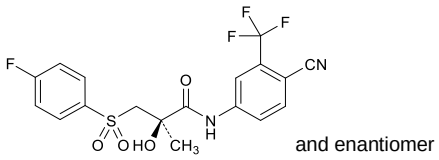
Bicalutamide

ビカルタミド



and enantiomer

$C_{18}H_{14}F_4N_2O_4S$: 430.37

(2*RS*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)
sulfonyl]-2-hydroxy-2-methylpropanamide
[*90357-06-5*]

Bicalutamide contains not less than 98.0% and not more than 102.0% of bicalutamide ($C_{18}H_{14}F_4N_2O_4S$), calculated on the dried basis.

Description Bicalutamide occurs as a white, powder or crystalline powder.

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

A solution of Bicalutamide in acetone (1 in 100) shows no optical rotation.

Melting point *<2.60>* 192 – 197°C

Bicalutamide shows crystal polymorphism.

Identification **(1)** Determine the absorption spectrum of a solution of Bicalutamide in methanol (1 in 100,000) as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Bicalutamide 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 Bicalutamide, as directed in the ATR method or the potassium bromide disk method under Infrared Spectrophotometry *<2.25>*, and compare the spectrum with the Reference Spectrum or the spectrum of Bicalutamide RS: both spectra exhibit similar intensities of absorption at the same wave numbers. When the ATR method is used, compare with the spectrum of Bicalutamide RS. If any difference appears between the spectra, recrystallize Bicalutamide and Bicalutamide RS with acetone, respectively, filter and dry the crystals, and perform the test in the same manner.

Purity **(1)** Heavy metals *<1.07>*—Proceed with 2.0 g of Bicalutamide according to Method 2, and perform the test. Prepare the control solution with 2.0 mL of Standard Lead Solution (not more than 10 ppm).

(2) Related substances—Dissolve 25 mg of Bicalutamide in 25 mL of a mixture of water, acetonitrile and phosphoric acid (1000:1000:1), and use this solution as the sample solution. Pipet 1 mL of the sample solution, and add a mixture of water, acetonitrile and phosphoric acid (1000:1000:1) to make exactly 100 mL. Pipet 10 mL of this solution, add a mixture of water, acetonitrile and phosphoric acid (1000:1000:1) to make exactly 100 mL, 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 each peak area by the automatic integration method: the peak areas of the related substance M having the related retention time of about 0.26 to bicalutamide, the related substance N having the relative retention time of about 0.34, the related substance L having the relative retention time of about 1.03 and the relative substance K having the relative retention time of about 1.13 from the sample solution are not larger than the peak area of bicalutamide from the standard solution, and the areas of the peaks other than bicalutamide and the peaks mentioned above from the sample solution are not larger than the peak area of bicalutamide from the standard solution. Furthermore, the total area of the peaks other than bicalutamide from the sample solution is not larger than 5 times the peak area of bicalutamide from the standard solution. For the related substance G having the relative retention times of about 0.21 and about 0.25, the related substances I, M and N having the relative retention times of about 0.23, the related substance O having the relative retention time of about 0.55, the related substances A and L having the relative retention times of about 0.95, and the related substance P having the relative retention time of about 1.09 from the sample solution, multiply their relative response factors 0.5, 0.5, 0.5, 0.4, 0.7, 0.5, 1.1, 0.9 and 0.7, respectively.

Operating conditions—

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

Time span of measurement: For 47 minutes after injection, beginning after the solvent peak.

System suitability—

Test for required detectability: Pipet 5 mL of the standard solution, and add a mixture of water, acetonitrile and phosphoric acid (1000: 1000: 1) to make exactly 10 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, the SN ratio of the peak of bicalutamide is not less than 10.

System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the

symmetry factor of the peak of bicalutamide are not less than 10,000 and not more than 1.5, respectively.

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 bicalutamide is not more than 5.0%.

Loss on drying *<2.41>* Not more than 0.5% (1 g, 105℃, 4 hours).

Residue on ignition *<2.44>* Not more than 0.1% (1 g, platinum crucible).

Assay Weigh accurately about 25 mg each of Bicalutamide and Bicalutamide RS (separately determine the loss on drying *<2.41>* under the same conditions as Bicalutamide), and dissolve each in a mixture of water, acetonitrile and phosphoric acid (1000:1000 1) to make exactly 25 mL. Pipet 5 mL each of these solutions, add a mixture of water, acetonitrile and phosphoric acid (1000:1000:1) to make exactly 25 mL, and use these solutions as the sample solution and the standard solution, respectively. 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 bicalutamide in each solution.

Amount (mg) of bicalutamide ($C_{18}H_{14}F_4N_2O_4S$)
$= M_S \times A_T / A_S$

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

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 210 nm).

Column: A stainless steel column 4 mm in inside diameter and 25 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

Column temperature: A constant temperature of about 50℃.

Mobile phase A: A mixture of diluted phosphoric acid (1 in 1000) and acetonitrile for liquid chromatography (19:1).

Mobile phase B: A mixture of acetonitrile for liquid chromatography and diluted phosphoric acid (1 in 1000) (19:1).

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 － 20	92 → 67	8 → 33
20 － 40	67 → 50	33 → 50
40 － 47	50	50

Flow rate: 1.0 mL per minute.

System suitability—

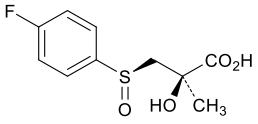
System performance: When the procedure is run with 10 μL of the standard solution under the above operating conditions, the number of theoretical plates and the symmetry factor of the peak of bicalutamide are not less than 10,000 and not more than 1.5, respectively.

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 bicalutamide is not more than 1.0%.

Containers and storage Containers—Well-closed containers.

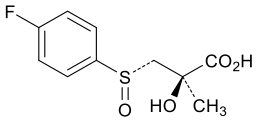
Others

Related substance G:
(2*RS*)-3-[(*RS*)-(4-Fluorophenyl)sulfinyl]-2-hydroxy-2-methylpropanoic acid



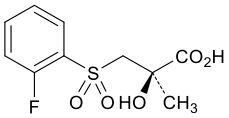
and enantiomer

Related substance G:
(2*RS*)-3-[(*SR*)-(4-Fluorophenyl)sulfinyl]-2-hydroxy-2-methylpropanoic acid



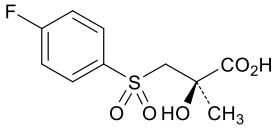
and enantiomer

Related substance I:
(2*RS*)-3-[(2-Fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanoic acid



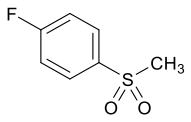
and enantiomer

Related substance M:
(2*RS*)-3-[(4-Fluorophenyl)sulfonyl]-2-hydroxy-2-methylpropanoic acid

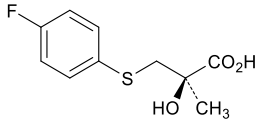


and enantiomer

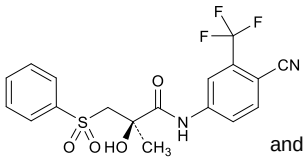
Related substance N:
1-Fluoro-4-(methylsulfonyl)benzene



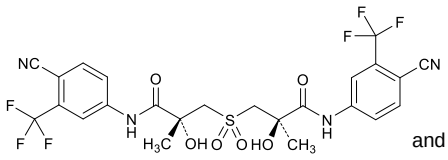
Related substance O:
(2*RS*)-3-[(4-Fluorophenyl)sulfanyl]-2-hydroxy-2-methylpropanoic acid


and enantiomer

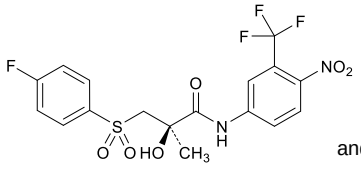
Related substance A:
(2*RS*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-2-methyl-3-(phenylsulfonyl)propanamide


and enantiomers

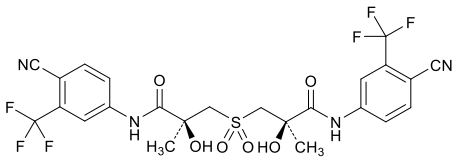
Related substance L:
(2*RS*,2'*RS*)-3,3'-Sulfonyl bis {*N*-[4-cyano-3-(trifluoromethyl) phenyl]-2-hydroxy-2-methylpropanamide}


and enantiomer

Related substance P:
(2*RS*)-3-[(4-Fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-*N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide


and enantiomer

Related substance K:
(2*R*,2'*S*)-3,3'-Sulfonyl bis {*N*-[4-cyano-3-(trifluoromethyl) phenyl]-2-hydroxy-2-methylpropanamide}



Add the following to 9.01 Reference Standards (1):

Bicalutamide RS