System suitability solution: Dissolve USP Telmisartan RS and USP Telmisartan Related Compound B RS in methanol (0.2 mL/mg of USP Telmisartan RS) and 100 µL of 1 M sodium hydroxide solution. Sonicate to dissolve. The final concentration is 2.5 mg/mL of the USP Telmisartan RS and 2.5 µg/mL of USP Telmisartan Related Compound B RS in methanol.

Standard solution: Dissolve USP Telmisartan RS in methanol (0.2 mL/mg of USP Telmisartan RS) and 100 µL of 1 M sodium hydroxide solution. Sonicate to dissolve. The final concentration is 0.025 mg/mL.

Sample solution: Dissolve Telmisartan in methanol (0.2 mL/mg of Telmisartan) and 100 µL of 1 M sodium hydroxide solution. Sonicate to dissolve. The final concentration is 2.5 mg/mL.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.0-mm × 12.5-cm; 5-µm packing L1
Column temperature: 40°
Flow rate: 1 mL/min
Injection size: 2 µL

System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between telmisartan and telmisartan related compound B, *System suitability solution*
Tailing factor: Between 0.9 and 1.5 for telmisartan related compound B, *System suitability solution*
Relative standard deviation: NMT 5.0% for the telmisartan peak, *Standard solution*

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of any individual impurity in the portion of Telmisartan taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of telmisartan from the *Standard solution*
C_S = concentration of USP Telmisartan RS in the *Standard solution*
C_U = concentration of Telmisartan in the *Sample solution*

Acceptance criteria: See *Table 2*. [NOTE—Calculate the total impurities from the sum of all impurity peaks greater than or equal to 0.05%.]

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Telmisartan related compound A[a]	0.3	0.1
Telmisartan amide[b]	0.7	0.1
Telmisartan related compound B[c]	0.9	0.1
Telmisartan diacid[d]	0.67	0.1
Telmisartan *tert*-butyl ester[e]	1.7	0.2
Telmisartan unknown impurity	1.8	0.2
Any other individual impurity	—	0.1
Total impurities	—	1.0

[a] 1,7′-Dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazole.
[b] 4′-[(1,7′-Dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazol-3′-yl)methyl] biphenyl-2-carboxamide.
[c] 4′-[(1,7′-Dimethyl-2′-propyl-1*H*,1′*H*-2,5′-bibenzo[*d*]imidazol-1′-yl)methyl] biphenyl-2-carboxylic acid.
[d] 1-[(2′-Carboxybiphenyl-4-yl)methyl]-4-methyl-2-propyl-1*H*-benzimidazole-6-carboxylic acid.
[e] *tert*-Butyl 4′-[(1,7′-dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazol-3′-yl)methyl]biphenyl-2-carboxylate.

SPECIFIC TESTS
- **LOSS ON DRYING** ⟨**731**⟩**:** Dry 1.0 g of the sample at 105° to constant weight: it loses NMT 1.5%.

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight containers, and protect from light.
- **USP REFERENCE STANDARDS** ⟨**11**⟩
  USP Telmisartan RS
  USP Telmisartan Related Compound B RS
  4′-[(1,7′-Dimethyl-2′-propyl-1*H*,1′*H*-2,5′-bibenzo[*d*]imidazol-1′-yl)methyl]biphenyl-2-carboxylic acid.
  $C_{33}H_{30}N_4O_2$ 514.62

Telmisartan and Hydrochlorothiazide Tablets

DEFINITION
Telmisartan and Hydrochlorothiazide Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) and NLT 90.0% and NMT 107.5% of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION
- **A. ULTRAVIOLET ABSORPTION** ⟨**197U**⟩**:** The spectrum of the solution under test corresponds to that of the *Standard solution*, as obtained in *Assay*.
- **B.** The retention time of the two major peaks of the *Sample solution* corresponds to that of the two major peaks in *Standard solution A*, as obtained in the *Assay*.

ASSAY
- **PROCEDURE**
  Diluent: 0.005 M methanolic solution of sodium hydroxide
  Buffer: 2.0 g/L of ammonium dihydrogen phosphate. Adjust with phosphoric acid to a pH of 3.0.
  Solution A: Methanol and acetonitrile (1:1)
  Mobile phase: See the gradient table below.

Time (min)	Buffer (%)	Solution A (%)
0	85	15
3.50	85	15
3.51	45	55
7.70	45	55
7.71	20	80
12.0	20	80
12.1	85	15
15.5	85	15

Standard stock solution 1: 0.025 mg/mL of USP Benzothiadiazine Related Compound A RS in *Diluent*

Standard stock solution 2: 1.6 mg/mL or 3.2 mg/mL (required for analyzing the Tablet strength of 80 mg/12.5 mg) of USP Telmisartan RS, 0.5 mg/mL of USP Hydrochlorothiazide RS, and 2.5 µg/mL of USP Benzothiadiazine Related Compound A RS (from *Standard stock solution 1*) in *Diluent*
Standard solution A: Dilute *Standard stock solution 2* with a 1:1 solution of *Buffer* and *Solution A* to prepare 0.32 mg/mL of telmisartan, 0.1 mg/mL of hydrochlorothiazide, and 0.5 µg/mL of benzothiadiazine related compound A for Tablet strengths of 80 mg/25 mg and 40 mg/12.5 mg. The final concentrations for analyzing the Tablet strength of 80 mg/12.5 mg are 0.32 mg/mL of telmisartan, 0.05 mg/mL of hydrochlorothiazide solution, and 0.25 µg/mL of benzothiadiazine related compound A.
Sample stock solution: Transfer NLT 10 Tablets into a suitable volumetric flask, add 0.1 N sodium hydroxide solution (5% of the total volume of the flask), and shake until the Tablets have completely disintegrated. Add methanol (80% of the total volume of the flask). Sonicate for 10 min and stir vigorously for 30 min. Allow to cool to room temperature, dilute with methanol to volume, and mix. The concentration of the *Sample stock solution* is about 1.6 mg/mL of telmisartan. [NOTE—The hydrochlorothiazide concentration may vary depending on the ratio of telmisartan to hydrochlorothiazide in the Tablet.] Centrifuge a portion of the solution at 4000 rpm. [NOTE—To prevent heat from degrading the sample, do not extend the sonication time and also maintain the bath temperature at NMT 22° by adding ice.]
Sample solution: Dilute 1 mL of the *Sample stock solution* to 5 mL in a 1:1 solution of *Buffer* and *Solution A*.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 270 nm for hydrochlorothiazide and 298 nm for telmisartan
Column: 4.0-mm × 12.5-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 1.2 mL/min
Injection size: 10 µL
System suitability
Sample: *Standard solution A*
Suitability requirements
Resolution: NLT 2.0 between hydrochlorothiazide and benzothiadiazine related compound A
Relative standard deviation: NMT 2.0% for both the telmisartan and hydrochlorothiazide peaks
Analysis
Samples: *Standard solution A* and *Sample solution*
Calculate the percentages of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of telmisartan or hydrochlorothiazide from the *Sample solution*
r_S = peak response of telmisartan or hydrochlorothiazide from *Standard solution A*
C_S = concentration of USP Telmisartan RS or the hydrochlorothiazide peak in *Standard solution A* (mg/mL)
C_U = nominal concentration of telmisartan or hydrochlorothiazide in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0% of telmisartan and 90.0%–107.5% of hydrochlorothiazide

PERFORMANCE TESTS

• **DISSOLUTION** ⟨711⟩
Telmisartan
Medium: pH 7.5 phosphate buffer (13.61 g/L of potassium dihydrogen phosphate in water. Adjust with 2 M sodium hydroxide to a pH of 7.5); 900 mL
Apparatus 2: 75 rpm
Time: 30 min
Hydrochlorothiazide
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 1: 100 rpm
Time: 30 min
Analysis: Determine the amounts of telmisartan and hydrochlorothiazide dissolved by the following method.
Solution A: 5.0 g/L of ammonium dihydrogen phosphate in water. Adjust with phosphoric acid to a pH of 3.0.
Solution B: Acetonitrile
Standard stock solution: Appropriate amounts of USP Telmisartan RS and USP Hydrochlorothiazide RS in methanol
Telmisartan standard solution: Dilute the *Standard stock solution* with *Telmisartan Medium* to obtain a solution having a known concentration of telmisartan similar to that expected in the *Sample solution*.
Hydrochlorothiazide standard solution: Dilute the *Standard stock solution* with *Hydrochlorothiazide Medium* to obtain a solution having a known concentration of hydrochlorothiazide similar to that expected in the *Sample solution*.
Sample solution: Pass a portion of the solution through a suitable filter of 0.45-µm pore size, discard the first few mL, and dilute with appropriate *Medium*, if necessary.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 270 nm for hydrochlorothiazide and 298 nm for telmisartan
Column: 3.0-mm × 6-cm; 5-µm packing L7
Column temperature: 40°
Flow rate: 0.6 mL/min from 0–5.00 min and 1.0 mL/min from 5.01–6.20 min. The flow rate goes back to 0.6 mL from 6.21–9.70.
Injection size: 4 µL
Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	85	15
1.50	85	15
1.51	60	40
5.00	60	40
5.01	20	80
6.20	20	80
6.21	85	15
9.70	85	15

System suitability
Samples: *Telmisartan standard solution* or *Hydrochlorothiazide standard solution*
[NOTE—The relative retention times for hydrochlorothiazide and telmisartan are 0.33 and 1.0, respectively.]
Suitability requirements
Tailing factor: NMT 2.5 for both hydrochlorothiazide and telmisartan
Relative standard deviation: NMT 2%
Calculate the percentage of telmisartan or hydrochlorothiazide dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S/L) \times V \times 100$$

r_U = peak response of telmisartan or hydrochlorothiazide in the *Sample solution*
r_S = peak response of telmisartan in the *Telmisartan standard solution* or hydrochlorothiazide in the *Hydrochlorothiazide standard solution*
C_S = concentration of telmisartan in the *Telmisartan standard solution* or hydrochlorothiazide in the *Hydrochlorothiazide standard solution* (mg/mL)
L = Tablet label claim for telmisartan or hydrochlorothiazide (mg)

V = volume of *Medium*, 900 mL

Tolerances: NLT 80% (Q) of the labeled amount of telmisartan and hydrochlorothiazide is dissolved.

- **UNIFORMITY OF DOSAGE UNITS ⟨905⟩:** Meet the requirements

IMPURITIES

Organic Impurities

- **PROCEDURE**

Diluent, Buffer, Solution A, Mobile phase, Standard stock solution 1, Standard solution A, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard solution B: 1.25 µg/mL of USP Benzothiadiazine Related Compound A RS in *Diluent* from *Standard stock solution 1*. Dilute further with a 1:1 solution of *Buffer* and *Solution A* to prepare a 0.25-µg/mL solution for a Tablet strength of 80 mg/12.5 mg, and a 0.5-µg/mL solution for Tablet strengths of 40 mg/12.5 mg and 80 mg/25 mg.

Standard stock solution 3: 1.6 mg/mL of USP Telmisartan RS and 0.5 mg/mL of USP Hydrochlorothiazide RS in *Diluent* for Tablet strengths of 40 mg/12.5 mg and 80 mg/25 mg. For the Tablet strength of 80 mg/12.5 mg, the concentrations are 1.6 mg/mL of USP Telmisartan RS and 0.25 mg/mL of USP Hydrochlorothiazide RS in *Diluent*.

Sensitivity solution: Dilute 10 mL of *Standard stock solution 3* with *Diluent* to 100 mL. Combine 1.0 mL of this solution with 2.0 mL of *Standard stock solution 1* and dilute with *Diluent* to 100 mL. Dilute 1 mL of this solution to 5 mL with a 1:1 solution of *Buffer* and *Solution A*.

System suitability

Samples: *Standard solution A* and *Sensitivity solution*

Suitability requirements

Resolution: NLT 2.0 between hydrochlorothiazide and benzothiadiazine related compound A, *Standard solution A*

Relative standard deviation: NMT 2.0% for both the telmisartan and hydrochlorothiazide peaks, *Standard solution A*

Signal-to-noise ratio: NLT 3.0 for the telmisartan, hydrochlorothiazide, and benzothiadiazine related compound A peaks from the *Sensitivity solution*

Analysis

Samples: *Standard solution A*, *Standard solution B*, and *Sample solution*

Calculate the percentage of benzothiadiazine related compound A in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of benzothiadiazine related compound A from the *Sample solution*

r_S = peak response of benzothiadiazine related compound A from *Standard solution B*

C_S = concentration of USP Benzothiadiazine Related Compound A RS in *Standard solution B* (mg/mL)

C_U = concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

Calculate the percentage of each unspecified degradation impurity related to hydrochlorothiazide in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each unspecified degradation impurity at 270 nm from the *Sample solution*

r_S = peak response of hydrochlorothiazide from *Standard solution A*

C_S = concentration of USP Hydrochlorothiazide RS in *Standard solution A* (mg/mL)

C_U = concentration of hydrochlorothiazide in the *Sample solution* (mg/mL)

Calculate the percentage of each unspecified degradation impurity related to telmisartan in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each unspecified degradation impurity at 298 nm from the *Sample solution*

r_S = peak response of telmisartan from *Standard solution A*

C_S = concentration of USP Telmisartan RS in *Standard solution A* (mg/mL)

C_U = concentration of telmisartan in the *Sample solution* (mg/mL)

Acceptance criteria

Individual impurities: NMT 1.0% of benzothiadiazine related compound A and NMT 0.2% of each individual unspecified degradation impurity related to hydrochlorothiazide or telmisartan

Total impurities: NMT 0.2% of the sum of all degradation products related to telmisartan and NMT 1.5% of the sum of all hydrochlorothiazide degradation products

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers and store at controlled room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Benzothiadiazine Related Compound A RS
4-Amino-6-chloro-1,3-benzenedisulfonamide.
$C_6H_8ClN_3O_4S_2$ 285.73
USP Hydrochlorothiazide RS
USP Telmisartan RS

Telmisartan Tablets

DEFINITION

Telmisartan Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$).

IDENTIFICATION

- **A. ULTRAVIOLET ABSORPTION ⟨197U⟩:** The spectrum of the solution under test corresponds to that of the *Standard solution*, as obtained in the test for *Dissolution*.
- **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Diluent: 0.005 N methanolic solution of sodium hydroxide

Buffer: 2.0 g/L ammonium dihydrogen phosphate. Adjust with 1 M phosphoric acid to a pH of 3.0.

Mobile phase: Methanol and *Buffer* (70:30)

Standard stock solution: 0.8 mg/mL of USP Telmisartan RS and 0.1 mg/mL of USP Telmisartan Related Compound A RS in *Diluent*

Standard solution: 0.11 mg/mL of USP Telmisartan RS and 0.013 mg/mL of USP Telmisartan Related Compound A RS in *Mobile phase*. Pass the solution through a membrane filter of 0.45-µm pore size.

Sample solution: Transfer NLT 20 Tablets into a suitable volumetric flask, and add about 80% of the volume of *Diluent*. Swirl to disperse, and sonicate for about 10 min. Allow to cool to room temperature, dilute with *Diluent* to volume, and mix. Pass the resulting solution through a membrane filter of 0.45-µm pore size. Further dilute quantitatively in *Mobile phase* to prepare a solution having a concentration of 0.11 mg/mL.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)