Edition: BP 2025 (Ph. Eur. 11.6 update)

Levothyroxine Tablets

General Notices

Action and use

Thyroid hormone replacement.

DEFINITION

Levothyroxine Tablets contain Levothyroxine Sodium.

The tablets comply with the requirements stated under Tablets and with the following requirements.

PRODUCTION

Levothyroxine Sodium used in the formulation of Levothyroxine Tablets exists primarily in its most stable form, a crystalline pentahydrate.

Care should be taken during manufacture to avoid exposure to higher temperatures (> 50°) or very low humidities.

Content of anhydrous levothyroxine sodium, $C_{15}H_{10}I_4NNaO_4$

90.0 to 105.0% of the stated amount.

IDENTIFICATION

In the test for Uniformity of content, record the UV spectrum of the principal peak in the chromatograms obtained with solutions (1) and (2) with a diode array detector in the range of 210 to 400 nm.

The UV spectrum of the principal peak in the chromatogram obtained with solution (1) is concordant with that of the peak in the chromatogram obtained with solution (2);

the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

Dissolution

Comply with the *dissolution test for tablets and capsules*, Appendix XII B1.

Plastic containers must not be used to prepare and store solutions.

TEST CONDITIONS

(a) Use Apparatus 2, rotating the paddle at 100 revolutions per minute.
(b) Use 500 mL of *water*, at a temperature of 37°, as the medium.
(c) For tablets containing the equivalent of 25 µg or less of anhydrous levothyroxine sodium, place two tablets in the dissolution vessel; for tablets containing more than the equivalent of 25 µg of anhydrous levothyroxine sodium, place one tablet in the dissolution vessel.

PROCEDURE

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) After 45 minutes withdraw a 5-mL sample of the medium and centrifuge, dilute with sufficient of the dissolution medium, if necessary, to produce a solution expected to contain 0.00001% w/v of anhydrous levothyroxine sodium. To a 5-mL aliquot add 200 µL of 0.1M *sodium hydroxide* and 125 µL of a 2% v/v solution of *diethylamine*.
(2) To 5 mL of 0.00001% w/v *levothyroxine sodium EPCRS* in 0.001M *sodium hydroxide* add 200 µL of 0.1M *sodium hydroxide* and 125 µL of a 2% v/v solution of *diethylamine* and mix.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Spherisorb S5 CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use a column temperature of 40°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 150 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile R1* and 700 volumes of *water*.

DETERMINATION OF CONTENT

Calculate the total content of anhydrous levothyroxine sodium, $C_{15}H_{10}I_4NNaO_4$, in the medium from the chromatograms obtained and using the declared content of $C_{15}H_{10}I_4NNaO_4$ in *levothyroxine sodium EPCRS*.

LIMITS

The amount of anhydrous levothyroxine sodium released is not less than 75% (Q) of the stated amount.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions, prepared in solution A, protected from light.

Solution A Equal volumes of *methanol* and 0.1M *sodium hydroxide*.

(1) Shake a quantity of powdered tablets containing the equivalent of 0.25 mg of anhydrous levothyroxine sodium with 2.5 mL of 0.1M *sodium hydroxide*. Dilute to 5 mL with *methanol*, shake and mix with the aid of ultrasound. Centrifuge and filter the supernatant liquid through a 0.7-µm glass microfibre filter (Whatman GMF is suitable).
(2) Dilute 1 volume of solution (1) to 50 volumes.
(3) 0.0005% w/v of *levothyroxine sodium impurity standard BPCRS*.
(4) Dilute 1 volume of solution (2) to 20 volumes.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (15 cm × 3.0 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (3.5 µm) (Waters Sunfire C18 is suitable).
(b) Use gradient elution and the mobile phase described below.
(c) Use a flow rate of 0.6 mL per minute.
(d) Use a column temperature of 30°.
(e) Use a detection wavelength of 225 nm.
(f) Inject 6 µL of each solution.

MOBILE PHASE

Mobile phase A 200 volumes of 0.098% w/v of *orthophosphoric acid* in *acetonitrile* and 800 volumes of 0.098% w/v of *orthophosphoric acid* in *water*.

Mobile phase B 180 volumes of 0.098% w/v of *orthophosphoric acid* in *water* and 820 volumes of 0.098% w/v of *orthophosphoric acid* in *acetonitrile*.

Time (Minutes)	Mobile phase A (% v/v)	Mobile phase B (% v/v)	Comment
0-2	100→89	0→11	linear gradient
2-17	89→72	11→28	linear gradient
17-45	72→0	28→100	linear gradient
45-50	0	100	isocratic
50-52	0→100	100→0	linear gradient
52-60	100	0	re-equilibration

When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to levothyroxine (retention time about 14 minutes) are: impurity A, about 0.7; impurity 1, about 0.8 and impurity D, about 2.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3):

the *resolution* between impurity A and levothyroxine is at least 10.0;

the *signal-to-noise ratio* of the principal peak in the chromatogram obtained with solution (4) is at least 20.

LIMITS

Identify any peak corresponding to impurity 1 in the chromatogram obtained with solution (1), using the chromatogram obtained with solution (3), and multiply the area of this peak by a correction factor of 1.8.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity 1 is not greater than 4 times the area of the principal peak in the chromatogram obtained with solution (2) (8%);

the area of any other *secondary peak* is not greater than half the area of the principal peak in the chromatogram obtained with solution (2) (1%);

the sum of the areas of any *secondary peaks*, excluding impurity 1, is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (5%);

the sum of the areas of all *secondary peaks*, is not greater than 5 times the area of the principal peak in the chromatogram obtained with solution (2) (10%).

Disregard any peak with an area less than the area of the principal peak in the chromatogram obtained with solution (4) (0.1%).

Uniformity of content

Tablets containing less than 2 mg and/or less than 2% w/w of Levothyroxine Sodium comply with the requirements stated under Tablets using the following method of analysis. Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions prepared in solution A, unless otherwise stated, protected from light.

Solution A Equal volumes of *methanol* and 0.1M *sodium hydroxide*.

(1) Add sufficient 0.05M *sodium hydroxide* to one tablet to produce a solution containing the equivalent of about 6 µg per mL of anhydrous levothyroxine sodium, mix with the aid of ultrasound until the tablet is fully dispersed, cool and shake for 2 minutes. Add sufficient 0.05M *sodium hydroxide* to produce a solution containing the equivalent of 0.0005% w/v of anhydrous levothyroxine sodium, filter through glass microfibre filter (Whatman GF/C is suitable) and use the filtrate.
(2) 0.00055% w/v of *levothyroxine sodium EPCRS* in 0.05M *sodium hydroxide*.
(3) 0.0005% w/v of *liothyronine sodium EPCRS* and 0.0005% w/v of *levothyroxine sodium EPCRS*.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *cyanosilyl silica gel for chromatography* (5 µm) (Nucleosil 5 CN is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 225 nm.
(f) Inject 20 µL of each solution.

MOBILE PHASE

5 volumes of *orthophosphoric acid*, 300 volumes of *acetonitrile* and 700 volumes of *water*.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the *resolution* between the peaks due to liothyronine and levothyroxine is at least 4.0.

DETERMINATION OF CONTENT

Calculate the content of $C_{15}H_{10}I_4NNaO_4$ in each tablet using the declared content of $C_{15}H_{10}I_4NNaO_4$ in *levothyroxine sodium EPCRS*.

ASSAY

Use the average of the individual results determined in the test for Uniformity of content.

STORAGE

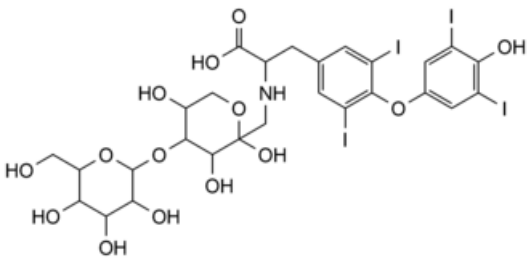
Levothyroxine Tablets should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of anhydrous levothyroxine sodium.

IMPURITIES

The impurities limited by the requirements of this monograph include impurities A, D, F and G listed under Levothyroxine Sodium and:



1. 3-(4-(4-hydroxy-3,5-diiodophenoxy)-3,5-diiodophenyl)-2-(((4,5,6-trihydroxy-3-((3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2*H*-pyran-2-yl)oxy)tetrahydro-2*H*-pyran-2-yl)methyl)amino)propanoic acid (levothyroxine-lactose maillard impurity).