(Note) The description of each of novel monographs "Dapagliflozin Propylene Glycolate Hydrate" [162KB] and "Dapagliflozin Propylene Glycolate Tablets" [193KB] differs from the description required in the Guideline for Drafting Monographs for The Japanese Pharmacopoeia, Nineteenth Edition (Partial revision) in that the final concentration of a solution is indicated in the procedure for preparing the solution. To be used as references for preparation of solutions, the preparation procedures of the solutions in accordance with the ordinary descriptions of the Japanese Pharmacopoeia describing specific weighing amounts are provided. The preparation procedure of solutions describing specific weighing amounts are provided as a reference and has been verified by the manufacturer who prepared the drafts. Please note that these procedures are not monographs listed in the Japanese Pharmacopoeia.

A reference for procedures for preparing solutions in the novel monograph "Dapagliflozin Propylene Glycolate Tablets"

Purity Related substances—Perform the test with 15 μL of the sample solution obtained in the Assay as directed under Chromatography *<2.00>* according to the following conditions. Determine each peak area by the automatic integration method, and calculate their amounts by the area percentage method: the amount of the peak of related substance TB having the relative retention time of 0.84 to dapagliflozin is not more than 0.4%, the amount of the peak other than dapagliflozin and the peak mentioned above is not more than 0.2%, and the total amount of the peaks other than dapagliflozin is not more than 0.9%. The reporting threshold is 0.1%.

Operating conditions—

Detector, column, column temperature, mobile phase, flowing of mobile phase, and flow rate: Proceed as directed in the operating conditions in the Assay

Time span of measurement: For 36 minutes after injection, beginning after the solvent peak.

System suitability—

Peak symmetry and resolution: Proceed as directed in the system suitability in the Assay.

System sensitivity: Pipet 1 mL of the standard solution obtained in the Assay, add a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to make exactly 100 mL. Pipet 1 mL of this solution add a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to make exactly 10 mL. When the procedure is run with 15 μL of this solution under the above operating conditions, the SN ratio of the peak of dapagliflozin is not less than 10.

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

To 1 tablet of Dapagliflozin Propylene Glycolate Tablets add a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1), sonicate, and shake until the tablet is completely disintegrated. Then, add a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to make exactly V mL so that each mL contains 0.1 mg of dapagliflozin ($C_{21}H_{25}ClO_6$), and filter. Discard 3 mL of the first filtrate, and use the subsequent filtrate as the sample solution. Then, proceed as directed in the Assay.

$$\text{Amount (mg) of dapagliflozin } (C_{21}H_{25}ClO_6) = M_S \times A_T / A_S \times 1 / 250 \times V$$

M_S: Amount (mg) of Dapagliflozin Propylene Glycolate RS taken

Dissolution *<6.10>* When the test is performed at 60 revolutions per minute according to the Paddle method, using 1000 mL of a solution prepared by adding 2.99 g of sodium acetate trihydrate to 14 mL of 2 mol/L acetic acid TS, adding water to make 1000 mL and, if necessary, adjusting to pH 4.5 with acetic acid or dilute sodium hydroxide TS as the dissolution medium, the value Q in 15 minutes of Dapagliflozin Propylene Glycolate Tablets is 80%.

Start the test with 1 tablet of Dapagliflozin Propylene Glycolate Tablets, withdraw not less than 10 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 not less than 5 mL of the first filtrate, and use the

subsequent filtrate as the sample solution. Separately, weigh accurately about 31 mg of Dapagliflozin Propylene Glycolate RS, dissolve in 5 mL of acetonitrile, add a mixture of the dissolution medium and acetonitrile (3:2) to make exactly 250 mL. Pipet V mL of this solution, add a mixture of the dissolution medium and acetonitrile (3:2) to make exactly 100 mL so that the labeled amount of dapaglifrozin ($C_{21}H_{25}ClO_6$) is contained in 1000 mL, and use this solution as the standard solution. Perform the test with exactly 40 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 dapagliflozin in each solution.

Dissolution rate (%) with respect to the labeled amount of dapagliflozin ($C_{21}H_{25}ClO_6$)
$= M_S \times A_T / A_S \times V / C \times 4$

M_S: Amount (mg) of Dapagliflozin Propylene Glycolate RS taken

C: Labeled amount (mg) of dapagliflozin ($C_{21}H_{25}ClO_6$) in 1 tablet

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 220 nm).

Column: A stainless steel column 3 mm in inside diameter and 10 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (3 μm in particle diameter).

Column temperature: A constant temperature of about 35℃.

Mobile phase: A mixture of water, acetonitrile for liquid chromatography and trifluoroacetic acid (1200:800:1).

Flow rate: 0.8 mL per minute (the retention time of dapagliflozin is 2.3 minutes).

System suitability—

System performance: When the procedure is run with 40 μL of the standard solution under the above operating conditions, the symmetry factor of the peak of dapagliflozin is 0.8 – 1.8.

System repeatability: When the test is repeated 6 times with 40 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of dapagliflozin is not more than 2%.

Assay To not less than 5 Dapagliflozin Propylene Glycolate Tablets, add a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1), sonicate, and shake until the tablets are completely disintegrated. Then, add a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to make exactly V mL so that each mL contains about 0.1 mg of dapagliflozin ($C_{21}H_{25}ClO_6$), and filter. Discard not less than 3 mL of the first filtrate, and use the subsequent filtrate as the sample solution. Separately, weigh accurately about 31 mg of Dapagliflozin Propylene Glycolate RS, dissolve in a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to make exactly 250 mL, and use this solution as the standard solution. Perform the test with 15 μL each of the sample solution and standard solution as directed under Chromatography *<2.00>* according to the following conditions, and determine the peak areas, A_T and A_S, of dapagliflozin in each solution.

Amount (mg) of dapagliflozin ($C_{21}H_{25}ClO_6$) $= M_S \times A_T / A_S \times V / 250$

M_S: Amount (mg) of Dapagliflozin Propylene Glycolate RS taken

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 220 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 (3 μm in particle diameter).

Column temperature: A constant temperature of about 35℃.

Mobile phase A: A mixture of water and trifluoroacetic acid (2000:1).

Mobile phase B: A mixture of acetonitrile for liquid chromatography and trifluoroacetic acid (2000:1).

Flowing of mobile phase: Control the gradient by mixing the mobile phases A and B as directed in the following table.

Time after injection of sample (min)	Mobile phase A (vol%)	Mobile phase B (vol%)
0 – 3	90	10
3 – 33	90 → 5	10 → 95
33 – 36	5	95

Flow rate: 1 mL per minute (the retention time of dapagliflozin is about 19 minutes).

System suitability—

Peak symmetry: When the procedure is run with 15 μL of the standard solution under the above operating conditions, the symmetry factor of the peak of dapagliflozin is 0.8 – 1.5.

Resolution: Dissolve 4 mg of Dapagliflozin Related Substance A for System Suitability RS in a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to make 25 mL. To 1 mL of this solution add a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to make 10 mL. Then, to 0.1 mL of this solution add the standard solution to make 10 mL. When the procedure is run with 15 μL of this solution under the above operating conditions, the resolution between dapagliflozin and the related substance A is not less than 2.0.

System repeatability: When the test is repeated 6 times with 15 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of dapagliflozin is not more than 1.0%.