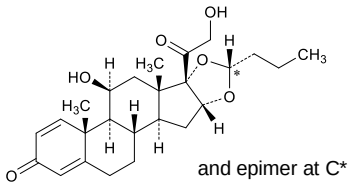
Budesonide

ブデソニド



and epimer at C*

$C_{25}H_{34}O_6$: 430.53

16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione

[*51333-22-3*]

Budesonide is a mixture of epimers at the asymmetric carbon C-22.

Budesonide contains not less than 98.0% and not more than 102.0% of budesonide ($C_{25}H_{34}O_6$), calculated on the dried basis.

Description Budesonide occurs as white to pale yellow-white, crystals or crystalline powder.

It is soluble in methanol, sparingly soluble in acetonitrile and in ethanol (99.5), and practically insoluble in water.

Optical rotation: $[\alpha]_D^{25}$: +102 – +109° (0.25 g, methanol, 25 mL, 100 mm).

Melting point: about 240°C (with decomposition).

Identification (1) Determine the absorption spectrum of a solution of Budesonide (1 in 40,000) as directed under Ultraviolet-visible Spectrophotometry <*2.24*>, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Budesonide RS prepared in the same manner as the sample solution: both spectra exhibit similar intensities of absorption at the same wavelengths.

(2) Determine the infrared absorption spectrum of Budesonide as directed in the potassium bromide disk method under Infrared Spectrophotometry <*2.25*>, and compare the spectrum with the Reference Spectrum or the spectrum of Budesonide RS: both spectra exhibit similar intensities of absorption at the same wave numbers.

Purity (1) Heavy metals—Being specified separately when the drug is granted approval based on the Law.

(2) Related substances—Conduct this procedure without exposure to light, using light-resistant vessels. Dissolve 50 mg of Budesonide in 15 mL of acetonitrile, add phosphate buffer solution (pH 3.2) to make 50 mL, and use this solution as the sample solution. Perform the test with 20 μL of the sample solution as directed under Liquid Chromatography <*2.01*> according to the following conditions. Determine each peak area by the automatic integration method, and calculate the amount of them by the area percentage method: the amounts of the peaks of related substances A and L, having the relative retention times of about 0.1 and about 0.95 to the first eluted peak (epimer B) of the two peaks of budesonide, are not more than 0.2%, respectively, the sum of the amounts of the peaks of related substance D, having the relative retention times of about 0.63 and about 0.67, and the sum of the amounts of the peaks of the related substance K, having the relative retention times of about 2.9 and about 3.0, are not more than 0.2%, respectively, and the amount of the peak other than budesonide and mentioned above is not more than 0.1%. Furthermore, the total amount of the peaks other than budesonide is not more than 0.5%. For the peak areas of the related substances D and K, multiply their relative response factors, 1.8 and 1.3, respectively.

Operating conditions—

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

Mobile phase A: A mixture of phosphate buffer solution (pH 3.2), acetonitrile for liquid chromatography and ethanol (99.5) (34:16:1).

Mobile phase B: A mixture of phosphate buffer solution (pH 3.2) and acetonitrile for liquid chromatography (1:1).

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 – 38	100	0
38 – 50	100 → 0	0 → 100
50 – 60	0	100

Time span of measurement: For 60 minutes after injection, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 1 mL of the sample solution add a mixture of phosphate buffer solution (pH 3.2) and acetonitrile (17:8) to make exactly 10 mL. Pipet 1 mL of this solution, add a mixture of phosphate buffer solution (pH 3.2) and acetonitrile (17:8) to make exactly 100 mL, and use this solution as the solution for system suitability test. When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the SN ratio of the second eluted peak (epimer A) of the two peaks of budesonide is not less than 10.

System performance: When the procedure is run with 20 μL of the solution for system suitability test under the above operating conditions, the resolution between the two peaks of budesonide is not less than 1.5.

Loss on drying <*2.41*> Not more than 0.5% (1 g, 105°C, 3 hours).

Isomer ratio Conduct this procedure without exposure to light, using light-resistant vessels. Perform the test with 20 μL of the sample solution obtained in the Assay as directed under Liquid Chromatography <2.01> according to the following conditions. Determine the peak areas, A_b and A_a, where A_b is the area of the early eluted peak and A_a is the area of the lately eluted peak of the two peaks of budesonide: $A_a/(A_a+A_b)$ is between 0.40 and 0.51.

Operating conditions—

Proceed as directed in the operating conditions in the Assay.

System suitability—

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

Assay Conduct this procedure without exposure to light, using light-resistant vessels. Weigh accurately about 25 mg each of Budesonide and Budesonide RS (separately determine the loss on drying <2.41> under the same conditions as Budesonide), dissolve each in 15 mL of acetonitrile, add phosphate buffer solution (pH 3.2) to make exactly 50 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 20 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 the sum of the two peak areas of budesonide in each solution.

Amount (mg) of budesonide ($C_{25}H_{34}O_6$) $= M_S \times A_T/A_S$

M_S: Amount (mg) of Budesonide RS taken, calculated on the dried basis

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 240 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 50°C.

Mobile phase: A mixture of phosphate buffer solution (pH 3.2), acetonitrile for liquid chromatography and ethanol (99.5) (34:16:1).

Flow rate: 1.0 mL per minute (the retention times of two peaks of budesonide are about 17 and about19 minutes).

System suitability—

System performance: When the procedure is run with 20 μL of the standard solution under the above operating conditions, the resolution between the two peaks of budesonide is not less than 1.5.

System repeatability: When the test is repeated 6 times with 20 μL of the standard solution under the above operating conditions, the relative standard deviation of the sum of the two peak areas of budesonide is not more than 1.0%.

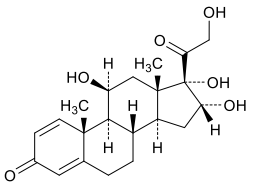
Containers and storage Containers—Tight containers.

Storage—Light-resistant.

Others

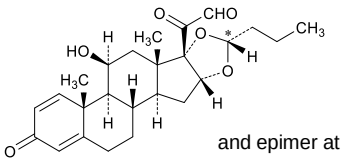
Related substance A:

11β,16α,17,21-Tetrahydroxypregna-1,4-diene-3,20-dione



Related substance D:

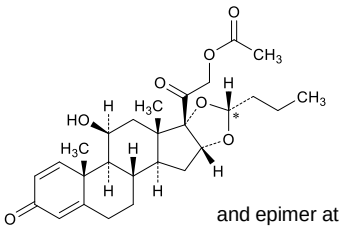
16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β-hydroxy-3,20-dioxopregna-1,4-dien-21-al



and epimer at C*

Related substance K:

16α,17-[(1*RS*)-Butylidenebis(oxy)]-11β,21-dihydroxypregna-1,4-diene-3,20-dione 21-acetate



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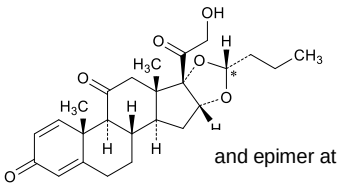
Related substance L:

16α,17-[(1*RS*)-Butylidenebis(oxy)]-21-hydroxypregna-1,4-diene-3,11,20-trione



and epimer at C*

Add the following to 9.01 Reference Standards (1):

Budesonide RS

Add the following to 9.41 Reagents, Test Solutions:

Phosphate buffer solution (pH 3.2) To 900 mL of a solution of sodium dihydrogenphosphate dihydrate (1 in 250) add 100 mL of a solution of phosphoric acid (1 in 400), and adjust to pH 3.2 with phosphoric acid or sodium hydroxide TS.