Limaprost Alfadex Tablets

リマプロスト　アルファデクス錠

Limaprost Alfadex Tablets contain not less than 90.0% and not more than 110.0% of the labeled amount of limaprost ($C_{22}H_{36}O_5$: 380.52).

Method of preparation Prepare as directed under Tablets, with Limaprost Alfadex.

Identification To a quantity of Limaprost Alfadex Tablets, equivalent to 0.1 mg of limaprost ($C_{22}H_{36}O_5$), add 10 mL of water, sonicate while shaking thoroughly until the tablets are completely disintegrated, and centrifuge. Filter the supernatant liquid through a membrane filter with a pore size not exceeding 0.8 μm, add 10 ml of ethyl acetate to the filtrate, shake, and centrifuge. Separate the ethyl acetate layer and evaporate ethyl acetate under reduced pressure. Dissolve the residue in 5 mL of methanol, and use this solution as the test solution (1). To 2 mL of the test solution (1), add 2 mL of a solution of potassium hydroxide in methanol (1 in 50) and allow to stand for 15 minutes, and use this solution as the test solution (2). Determine the absorption spectrum of the test solutions (1) and (2) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>: the test solution (2) exhibits a maximum between 275 nm and 280 nm, and the absorption is larger than that of the test solution (1).

Purity Related substances—Keep the sample solution and the standard solution at 2 – 8℃. To 10 tablets of Limaprost Alfadex Tablets add a mixture of water and ethanol (99.5) (3:2), and sonicate while shaking thoroughly until the tablets are completely disintegrated. Add a mixture of water and ethanol (99.5) (3:2) to make exactly *V* mL so that each mL contains about 5 μg of limaprost ($C_{22}H_{36}O_5$). Allow to stand at 2 – 8℃ for not less than 1 hour, and centrifuge. Filter the supernatant liquid through a membrane filter with a pore size not exceeding 0.45 μm, and use the filtrate as the sample solution. Separately, weigh accurately about 10 mg of Limaprost RS, and add ethanol (99.5) to make exactly 10 mL. Pipet 2.5 mL of this solution, and add ethanol (99.5) to make exactly 100 mL. Pipet 1 mL of this solution, add a mixture of water and ethanol (99.5) (3:2) to make exactly 50 mL, and use this solution as the standard solution. Perform the test with exactly 400 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 of related substances TA and B, having the relative retention times of about 0.9 and about 2.1 to limaprost respectively, from the sample solution and the peak area of limaprost from the standard solution by the automatic integration method. Calculate the amounts of related substances by the following equation: the amounts of related substances TA and B are not more than 1.0% and not more than 5.0%, respectively. For the peak areas of related substances TA and B, multiply their correction factors, 1.33 and 0.566, respectively.

$$\text{Amount (\%) of related substance} = Ms \times A_T / A_S \times V / C \times 1 / 2$$

*M*s: Amount (mg) of Limaprost RS taken
C: Labeled amount (μg) of limaprost ($C_{22}H_{36}O_5$) in 1 tablet
A_S: Peak area of limaprost from the standard solution
A_T: Peak area of related substances from the sample solution

Operating conditions—

Detector, column and column temperature: Proceed as directed in the operating conditions in the Assay.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS adjusted to pH 3.0 with phosphoric acid, acetonitrile for liquid chromatography and 2-propanol for liquid chromatography (9:4:2)

Flow rate: Adjust so that the retention time of limaprost is about 20 minutes.

System suitability—

Test for required detectability: Pipet 1 mL of the standard solution, add a mixture of water and ethanol (99.5) (3:2) to make exactly 100 mL. Confirm that the peak area of limaprost obtained with 400 μL of this solution is equivalent to 0.5 to 1.5% of that with 400 μL of the standard solution.

System performance: To 10 mg of limaprost alfadex add 1 mL of 0.05 mol/L hydrochloric acid TS, sonicate while shaking thoroughly to dissolve completely. Allow to stand in a dark place at room temperature for 10 to 30 minutes, add 1 mL of 0.05 mol/L sodium hydroxide TS, and then add ethanol (99.5) to make 25 mL. To 1 mL of this solution add 1.5 mL of water, and shake. When the procedure is run with 400 μL of this solution under the above operating conditions, related substance TA, limaprost and related substance B are eluted in this order with the resolution between related substance TA and limaprost being not less than 2.0.

System repeatability: Pipet 2 mL of the standard solution and add a mixture of water and ethanol (99.5) (3:2) to make exactly 20 mL. When the test is repeated 6 times with 400 μL of this solution under the above operating conditions, the relative standard deviation of the peak area of limaprost is not more than 2.0%.

Uniformity of dosage units <*6.02*> Perform the test according to the following method: it meets the requirement of the Content uniformity test.

To 1 tablet of Limaprost Alfadex Tablets add the mobile phase, sonicate while shaking thoroughly until the tablet is completely disintegrated, then add the mobile phase to make

exactly V mL so that each ml contains about 0.5 μg of limaprost ($C_{22}H_{36}O_5$), and shake. Centrifuge this solution, and use the supernatant liquid as the sample solution. Then, proceed as directed in the Assay.

$$\text{Amount } (\mu g) \text{ of limaprost } (C_{22}H_{36}O_5) = M_S \times A_T / A_S \times V / 20$$

M_S: Amount (mg) of Limaprost RS taken

Disintegration <*6.09*> It meets the requirements.

Assay To 20 tablets of Limaprost Alfadex Tablets add the mobile phase, and sonicate while thoroughly shaking until the tablets are completely disintegrated. Add the mobile phase to make exactly V mL so that each mL contains about 0.5 μg of Limaprost ($C_{22}H_{36}O_5$). After shaking, centrifuge and use the supernatant liquid as the sample solution. Separately, weigh accurately about 10 mg of Limaprost RS and add ethanol (99.5) to make exactly 10 mL. Pipet 2.5 mL of this solution, add ethanol (99.5) to make exactly 100 mL. Pipet 2 mL of this solution, add the mobile phase to make exactly 100 mL and use this solution as the standard solution. Perform the test with exactly 80 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 As, of limaprost in each solution.

$$\text{Amount } (\mu g) \text{ of limaprost } (C_{22}H_{36}O_5) \text{ in 1 tablet} = M\text{s} \times A_T / A_S \times V / 400$$

Ms: Amount (mg) of Limaprost RS taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 215 nm)

Column: A stainless steel column 4.6 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 35°C.

Mobile phase: A mixture of 0.02 mol/L potassium dihydrogen phosphate TS, acetonitrile for liquid chromatography and 2-propanol for liquid chromatography (9∶5∶2)

Flow rate: Adjust so that the retention time of limaprost is about 12 minutes.

System suitability—

System performance: When the procedure is run with 80 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of limaprost are not less than 6000 and not more than 1.5, respectively.

System repeatability: When the test is repeated 6 times with 80 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of limaprost is not more than 1.0%.

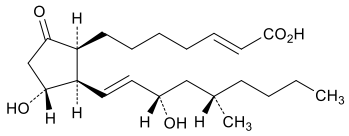
Containers and storage Container—Tight containers.

Others

Related substance B: Refer to it described in Limaprost Alfadex.

Related substance TA:

(2*E*)-7-{(1*S*,2*R*,3*R*)-3-Hydroxy-2-[(1*E*,3*S*,5*S*)-3-hydroxy-5-methylnon-1-en-1-yl]-5-oxocyclopentyl}hept-2-enoic acid



Add the following to 9.41 Reagents, Test Solutions:

Limaprost Alfadex $C_{22}H_{36}O_5.xC_{36}H_{60}O_{30}$ [Same as the namesake monograph]