# Irbesartan and Amlodipine Besilate Tablets

イルベサルタン・アムロジピンベシル酸塩錠

Irbesartan and Amlodipine Besilate Tablets contain not less than 95.0% and not more than 105.0% of the labeled amount of irbesartan ($C_{25}H_{28}N_6O$: 428.53) and amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$: 567.05).

**Method of preparation** Prepare as directed under Tablets, with Irbesartan and Amlodipine Besilate.

**Identification** **(1)** Perform the test with 5 $\mu$L each of the sample solution and standard solution obtained in the Assay (1) as directed under Liquid Chromatography *<2.01>* according to the following conditions: the retention time of the peak of irbesartan obtained from the sample solution is the same with that of the principal peak obtained from the standard solution, and both absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

*Operating conditions* －

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1).

Detector: A photodiode array detector (wavelength: 237 nm, spectrum range of measurement: 210 – 400 nm).

*System suitability* －

System performance: Proceed as directed in the system suitability in the Assay (1).

**(2)** Perform the test with 5 $\mu$L each of the sample solution and standard solution obtained in the Assay (2) as directed under Liquid Chromatography *<2.01>* according to the following conditions: the retention time of the peak of amlodipine obtained from the sample solution is the same with that of the principal peak obtained from the standard solution and both absorption spectra of these peaks exhibit similar intensities of absorption at the same wavelengths.

*Operating conditions* －

Column, column temperature, mobile phase and flow rate: Proceed as directed in the operating conditions in the Assay (1).

Detector: A photodiode array detector (wavelength: 237 nm, spectrum range of measurement: 210 – 400 nm).

*System suitability* －

System performance: Proceed as directed in the system suitability in the Assay (2).

**Uniformity of dosage unit** *<6.02>* **(1)** Irbesartan － Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

To 1 tablet of Irbesartan and Amlodipine Besilate Tablets add 4 mL of 0.02 mol/L phosphate buffer (pH 3.0), and sonicate. Add 16 mL of methanol, shake vigorously until the tablet is disintegrated completely, and add the mobile phase to make exactly 100 mL. Pipet $V$ mL of this solution, add the mobile phase to make exactly $V'$ mL so that each mL contains about 1 mg of irbesartan ($C_{25}H_{28}N_6O$), and filter through a membrane filter with a pore size not exceeding 0.45 $\mu$m. Discard the first 5 mL of the filtrate, and use the subsequent filtrate as the sample solution. Then, proceed as directed under the Assay (1).

$$\text{Amount (mg) of irbesartan } (C_{25}H_{28}N_6O) = M_S \times A_T / A_S \times V'/V \times 2$$

$M_S$: Amount (mg) of irbesartan for assay taken, calculated on the anhydrous basis

**(2)** Amlodipine besilate － Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 tablet of Irbesartan and Amlodipine Besilate Tablets add 4 mL of 0.02 mol/L phosphate buffer (pH 3.0), and sonicate. Add 16 ml of methanol, shake vigorously until the tablet is disintegrated completely, and add the mobile phase to make exactly 100 mL. Pipet $V$ mL of this solution, add the mobile phase to make exactly $V'$ mL so that each mL contains about 69 $\mu$g of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$), and filter through a membrane filter with a pore size not exceeding 0.45 $\mu$m. Discard the first 5 mL of the filtrate, and use the subsequent filtrate as the sample solution. Then, proceed as directed under the Assay (2).

$$\text{Amount (mg) of amlodipine besilate } (C_{20}H_{25}ClN_2O_5.C_6H_6O_3S) = M_S \times A_T / A_S \times V'/V \times 1/5$$

$M_S$: Amount (mg) of Amlodipine Besilate RS taken, calculated on the anhydrous basis

**Dissolution** *<6.10>* **(1)** Irbesartan － When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rate in 30 minutes of Irbesartan and Amlodipine Besilate Tablets is not less than 70%.

Start the test with 1 tablet of Irbesartan and Amlodipine Besilate Tablets, withdraw not less than 15 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 $\mu$m. Discard the first 10 mL of the filtrate, pipet $V$ mL of the subsequent filtrate, and add the mobile phase to make exactly $V'$ mL so that each mL contains about 0.11 mg of irbesartan ($C_{25}H_{28}N_6O$). Pipet 2 mL of this solution, add exactly 2 mL of the mobile phase, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of Irbesartan for assay (separately determine the water *<2.48>* in the same manner as Irbesartan), dissolve in the mobile phase to make exactly 25 mL, and use this solution as the irbesartan standard stock solution. Pipet 7 mL of the standard stock solution, and add the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of the dissolution medium, and use this solution as the standard solution. Perform the test with exactly 10 $\mu$L each of the sample solution and standard solution as directed under Liquid Chromatography *<2.01>* according to the following conditions, and determine the peak areas, $A_T$ and $A_S$, of irbesartan in each solution.

Dissolution rate (%) with respect to the labeled amount of irbesartan ($C_{25}H_{28}N_6O$)

$= M_S \times A_T / A_S \times V'/V \times 1/C \times 504$

$M_S$: Amount (mg) of Irbesartan for assay taken, calculated on the anhydrous basis

$C$: Labeled amount (mg) of irbesartan ($C_{25}H_{28}N_6O$) in 1 tablet

*Operating Conditions* —

Proceed as directed in the operating conditions in the Assay (1).

*System suitability* —

System performance: To 7 mL of the irbesartan standard stock solution and 5 mL of the amlodipine besilate standard stock solution obtained in (2) add the mobile phase to make 50 mL. To 5 mL of this solution add 5 mL of the dissolution medium. When the procedure is run with 10 μL of this solution under the above operating conditions, amlodipine and irbesartan are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of irbesartan is not more than 2.0%.

**(2)** Amlodipine besilate — When the test is performed at 50 revolutions per minute according to the Paddle method, using 900 mL of 2nd fluid for dissolution test as the dissolution medium, the dissolution rate in 30 minutes of Irbesartan and Amlodipine Besilate Tablets is not less than 75%.

Start the test with 1 tablet of Irbesartan and Amlodipine Besilate Tablets, withdraw not less than 15 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 10 mL of the filtrate, pipet $V$ mL of the subsequent filtrate, and add the mobile phase to make exactly $V'$ mL so that each mL contains about 7.7 μg of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$). Pipet 2 mL of this solution, add exactly 2 mL of the mobile phase, and use this solution as the sample solution. Separately, weigh accurately about 26 mg of Amlodipine Besilate RS (separately determine the water <*2.48*> in the same manner as Amlodipine Besilate), dissolve in the mobile phase to make exactly 50 mL. Pipet 15 mL of this solution, add the mobile phase to make exactly 100 mL, and use this solution as the amlodipine besilate standard stock solution. Pipet 5 mL of the standard stock solution, and add the mobile phase to make exactly 50 mL. Pipet 5 mL of this solution, add exactly 5 mL of the dissolution medium, and use this solution as the standard solution. Perform the test with exactly 10 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, $A_T$ and $A_S$, of amlodipine in each solution.

Dissolution rate (%) with respect to the labeled amount of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$)

$= M_S \times A_T / A_S \times V'/V \times 1/C \times 27$

$M_S$: Amount (mg) of Amlodipine Besilate RS taken, calculated on the anhydrous basis

$C$: Labeled amount (mg) of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$) in 1 tablet

*Operating Conditions* —

Proceed as directed in the operating conditions in the Assay (1).

*System suitability* —

System performance: To 7 mL of the irbesartan standard stock solution obtained in (1) and 5 mL of the amlodipine besilate standard stock solution add the mobile phase to make 50 mL. To 5 mL of this solution add 5 mL of the dissolution medium. When the procedure is run with 10 μL of this solution under the above operating conditions, amlodipine and irbesartan are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 10 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of amlodipine is not more than 2.0%.

**Assay (1)** Irbesartan — To 10 tablets of Irbesartan and Amlodipine Besilate Tablets add 20 mL of 0.02 mol/L phosphate buffer (pH 3.0), and sonicate. Add 120 ml of methanol, shake vigorously until the tablets are disintegrated completely, and add the mobile phase to make exactly 200 mL. Pipet $V$ mL of this solution, add the mobile phase to make exactly $V'$ mL so that each mL contains about 1 mg of irbesartan ($C_{25}H_{28}N_6O$), and filter through a membrane filter with a pore size not exceeding 0.45 μm. Discard the first 5 mL of the filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 50 mg of irbesartan for assay (separately determine the water <*2.48*> in the same manner as Irbesartan), dissolve in methanol to make exactly 25 mL, and use this solution as the irbesartan standard stock solution. Pipet 10 mL of the standard stock solution, add 0.02 mol/L phosphate buffer (pH 3.0) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, $A_T$ and $A_S$, of irbesartan in each solution.

Amount (mg) of irbesartan ($C_{25}H_{28}N_6O$) in 1 tablet

$= M_S \times A_T / A_S \times V'/V \times 2/5$

$M_S$: Amount (mg) of irbesartan for assay taken, calculated on the anhydrous basis

*Operating conditions* —

Detector: An ultraviolet absorption photometer (wavelength: 237 nm).

Column: A stainless steel column 3.0 mm in inside diameter and 75 mm in length, packed with octadecylsilanized silica gel for liquid chromatography (2.2 μm in particle diameter).

Column temperature: A constant temperature of about 40℃.

Mobile phase: A mixture of methanol and 0.02 mol/L phosphate buffer (pH 3.0) (3:2).

Flow rate: Adjust so that the retention time of irbesartan is about 3 minutes.

*System suitability* —

System performance: To 10 mL of the irbesartan standard stock solution and 2 mL of the amlodipine besilate standard stock solution obtained in (2) add 0.02 mol/L phosphate buffer (pH 3.0) to make 20 mL. When the procedure is run with 5 $\mu$L of this solution under the above operating conditions, amlodipine and irbesartan are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 5 $\mu$L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of irbesartan is not more than 1.0%.

**(2)** Amlodipine besilate — To 10 tablets of Irbesartan and Amlodipine Besilate Tablets add 20 mL of 0.02 mol/L phosphate buffer (pH 3.0), and sonicate. Add 120 mL of methanol, shake vigorously until the tablets are disintegrated completely, and add the mobile phase to make exactly 200 mL. Pipet $V$ mL of this solution, add the mobile phase to make exactly $V'$ mL so that each mL contains about 69 $\mu$g of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$), and filter through a membrane filter with a pore size not exceeding 0.45 $\mu$m. Discard the first 5 mL of the filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 35 mg of Amlodipine Besilate RS (separately determine the water <*2.48*> in the same manner as Amlodipine Besilate), dissolve in methanol to make exactly 50 mL, and use this solution as the amlodipine besilate standard stock solution. Pipet 2 mL of the standard stock solution, add 0.02 mol/L phosphate buffer (pH 3.0) to make exactly 20 mL, and use this solution as the standard solution. Perform the test with exactly 5 $\mu$L each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and determine the peak areas, $A_T$ and $A_S$, of amlodipine in each solution.

Amount (mg) of amlodipine besilate ($C_{20}H_{25}ClN_2O_5.C_6H_6O_3S$) in 1 tablet

$$= M_S \times A_T / A_S \times V' / V \times 1 / 25$$

$M_S$: Amount (mg) of Amlodipine Besilate RS taken, calculated on the anhydrous basis

*Operating conditions* —

Proceed as directed in the operating conditions in (1).

*System suitability* —

System performance: To 10 mL of the irbesartan standard stock solution obtained in (1) and 2 mL of the amlodipine besilate standard stock solution add 0.02 mol/L phosphate buffer (pH 3.0) to make 20 mL. When the procedure is run with 5 $\mu$L of this solution under the above operating conditions, amlodipine and irbesartan are eluted in this order with the resolution between these peaks being not less than 5.

System repeatability: When the test is repeated 6 times with 5 $\mu$L of the standard solution under the above operating conditions, the relative standard deviation of the peak area of amlodipine is not more than 1.0%.

**Containers and storage** Containers — Tight containers.

***Add the following to 9.41 Reagents, Test Solutions:***

**Irbesartan for assay** $C_{25}H_{28}N_6O$ [Same as the monograph Irbesartan]