Teriparatide

Recombinant Human Parathyroid Hormone (rhPTH\(^{1-34}\))

SVSEIQLMHNLGKHLNSMERVEWLKKLDQVHNFC\(_{181}\)H\(_{291}\)N\(_{55}\)O\(_{51}\)S\(_{2}\)

Mol. Wt. approx. 4117.8 Da

Teriparatide is a biologically active N-terminal fragment of endogenous (native) human parathyroid hormone produced by recombinant DNA technology in bacteria as host cells. It is produced under conditions designated to minimize microbial contamination of the product.

Teriparatide contains not less than 90.0 per cent and not more than 110.0 per cent of teriparatide (C\(_{181}\)H\(_{291}\)N\(_{55}\)O\(_{51}\)S\(_{2}\)) calculated on anhydrous, acetic acid-free, and chloride-free basis.

**Category.** Bone forming agent.

**Description.** White to practically white solid (Lyophilized powder / cake).

**Host cell-derived proteins.** Not more than 100 ppm.

**Host cell-derived DNA.** Not more than 10 ng per dose.

Each batch of Teriparatide complies with the following requirements.

**Identification.** Determine by A, B and C or D or E

A. It shows the biological activity as described under potency.

B. Determine by Peptide mapping (2.3.47). Use either method A or method B.

**Method A**

*Test solution.* Dilute the preparation under examination in 0.05 M Tris-hydrochloride buffer solution pH 7.0 to obtain a concentration of 1 mg per ml and transfer 500 µl of it to a clean sample container. Add 10 µl of 1 mg per ml trypsin solution (in water) and incubate for 24 hours at 37°. Stop the reaction by freezing at or below -20°.

*Reference solution.* Dissolve the content of teriparatide RS in 0.05 M Tris-hydrochloride buffer solution pH 7.0 to obtain a concentration of 1 mg per ml and transfer 500 µl of it to a clean sample container. Add 10 µl of 1 mg per ml trypsin solution (in water) and incubate for 24 hours at 37°. Stop the reaction by freezing at or below -20°.

**Chromatographic system**

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilyl silica gel (3 µm) with a pore size of 20 nm,
mobile phase: A. 0.05 per cent v/v solution of trifluoroacetic acid.

B. to 800 ml of acetonitrile, add 0.5 ml of trifluoroacetic acid and 200 ml of acetonitrile.

- a linear gradient programme using the conditions given below,
- flow rate: 1 ml per minute,
- spectrophotometer set at 214 nm.
- injection volume: 50 µl.

<table>
<thead>
<tr>
<th>Time (in min)</th>
<th>Mobile phase A (per cent v/v)</th>
<th>Mobile phase B (per cent v/v)</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>95</td>
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<td>5</td>
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<tr>
<td>5</td>
<td>45</td>
<td>95</td>
</tr>
</tbody>
</table>

Equilibrate the column for at least 15 minutes maintaining the temperature of the column at 40°C.

Inject the reference solution. The test is not valid unless the chromatogram obtained with the reference solution shows eight prominent peaks as given in Figure I.

![Figure I](image)

Inject the test solution. The profile of the chromatogram obtained with test solution corresponds to that of the chromatogram obtained with the reference solution.
Method B

Peptide mapping using *S. aureus* V-8 Protease.

*Sample dilution buffer.* 20 mM Sodium Phosphate, pH adjusted to 7.8 with sodium hydroxide or phosphoric acid reagent grade.

*Test solution.* Dissolve the preparation under examination in dilution buffer to obtain a concentration of 1.5 mg per ml. To 0.15 ml of this solution, add 0.09 ml of 0.25 mg per ml enzyme solution. Mix and incubate at 37° for 18 to 24 hours. Quench the digest by adding 0.66 ml of mobile phase (a) to obtain a final digested protein concentration of 0.25 mg per ml.

*Reference solution.* Dissolve the contents of teriparatide RS in dilution buffer to obtain a concentration of 1.5 mg per ml. To 0.15 ml of this solution, add 0.09 ml of 0.25 mg per ml enzyme solution. Mix and incubate at 37° for 18 to 24 hours. Quench the digest by adding 0.66 ml of mobile phase (a) to obtain a final digested protein concentration of 0.25 mg per ml.

*Blank solution:* Combine 0.15 mL of *sample dilution buffer* to 0.09 ml of 0.25 mg per ml enzyme solution. Mix and incubate at 37 ° for 18 to 24 hours. Quench the digest by adding 0.66 ml of mobile phase (a).

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecysilyl silica gel (3.5 μm),
- column temperature: 40°
- mobile phase: A. 0.1 per cent v/v solution of trifluoroacetic acid in water
  B. 0.1 per cent v/v trifluoroacetic acid in a mixture of 40 volumes of water and 60 volumes of acetonitrile.
- a gradient programme using the conditions given below,
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 20 μl
- run time: 25 minutes.

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<thead>
<tr>
<th>Time (in mins.)</th>
<th>Mobile phase A (per cent v/v)</th>
<th>Mobile phase B (per cent v/v)</th>
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<tr>
<td>0</td>
<td>96</td>
<td>4</td>
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<tr>
<td>6</td>
<td>96</td>
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<td>55</td>
</tr>
<tr>
<td>25</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>25.1</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>35</td>
<td>96</td>
<td>4</td>
</tr>
</tbody>
</table>
Equilibrate the column at the initial condition for at least 10 minutes.

Inject the reference solution. The test is not valid unless the chromatogram obtained with reference solution shows five prominent peaks as given in Figure II.

Inject the test solution. The profile of the chromatogram obtained with test solution corresponds to that of the chromatogram obtained with the reference solution showing five major fragments.

![Figure II: Typical Chromatogram of a S. aureus V- Protease Digest of teriparatide (1-34)](image)

C. Determine by Liquid chromatography (2.4.14) as described in test for assay. In the test for assay, the principle peak in the chromatogram obtained with the test solution corresponds to the peak in the chromatogram obtained with the reference solution.

D. Determine by sodium dodecyl sulphate polyacrylamide gel electrophoresis (SDS-PAGE) (2.4.12) under non-reducing conditions.

**Gel dimensions.** 1.5 mm thick. 10 cm × 10.5 cm.

**Resolving gel.** 20 per cent acrylamide. Mix the components in the order shown.

<table>
<thead>
<tr>
<th>Solution components</th>
<th>Component volume (ml) per gel volume of 7.5 ml</th>
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</thead>
<tbody>
<tr>
<td>Water</td>
<td>1.20</td>
</tr>
<tr>
<td>50 per cent acrylamide solution*</td>
<td>3.00</td>
</tr>
<tr>
<td>Tris-SDS solution (pH 8.45)</td>
<td>2.49</td>
</tr>
<tr>
<td>Glycerol</td>
<td>0.79</td>
</tr>
<tr>
<td>10 per cent APS§</td>
<td>0.025</td>
</tr>
<tr>
<td>TEMED†</td>
<td>0.007</td>
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</tbody>
</table>
Stacking gel. 4 per cent acrylamide. Mix the components in the order shown.

<table>
<thead>
<tr>
<th>Solution components</th>
<th>Component volume (ml) per gel volume of 5.0 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
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</tr>
<tr>
<td>30 per cent acrylamide solution*</td>
<td>0.65</td>
</tr>
<tr>
<td>Tris SDS solution (pH 8.45)</td>
<td>1.25</td>
</tr>
<tr>
<td>10 per cent APSφ</td>
<td>0.05</td>
</tr>
<tr>
<td>TEMED†</td>
<td>0.01</td>
</tr>
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</table>

*30 per cent acrylamide solution: 30 per cent acrylamide / bisacrylamide (29.2:0.8) solution
* 10 per cent APS: a 100 g per litre solution of ammonium persulfate. Prepare freshly.
†TEMED: tetramethylethylenediamine

Tris-SDS solution. Mix 0.3 per cent sodium dodecyl sulfate in 3.0 M tris-hydrochloride buffer solution pH adjusted to 8.45.

Sample buffer. 0.2 M tris-hydrochloride buffer solution pH 6.8 containing 48 per cent glycerol, 2 per cent sodium dodecyl sulfate and 0.4 mg per ml coomassie G250.

Test solution. Dilute the preparation under examination with sample buffer to obtain a concentration of 8µg per well.

Reference solution (a). A solution of protein molecular weight markers suitable for calibrating SDS-polyacrylamide gels.

Reference solution (b). Dilute the contents of teriparatide RS in water to obtain a concentration of 0.25 mg per ml. To 38.4 µl of this solution add 15 µl of sample buffer. Dilute to 60 µl with water.

Reference solution (c). Dilute the test solution in water to obtain a concentration of 8 µg per well.

Sample treatment. Boil for 2 minutes.

Application:

<table>
<thead>
<tr>
<th>Well</th>
<th>Solution(s)</th>
<th>Volume (µl)</th>
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<tbody>
<tr>
<td>1</td>
<td>Reference solution (a)</td>
<td>50</td>
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<tr>
<td>2</td>
<td>Reference solution (b)</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Test solution</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>Reference solution (c)</td>
<td>50</td>
</tr>
</tbody>
</table>
**Cathode buffer.** 0.1 M tris and 0.1 M tricine and 0.1 per cent sodium dodecyl sulfate. Do not adjust pH.

**Anode buffer.** 0.2 M tris-hydrochloride buffer solution pH 8.9.

**Detection.** By silver staining.

The test is not valid unless; a band is seen in the electropherogram obtained with reference solution (c).

The electropherogram obtained with the test solution shows a single broad band corresponding in position and intensity to the single broad band obtained with the reference solution (b).

E. Determine by capillary electrophoresis (Capillary Isoelectric Focusing) (2.4.32).

**Ampholyte gel solution pI range 3.0 to 10.0.** Prepare and use according to the manufacturer’s instructions.

**Test solution.** Dilute the preparation under examination with water, if required to a protein concentration of 1 mg per ml. To the ampholyte gel solution, add 5 µl of sample under examination. Centrifuge the mixture at 7000g × 2 minutes.

**Reference solution.** To the ampholyte gel solution add pI marker(s) suitable for calibrating in pI range of 3 to 10 as per manufacturer’s instructions. Centrifuge the mixture at 7000g × 2 minutes.

**Capillary system**

- material: neutral capillary,

- size: effective length = 20 cm, internal diameter = 50 µm,

- spectrophotometer at 214 nm,

- injection. Fill the capillary with reference solution / test solution for 1.5 minutes under pressure or vacuum.

**Prewashing.** Rinse the capillary with 10 mM phosphoric buffer for 1 minute, with water for 1 minute under pressure / vacuum.

**Prefocusing.** Apply a voltage of 15 kV for 6 minutes with 0.17 minutes ramping time, using anolyte (containing cIEF gel and 91 mM phosphoric acid as per manufacturers’ instructions) and 20 mM sodium hydroxide as catholyte in both buffer reservoirs.

**Migration.** Apply a voltage of 21 kV for 64 minutes at 0.5 psi using above electrolytes.

Rinse with water for 1 minute under pressure or vacuum.

The electropherogram obtained with the test solution corresponds to that obtained with the reference solution. The Isoelectric point of the test solution should appear between 8.2 and 8.4.
Tests

Related Impurities. Determine by Liquid chromatography (2.4.14) using method A or method B.

Method A

Test solution. Dilute the preparation under examination with mobile phase A to obtain a protein concentration of 0.25 mg per ml.

Reference solution for System suitability. To a volume of the test solution, add a suitable volume of 0.06 per cent hydrogen peroxide and 3 mM acetic acid to obtain a final protein concentration of 0.88 mg per ml. Allow to stand at room temperature for 1 hour. Add approx. 30 mg of L-methionine per ml of solution and mix.

Chromatographic system
- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilyl silica gel (3 µm) with a pore size of 20 nm,
- mobile phase: A. 0.1 per cent v/v solution of trifluoroacetic acid,
  B. to 800 ml of acetonitrile add 1.0 ml of trifluoroacetic acid and 200 ml of water for chromatography,
- a gradient programme using the conditions given below,
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 40 µl

Equilibrate the column for at least 15 minutes maintaining the temperature of the column at 40°.

<table>
<thead>
<tr>
<th>Time (in min)</th>
<th>Mobile phase A (per cent v/v)</th>
<th>Mobile phase B (per cent v/v)</th>
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<tbody>
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<tr>
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<td>24</td>
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<tr>
<td>40</td>
<td>76</td>
<td>24</td>
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</table>

Inject the reference solution. The test is not valid unless in the chromatogram obtained with the reference solution three peaks corresponding to oxidized teriparatide appear at retention time of 0.79, 0.66 and 0.46 relative to principal peak.

Inject the test solution. The chromatogram obtained with the test solution corresponds to that obtained with the reference solution. In the chromatogram obtained with the test solution, the sum of the area of any peaks other than
the principal peak is not greater than 3.0 per cent of the total area of the peaks. The sum of the area of peaks corresponding to the oxidized form is not greater than 2.0 per cent of the total area of the peaks.

**Method B**

*Test solution.* Dissolve the preparation under examination in mobile phase A to obtain a concentration of 0.7 mg per ml.

*Reference solution.* Use an appropriate solution containing approximately 0.8% of the first post-main peak in mobile phase A or dissolve the content of teriparatide RS in water to obtain a concentration of 2 mg per ml. Adjust the pH to 3.0 with hydrochloric acid. Incubate at 50° for 9 days. The solution may be aliquoted and stored frozen. Dilute 1 volume of this solution with 1 volume of mobile phase A prior to injection. This gives approximately 0.8 per cent solution of first post-main peak. The first post-main peak is a degradation product resulting from this process and elutes immediately after teriparatide peak.

**Chromatographic system**

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilyl silica gel (3.5 µm),
- autosampler temperature: 2° to 8°,
- mobile phase: A. A mixture of 10 volumes of acetonitrile and 90 volumes of 0.2 M sulfate buffer prepared by dissolving 28.4 g of anhydrous sodium sulphate in 1000 ml water, pH adjusted to 2.3 with 85 per cent phosphoric acid.

  B. A mixture of 50 volumes of acetonitrile and 50 volumes of 0.2 M sulfate buffer (pH 2.3).

*Note - If the sodium sulfate precipitates, gentle heating and continuous stirring may be required. The sodium sulfate should not re-precipitate if this exercise is followed)*

- a gradient programme using the conditions given below,
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 20 µl.

<table>
<thead>
<tr>
<th>Time (in min)</th>
<th>Mobile phase A (per cent v/v)</th>
<th>Mobile phase B (per cent v/v)</th>
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</thead>
<tbody>
<tr>
<td>0</td>
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<tr>
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<tr>
<td>55</td>
<td>100</td>
<td>0</td>
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</table>
Note. The mobile phase composition may be adjusted in order to obtain the desired retention time of teriparatide peak. The mobile phase B (per cent) at 5 and 35 minutes should be changed to alter the retention time, but the same gradient slope should be maintained.

Equilibrate the column for at least 15 minutes maintaining the temperature of the column at 40°.

Inject the reference solution. The test is not valid unless (i) the ratio of the height of first post main peak to the valley between the teriparatide peak and the first post peak is not less than 1.5 (ii) the tailing factor for the teriparatide peak is not more than 2.0.

Inject the test solution. The chromatogram obtained with the test solution corresponds to that obtained with the reference solution. The relative retention time of Met+O(8)teriparatide is about 0.48, Met+O(18)teriparatide is about 0.58 and Met+O(8,18) teriparatide is about 0.38 approximately with reference to teriparatide.

Calculate the percentage of methionyl sulfoxides of teriparatide in the portion of teriparatide taken using the following expression:

\[
\frac{(r_{\text{Met}+O(8)} + r_{\text{Met}+O(18)} + r_{\text{Met}+O(8,18)})}{r_T} \times 100
\]

where,

- \( r_{\text{Met}+O(8)} \) = peak response of Met+O(8) teriparatide (oxidized on Met 8)
- \( r_{\text{Met}+O(18)} \) = peak response of Met+O(18) teriparatide (oxidized on Met 18)
- \( r_{\text{Met}+O(8,18)} \) = peak response of Met+O(8,18) teriparatide (oxidized on Met 8 and Met 18)
- \( r_T \) = sum of the responses for all of the peaks

Calculate the percentage of the largest other related impurity of teriparatide in the portion of teriparatide taken using the following expression:

\[(r_i/r_T) \times 100\]

where,

- \( r_i \) = peak response of the largest other related impurity of teriparatide
- \( r_T \) = sum of the responses for all of the peaks

Calculate the total percentage of teriparatide related impurities in the portion of teriparatide taken using the following expression:

\[(r_l/r_T) \times 100\]

where,
\[ r_I = \text{sum of peak response of the teriparatide related compound} \]

The content of (i) Methionyl sulfoxides of teriparatide [consisting of Met+O (8) teriparatide, Met+O (18) teriparatide & Met +O (8, 18)] is not more than 0.5 per cent, (ii) largest other individual related impurities is not more than 0.5 per cent and (iii) the total related impurities is not more than 2.5 per cent.

**Acetate.** Determine by Liquid chromatography (2.4.14) using the normalisation procedure.

Store the solutions at 2º to 8º and use them within 72 hours.

**Test solution.** Dissolve the preparation under examination in mobile phase to obtain a concentration of 5 mg per ml.

**Reference solution.** Dissolve separately 100 mg, 200 mg and 300 mg of anhydrous sodium acetate in mobile phase and dilute to 100 ml with mobile phase. Further dilute 1 ml of each solution to 10 ml with the mobile phase to prepare a standard curve with acetate concentrations in the range of 0.072-0.216 mg per ml.

**Chromatographic system**
- a stainless steel column 25 cm x 9.0 mm, packed with ion exclusion resin (7.5 µm),
- autosampler temperature: 2º to 8º
- mobile phase: 0.5 per cent v/v solution of dilute sulphuric acid,
- flow rate: 1.0 ml per minute,
- spectrophotometer set at 210 nm,
- injection volume: 100 µl,
- run time: 1.5 times the retention time of acetate.

Inject each concentration of reference solutions in triplicate. The test is not valid unless (i) the area of the principal peak obtained with the repeatability of triplicate injections of 200 mg concentration reference solution has the relative standard deviation of not more than 1.25 per cent; (ii) the correlation coefficient \( r \) calculated for the standard curve is not less than 0.999.

Inject the test solution. The retention time of acetate is about 10 minutes. Plot peak areas versus injected acetate content and perform linear regression to create a standard curve. Calculate the acetate content using the standard curve and the area of the peak due to acetate in the chromatogram obtained with the test solution. The acetate content is not more than 5.0 per cent.

**Chloride.** Determine by Liquid chromatography (2.4.14) using the normalisation procedure. Use the solutions within 72 hours.

**Test solution.** Dissolve the preparation under examination in water to obtain a concentration of 1 mg per ml.

**Reference solution (a).** Dissolve 165.9 mg of sodium chloride, previously dried at 105º for 30 minutes, in water and dilute to 100 ml with the same solvent.
Reference solution (b). Dissolve 150 mg of sodium nitrite in water and dilute to 100 ml with the same solvent. Mix 1.0 ml of the solution and 2.5 ml of reference solution (a) and dilute to 100 ml with water.

Reference solutions. Dilute reference solution (a) with water to prepare a standard curve with at least 4 concentrations in the range of 10 to 40 µg per ml.

Chromatographic system

- a stainless steel pre-column 5 cm x 4.0 mm, packed with strongly basic anion-exchange resin (15 µm),
- a stainless steel column 25 cm x 4.0 mm, packed with strongly basic anion-exchange resin (15 µm),
- mobile phase: Dissolve 285.7 mg of sodium hydrogen carbonate and 381.6 mg of anhydrous sodium carbonate in water and dilute to 2 liters with the same solvent,
- flow rate: 2.0 ml per minute,
- conductivity detector: use a self regenerating anion suppressor at 100 mA,
- injection volume: 50 µl,
- run time: 6 times the retention time of chloride.

Inject reference solution (b). The test is not valid unless (i) the resolution between the peaks due to chloride and nitrite is not less than 1.5; (ii) the symmetry factor for the peaks due to chloride and nitrite is not more than 2.0 (iii) the area of the principal peak due to chloride and nitrite obtained with the repeatability of five injections has the relative standard deviation of not more than 2.0 per cent; (iv) the correlation coefficient (r) calculated for the standard curve is not less than 0.999.

Inject the test solution. The retention time of chloride is about 1.6 minutes and of nitrite is about 1.8 minutes. Plot peak areas versus injected chloride content and perform linear regression to create a standard curve. Calculate the chloride content using the standard curve and the area of the peak due to chloride in the chromatogram obtained with the test solution. The chloride content is not more than 4.0 per cent.

Water (2.3.43): Not more than 10 per cent.

Bacterial endotoxins (2.2.3). Not more than 50 EU in the volume containing 1 mg of protein.

Microbial enumeration tests. The total microbial count is not more than 100 cfu per g.

Assay

A. Potency. The biological activity of teriparatide is estimated to be equipotent to that teriparatide RS based on its comparative ability to stimulate the accumulation of cAMP in UMR-106 cells with respect to the appropriate international reference standard of teriparatide.

Determination of the biological activity of teriparatide is based on the stimulation of adenylate cyclase activity in the rat osteosarcoma cell line UMR 106. Activation of the PTH receptor initiates a cascade event which culminates in an intracellular rise in cAMP concentration.
The method uses cAMP end-point measurement by ELISA. Incubate UMR-106 cells in tissue culture plate until an even monolayer is observed. Maintain the cells in serum free media for 18 to 26 hours in order to decrease the levels of endogenous cAMP. Suitably wash the cells and incubate with varying dilutions of test and reference preparations for up to 8 dilutions for the suitable time. Collect the cell lysate containing the cAMP and determine the cAMP accumulation by using a suitable ELISA or suitable detection assay.

Analyze the data by fitting a sigmoidal dose - response curve to the data obtained and by using a suitable statistical method, for example the 4-parameter or parallel line model.

The estimated potency is not less than 80 per cent and not more than 125 per cent of the stated potency.

B. Determine by liquid chromatography (2.4. 14). Store the solution at 2° to 8° and use within 48 hours.

Solution (a). Dissolve 28.4 g of anhydrous sodium sulfate in 900 ml water and adjust to pH 2.3 with phosphoric acid. Dilute to 1000 ml with water.

Solution (b). Prepare a mixture of 25 volumes of acetonitrile and 75 volumes of solution (a).

Test solution. Dissolve the preparation under examination in solution (b) to obtain a concentration of 250 µg per ml. Test solution is stable for not more than 72 hours when stored at refrigerated temperature in sealed container.

(Note - Teriparatide should be equilibrated and weighed in a controlled humidity chamber of 25 ± 5 per cent relative humidity, then dissolved in Diluent. Determine the water content within 24 hours of weighing).

Reference solution. Dissolve the content of teriparatide RS in solution (b) to obtain a concentration of 250 µg per ml. Reference solution is stable for not more than 72 hours when stored at refrigerated temperature in sealed container.

Chromatographic system

- a stainless steel column 15 cm x 4.6 mm, packed with octadecylsilyl silica gel (3.5 µm),
- mobile phase: A. a mixture of 90 volumes of sulphate buffer pH 2.3 ± 0.2 and 10 volumes of acetonitrile,
  B. a mixture of 50 volumes of sulphate buffer pH 2.3 ± 0.2 and 50 volumes of acetonitrile.
- a linear gradient programme using the conditions given below,
- flow rate: 0.8 ml per minute,
- spectrophotometer set at 214 nm,
- injection volume: 20 µl,
- run time: 20 minutes (approx.).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>0</td>
<td>63</td>
<td>37</td>
</tr>
<tr>
<td>15</td>
<td>63</td>
<td>37</td>
</tr>
</tbody>
</table>
Equilibrate the column for at least 15 minutes maintaining the temperature of the column at 40°.

Inject the reference solution in triplicate. The test is not valid unless (i) The relative standard deviation (RSD) of teriparatide peak area is not more than 1.25 per cent; (ii) the tailing factor of the teriparatide peak is not more than 1.5.

Inject the test solution. The retention time of teriparatide is 7.5 minutes to 11.7 minutes. The estimated potency of teriparatide is not less than 90.0 per cent and not more than 110.0 per cent calculated on an anhydrous, acetic acid-free and chloride-free basis.

**Storage.** Store in sterile airtight container at or below the temperature of -10°.

**Labelling.** The label states (i) the teriparatide content in µg per ml; (ii) the name and the concentration of any other excipients; (iii) indication that the material has been produced by methods based on recombinant DNA technology.