodium hydroxide or dilute orthophospheric acid and mixed well.

Blank preparation: Use dissolution media as blank.

Standard Preparation-1: Weigh accurately and transfer about 66.0 mg of Linezolid working standard into 200.0 ml volumetric flask, add 50 ml of methanol, sonicate for 5 min to dissolve it completely, and make up to the mark with dissolution media and mix well. Further dilute 5.0 ml of this solution to 50.0 ml with dissolution media and mix well.

Standard Preparation-2: : Weigh accurately and transfer about 66.0 mg of Linezolid working standard into 200.0 ml volumetric flask, add 50 ml of methanol, sonicate for 5 min to dissolve it completely, and make up to the mark with dissolution media and mix well. Further dilute 5.0 ml of this solution to 50.0 ml with dissolution media and mix well.

Similarity Factor Calculation: Calculate the similarity factor as given below:

$$\frac{\text{Absorbance of standard preparation-1}}{\text{Absorbance of standard preparation-2}} \times \frac{\text{Standard -2 weight}}{\text{Standard -1 weight}}$$

Note: Do not proceed further unless and until the similarity factor is within the limits of 0.98 and 1.02. Measure the test solution as per procedure, if the similarity factor is within the limits.

Test Preparation: At the specified time intervals, withdraw 20.0 ml of aliquots. Filter the solution through 0.45 µ nylon filter. Further dilute 5 mL of this solution to 100 ml with dissolution media and mix well.

Procedure: Filter the standard and test preparation through 0.45 µ Nylon membrane filter. Inject blank, standard preparation-1 in single, standard preparation-2 in 6 replicates, and test in single. Calculate the system suitability parameters except % RSD from the chromatogram of the first injection of standard preparation-2 and % RSD from the chromatograms of 6 replicate injections of standard preparation-2.

The test is not valid unless it meets the following system suitability requirements:

Theoretical Plates: NLT 2000 for Linezolid peak.

Tailing factor : NMT 2.0 for Linezolid peak.

% RSD : NMT 2.0 for replicate injections of standard.

Calculation: Calculate the % drug release of Linezolid as follows:

$$\frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{1} \times \frac{P}{100} \times \frac{100}{LC}$$

Where,

AT = Area of Linezolid peak from test solution.
AS = Average area of Linezolid peak from standard solution.
DS = Dilution of standard preparation.
DT = Dilution of test preparation.
P = Potency of Linezolid working standard in % on as is basis.
LC = Label Claim (mg/tablet).
WS = Weight of Linezolid working standard in mg.

08. Related substances: (By HPLC Method):
Chromatographic Conditions:

Column	: Waters Symmetry C18, 250 x 4.6 mm, 5µ
Flow Rate	: 1.3 ml/min.
Wavelength	: 254 nm.
Injection Volume	: 10 µl.
Column oven temperature	: 40 ºC.
Sampler temperature	: 25 ºC.
Run time	: 65 minutes
Retention time	: 10.8 minutes

Buffer solution: Dissolve 2.3 g of Ammonium dihydrogen phosphate in 2000 mL of purified water. Adjust pH 6.0±0.05 with 5% v/v Ammonia solution.

Preparation of Solvent mixture: Prepare a mixture of Acetonitrile and Methanol in the ratio of 75:25 v/v and mix well.

Mobile Phase A Preparation: Prepare a mixture of Buffer and Solvent mixture in the ratio of 90:10 v/v and mix well.

Mobile Phase B Preparation: Prepare a mixture of Buffer and Solvent mixture in the ratio of 20:80 v/v and mix well.

Diluent preparation: Prepare a mixture of water and Acetonitrile in the ratio of 80:20 v/v and mix well.

Blank preparation: Use diluent as blank.

Gradient Program

Retention time	Mobile phase A%	Mobile phase B%
0	80	20
15	90	10
35	50	50
40	50	50
55	20	80
57	80	20
65	80	20

Standard stock preparation 1: Weigh and transfer 48.0 mg of Linezolid working standard into 200.0 ml volumetric flask, add 70 ml of diluent sonicate to dissolve and dilute up to the mark with diluent and mix. Further dilute 5.0 ml of this solution to 50 ml with diluent and mix well.

Standard preparation 1: Dilute 5mL of standard stock solution (1) to 50 mL with diluent and mix well.

Standard stock preparation 2: weigh accurately about 48 mg of linezolid working standard into 200.0 ml volumetric flask, add 70 ml of diluent and sonicate to dissolve. Dilute up to the mark with diluent and mix. Further dilute 5.0 ml of this sonication to 50 ml with diluent and mix well.

Standard preparation 2: Dilute 5mL of standard stock solution (2) to 50 mL with diluent and mix well.

Similarity Factor calculation: calculate the similarity factor as given below:

$$\frac{\text{Area of standard preparation -1}}{\text{Area of standard preparation -2}} \times \frac{\text{Standard -2 weight}}{\text{Standard -1 weight}}$$

Note: Do not proceed further unless and until the similarity factor us within the limits of 0.95 and 1.05. Inject the test solution as per procedure, if the similarity factor % difference and system suitability are within limits.

% Difference: Not more than 5.

$$\frac{\text{(Mean response standard preparation) – (Response of the first injection standard preparation 2)}}{\text{(Mean response standard preparation -2).}}$$

Placebo Preparation: Weigh placebo powder equivalent to 600.0 mg of linezolid into 500.0 ml volumetric flask. Add 130 ml of diluent for 15 minute with intermittent shaking in cool water and dilute up to the mark with diluent and mix well**.**

Test preparation: Weigh and determine average weigh of NLT 20 tablets. Crush the tablets to a fine powder. Weigh tablet powder equivalent to 600.0 mg of linezolid into 500 ml volumetric flask. Add 130 ml of diluent sonicate for 15 minute with intermittent shaking in cool water and dilute up to the mark with diluent and mix well.

Note: solution stability of standard and sample solution is 48 hrs. at 25˚c

Procedure: Filter the standard, diluent, placebo and test Preparation through 0.45µ nylon filter. Inject the diluent as blank in single, Placebo in single, Standard-1 in single, standard-2 in six replicates and sample in single and record the chromatogram. The test is not less it meets the following system suitability criteria.

Theoretical plate : NLT 2000 for linezolid peak

Tailing factor : NMT 2.0 for linezolid peak

% RDS : NMT 5.0 for replicate injection of linezolid standard preparation.

Sr. No.	Name	RT	RRT	Nature of impurity
1	**Linezolid**	10.8	1.00	A
2	**Linezolid Impurity A**	4.3	0.40	P and D
3	**Linezolid Impurity B**	39.50	3.66	P
4	**Linezolid Impurity C**	35.7	3.30	P

Where,

A= Active ingredient

D= Degradation impurity

P= Process impurity

Calculations: Disregard the peaks due to diluent and placebo from the test chromatogram. Also disregard the peaks below 0.05% and the peak due to process impurities as those are control in drug substance.

Calculate the% known impurities, % Any other impurities And % total impurities of Linezolid as follows:

Total impurity (%) = Sum of Known Impurity (%) + any other impurity (%)

Known impurity (%):

$$\frac{Al_o}{AS_1} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P_1}{100} \times \frac{AW}{LC} \times 100$$

Any other impurity (%)

$$\frac{Al_1}{AS_1} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P_1}{100} \times \frac{AW}{LC} \times 100$$

Where,

Al_o = Area of the known impurity peak from test preparation.
Al_1 = Area of the any other impurity peak from test preparation
AS_1 = Average area of the Linezolid peak in the standard preparation.
WS = Weight of the Linezolid working standard in mg
DS = Dilution of standard preparation.
WT = Weight of test in mg.
DT = Dilution of test preparation.
P_1 = Potency of linezolid working standard (on % as is basis)
LC = Label claim in mg/tablet.
AW = Average weight of tablets (mg/tablet).

09. Assay: (By HPLC):

Note: Solution stability of standard and sample solution is 48 hrs at 25˚c.

Chromatographic Conditions:

Column	:	Inertsil ODS 3V, 250 x 4.6 mm, 5µ
Flow Rate	:	1.0 ml/min.
Wavelength	:	254 nm.
Injection Volume	:	10 µl.
Column temperature	:	40 ºC.
Sampler temperature	:	25 ºC.
Run time	:	17 min
Retention time	:	About 5.0 minutes for Linezolid peak.

Buffer preparation: Dissolve 0.23 gm of Ammonium Dihydrogen phosphate in 1000 mL of purified water and mix.

Mobile Phase Preparation: Prepare a mixture of Buffer and Methanol in the ratio of 45:55 v/v. Filter and degas.

Diluent preparation: Prepare a mixture of Buffer and Methanol in the ratio of 55:45 v/v and mix.

Blank preparation: Use diluent as blank.

Standard preparation-1: Weigh accurately about 60.0 mg of Linezolid working standard and transfer into a 200.0 ml volumetric flask, add about 120 mL diluent, sonicate to dissolve in cool water and dilute up to the mark with diluent and mix. Further dilute 5 ml of this solution to 25 mL with diluent and mix.

Standard preparation-2: Weigh accurately about 60.0 mg of Linezolid working standard and transfer into a 200.0 ml volumetric flask, add about 120 ml diluent, sonicate to dissolve in cool water and dilute up to the mark with diluent and mix. Further dilute 5 mL of this solution to 25 mL with diluent and mix.

Similarity Factor Calculation: Calculate the similarity factor as given below:

$$\frac{\text{Area of standard preparation-1}}{\text{Area of standard preparation-2\_1}} \times \frac{\text{Standard -2 weight}}{\text{Standard -1 weight}}$$

Note: Do not proceed further unless and until the similarity factor is within the limits of 0.98 and 1.02. Measure the test solution as per procedure, if the similarity factor is within the limits

Test preparation: Weigh and determine average weight from NLT 20 tablets. Crush the tablets to fine powder. Weigh and transfer sample powder equivalent to 600.0 mg of Linezolid into 500 mL volumetric flask. Add 100 ml of buffer shake well to disperse the powder. Further add 175 ml of buffer and shake for 10 minutes. Add 100 ml of Methanol and sonicate for 10 min. Dilute up to the mark with Methanol and mix well. Centrifuge the solution at 4000 RPM for 10 min. Pipette out 5 ml of this solution and transfer to 100 ml volumetric flask and dilute up to the mark with diluent and mix well.

Procedure: Filter all the preparations through 0.45 µm filter. Inject blank, standard preparation-1 in single, standard preparation-2 in 6 replicates, and test in Single. Calculate the system suitability parameters and test is not valid unless it meets the following system suitability parameters:

Theoretical plates	: Not less than 2000 for the Linezolid peak.
Tailing factor	: Not more than 2.0 for the Linezolid peak.
Relative standard deviation	: Not more than 2.0% for replicate injections of the standard Peak area of Linezolid.

Calculation:

Calculate the assay of Linezolid in mg/tablet as follows:

$$\frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times AW$$

$$\% \text{ Assay} = \frac{\text{mg/tablet}}{LC} \times 100$$

Where,

AT = Average area of the test preparation.
AS = Average area of standard preparation.
WS = Weight of Linezolid working standard in mg.
DS = Dilution of standard preparation.
DT = Dilution of test preparation.
WT = Weight of the test sample in mg.
P = Potency of Linezolid working standard in % on as is basis.
AW = Average weight of tablets in mg.
LC = Label Claim (mg/tablet).

10. Microbial test: Refer to the Microbial Test Procedure SOP_JM_QC_028673.

11. Tablet divisibility by average mass:

Procedure: Take 30 tablets at random, break them by hand and from all the parts obtained from 1 tablet, take one part for the test and reject the other parts. Weigh each of the 30 parts individually and calculate the average mass.The tablet comply with the test if not more than one individual mass is outside the limits of 85% to 115% of the average mass.

Title : Linezolid Tab 600 mg_316367

Filter criteria

Name/Number : JM_MFDP_008157 **Sorted by** : Title

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1.0	31-Oct-2023	**Change :** Prepared first time due to under periodic revision. **Reason :** Refer-CCP-JA-471-23-0136