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Announcement:

This draft differs from the ordinary draft of the Japanese Pharmacopoeia (JP) in that some parts do not comply with the Guideline for Drafting Monographs for The Japanese Pharmacopoeia, Nineteenth Edition (Partial revision), e.g., the concentration of a solution is indicated in the procedure for preparing the solutioin. This draft is one of the first monographs to which General Tests, Processes and Apparatus 2.00 Chromatography is applied. Therefore, we would like to ask for public comments on this draft separately from other drafts. Please note the following background information when reviewing the draft.

"①Promotion of international harmonization of monographs" is listed in "(3) Further promoting internationalization in response to globalization of drug market" in "3. Specific measures for the nineteenth edition in line with the preparation principle" in the Basic Principles for the Preparation of the JP 19th Edition. On the other hand, international harmonization of monographs has not been done principally other than excipients listed as "③Promotion of international harmonization of general tests and excipient monographs through the Pharmacopoeial Discussion Group (PDG), swift implementation of harmonized test methods and specifications in the JP and promotion of international utilization of the achievements" in the item (3). In recent years, the European Pharmacopoeia (EP) and the United States Pharmacopeia (USP) have been promoting prospective bilateral international harmonization of drug substances and drug products, independent of the PDG. Therefore, the JP and the USP have decided to work on the bilateral harmonization of monographs, "Dapagliflozin Propylene Glycolate Hydrate" and "Dapagliflozin Propylene Glycolate Tablets", with the aim of expanding the work of harmonization of pharmacopoeial standards currently performed by the PDG to drug substances and drug products. The WG on Harmonization Pilot on Chemicals was newly organized in the JP Expert Committees, and the work of bilateral harmonization was carried out on a trial basis.

The description of this draft, obtained as a result of this work, 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, and General Tests, Processes and Apparatus 2.00 Chromatography is applied for the first time. We would like to ask all those concerned to give their opinions on this draft so that it can be used as a reference for the international harmonization activities of the Japanese Pharmacopoeia and the principles for drafting monographs in the future.

We will later inform how to adopt the procedure for preparing solutions and the application of General Tests, Processes and Apparatus 2.00 Chromatography.

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Dapagliflozin Propylene Glycolate Tablets

ダパグリフロジンプロピレングリコール錠

Dapagliflozin Propylene Glycolate Tablets contain not less than 93.5% and not more than 105.0% of the labeled amount of dapagliflozin ($C_{21}H_{25}ClO_6$: 408.87).

Method of preparation Prepare as directed under Tablets, with Dapagliflozin Propylene Glycolate Hydrate.

Manufacture The management strategy of Dapagliflozin Propylene Glycolate Tablets is based on systematic development methods, which put emphasis on prior setting targets, understanding of products and processes, and process control, and which is based on quality risk management and proven science. In addition, when it can be scientifically possible to explain that a disintegration test ensure quality with distinguishability equal or better than a dissolution test, the following disintegration is alternative for the estimation of dissolution.

Disintegration *<6.09>* Perform the test using the disk: it meets the requirement. Carry out the test for 12 minutes, and use 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 immersion fluid.

Identification **(1)** Weigh a quantity of powdered Dapagliflozin Propylene Glycolate Tablets, equivalent to 10 mg of dapagliflozin, add 10 mL of acetone, and stir for more than 1 minute. Filter this solution, place on a watch glass, and evaporate to dryness. Determine the infrared absorption spectrum of the residue as directed in the ATR method under Infrared Spectrophotometry *<2.25>*: it exhibits absorption at the wave numbers of about 1611 cm^{-1}, 1583 cm^{-1}, 1477 cm^{-1}, 1393 cm^{-1}, 1300 cm^{-1}, 1177 cm^{-1}, 1085 cm^{-1}, 1039 cm^{-1}, 821 cm^{-1}, 771 cm^{-1} and 688 cm^{-1}.

(2) Perform the test with 15 μL each of the sample solution and standard solution obtained in the Assy as directed under Chromatography *<2.00>* according to the operating conditions in the Assay: the retention times of the principal peaks in the chromatograms obtained from the sample solution and standard solution are the same.

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 times of 0.84 to dapagliflozin is not more than 0.4%, the amount of other related substances is not more than 0.2%, and the total amount of the related

substances is not more than 0.9%. The reporting threshold is 0.1%.

Operating conditions—

Detector, column, column temperature, mobile phase, and 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: Dilute the standard solution obtained in the Assay with a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) to prepare a solution containing 0.1 μg of dapagliflozin per 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.

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

C_S: Concentration (mg/mL) of dapagliflozin in the standard solution

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, dissolve Dapagliflozin Propylene Glycolate RS in a mixture of the dissolution medium and acetonitrile (3:2) to make a solution containing the labeled amount of dapagliflozin ($C_{21}H_{25}ClO_6$) 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 ($C_{21}H_{25}ClO_6$)
$= C_S \times A_T / A_S \times 1 / C \times 100{,}000$

C_S: Concentration (mg/mL) of dapagliflozin ($C_{21}H_{25}ClO_6$) in the standard solution

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°C.

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 Dapagliflozin Propylene Glycolate RS, dissolve in a mixture of 0.05 mol/L potassium phosphate buffer (pH 11) and acetonitrile (1:1) so that each mL contains about 0.1 mg of dapagliflozin ($C_{21}H_{25}ClO_6$), 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 ($C_{21}H_{25}ClO_6$) in 1 tablet
$= C_S \times A_T / A_S \times V / 5$

C_S: Concentration (mg/mL) of dapagliflozin in the standard solution

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°C.

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: To the standard solution add Dapagliflozin Related Substance A for System Suitability RS so that the concentration of the RS is about 0.2% to dapagliflozin. 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%.

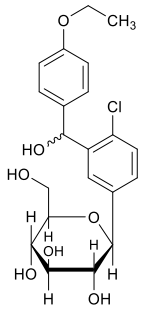
Containers and storage Containers—Tight containers.

Others

Related substance A: Refer to it described in Dapagliflozin Propylene Glycolate Hydrate.

Related substance TB:

(1*S*)-1,5-Anhydro-1-*C*-{4-chloro-3-[(4-ethoxyphenyl)(hydroxy)methyl]phenyl}-D-glucitol



Points to consider in conducting tests: Operate with precision and accuracy as necessary.

Add the following to 9.01 Reference Standards (1):

Dapagliflozin Propylene Glycolate RS
Dapagliflozin Related Substance A for System Suitability RS

Add the following to 9.41 Test Solution and Reagent:

0.05 mol/L potassium phosphate buffer (pH 11) Adjust a solution of potassium dihydrogen phosphate (17 in 2500) to pH 11 with a solution of potassium hydroxide (9 in 20).