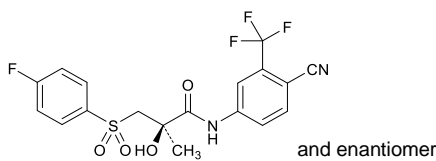


1 **Bicalutamide**

2 ビカルタミド

4 $C_{18}H_{14}F_4N_2O_4S$: 430.375 (2*RS*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluoro-

6 phenyl)

7 sulfonyl]-2-hydroxy-2-methylpropanamide

8 [90357-06-5]

9

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

13 **Description** Bicalutamide occurs as a white, powder or
14 crystalline powder.

15 It is freely soluble in acetone, sparingly soluble in meth-
16 anol, slightly soluble in ethanol (99.5), and practically in-
17 soluble in water.

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

20 Melting point <2.60> 192 – 197°C

21 Bicalutamide shows crystal polymorphism.

22 **Identification** (1) Determine the absorption spectrum
23 of a solution of Bicalutamide in methanol (1 in 100,000) as
24 directed under Ultraviolet-visible Spectrophotometry
25 <2.24>, and compare the spectrum with the Reference Spec-
26 trum or the spectrum of a solution of Bicalutamide RS pre-
27 pared in the same manner as the sample solution: both spec-
28 tra exhibit similar intensities of absorption at the same
29 wavelengths.

30 (2) Determine the infrared absorption spectrum of Bi-
31 calutamide, as directed in the ATR method or the potassium
32 bromide disk method under Infrared Spectrophotometry
33 <2.25>, and compare the spectrum with the Reference Spec-
34 trum or the spectrum of Bicalutamide RS: both spectra ex-
35 hibit similar intensities of absorption at the same wave num-
36 bers. When the ATR method is used, compare with the
37 spectrum of Bicalutamide RS. If any difference appears be-
38 tween the spectra, recrystallize Bicalutamide and Bicalu-
39 tamide RS with acetone, respectively, filter and dry the
40 crystals, and perform the test in the same manner.

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

45 (2) Related substances—Dissolve 25 mg of Bicalutam-
46 ide in 25 mL of a mixture of water, acetonitrile and phos-
47 phoric acid (1000:1000:1), and use this solution as the sam-
48 ple solution. Pipet 1 mL of the sample solution, and add a
49 mixture of water, acetonitrile and phosphoric acid
50 (1000:1000:1) to make exactly 100 mL. Pipet 10 mL of this
51 solution, add a mixture of water, acetonitrile and phosphoric
52 acid (1000:1000:1) to make exactly 100 mL, and use this
53 solution as the standard solution. Perform the test with ex-
54 actly 10 μ L each of the sample solution and standard solu-
55 tion as directed under Liquid Chromatography <2.01> ac-
56 cording to the following conditions, and determine each
57 peak area by the automatic integration method: the peak ar-
58 eas of the related substance M having the related retention
59 time of about 0.26 to bicalutamide, the related substance N
60 having the relative retention time of about 0.34, the related
61 substance L having the relative retention time of about 1.03
62 and the relative substance K having the relative retention
63 time of about 1.13 from the sample solution are not larger
64 than the peak area of bicalutamide from the standard solu-
65 tion, and the areas of the peaks other than bicalutamide and
66 the peaks mentioned above from the sample solution are not
67 larger than the peak area of bicalutamide from the standard
68 solution. Furthermore, the total area of the peaks other than
69 bicalutamide from the sample solution is not larger than 5
70 times the peak area of bicalutamide from the standard solu-
71 tion. For the related substance G having the relative reten-
72 tion times of about 0.21 and about 0.25, the related sub-
73 stances I, M and N having the relative retention times of
74 about 0.23, the related substance O having the relative re-
75 tention time of about 0.55, the related substances A and L
76 having the relative retention times of about 0.95, and the
77 related substance P having the relative retention time of
78 about 1.09 from the sample solution, multiply their relative
79 response factors 0.5, 0.5, 0.5, 0.4, 0.7, 0.5, 1.1, 0.9 and 0.7,
80 respectively.

81 *Operating conditions*—

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

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

87 *System suitability*—

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

94 System performance: When the procedure is run with 10
95 μ L of the standard solution under the above operating
96 conditions, the number of theoretical plates and the

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

99 System repeatability: When the test is repeated 6 times
100 with 10 μL of the standard solution under the above
101 operating conditions, the relative standard deviation of the
102 peak area of bicalutamide is not more than 5.0%.

103 **Loss on drying** <2.41> Not more than 0.5% (1 g, 105°C,
104 4 hours).

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

107 **Assay** Weigh accurately about 25 mg each of Bicalutam-
108 ide and Bicalutamide RS (separately determine the loss on
109 drying <2.41> under the same conditions as Bicalutamide),
110 and dissolve each in a mixture of water, acetonitrile and
111 phosphoric acid (1000:1000:1) to make exactly 25 mL. Pi-
112 pet 5 mL each of these solutions, add a mixture of water,
113 acetonitrile and phosphoric acid (1000:1000:1) to make ex-
114 actly 25 mL, and use these solutions as the sample solution
115 and the standard solution, respectively. Perform the test
116 with exactly 10 μL each of the sample solution and standard
117 solution as directed under Liquid Chromatography <2.01>
118 according to the following conditions, and determine the
119 peak areas, A_T and A_S , of bicalutamide in each solution.

$$120 \quad \text{Amount (mg) of bicalutamide (C}_{18}\text{H}_{14}\text{F}_4\text{N}_2\text{O}_4\text{S)} \\ 121 \quad = M_S \times A_T / A_S$$

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

124 **Operating conditions**—

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

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

131 **Column temperature:** A constant temperature of about
132 50°C.

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

135 **Mobile phase B:** A mixture of acetonitrile for liquid
136 chromatography and diluted phosphoric acid (1 in 1000)
137 (19:1).

138 **Flowing of mobile phase:** Control the gradient by mixing
139 the mobile phases A and B as directed in the following table.
140

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

141

142 Flow rate: 1.0 mL per minute.

143 **System suitability**—

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

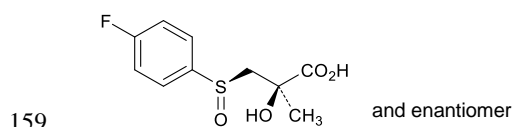
149 System repeatability: When the test is repeated 6 times
150 with 10 μL of the standard solution under the above
151 operating conditions, the relative standard deviation of the
152 peak area of bicalutamide is not more than 1.0%.

153 **Containers and storage** Containers— Well-closed con-
154 tainers.

155 **Others**

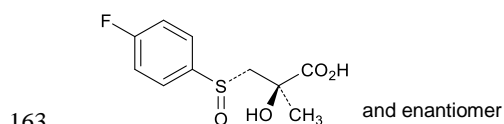
156 Related substance G:

157 (2*RS*)-3-[(*RS*)-(4-Fluorophenyl)sulfinyl]-2-hydroxy-2-
158 methylpropanoic acid



160 Related substance G:

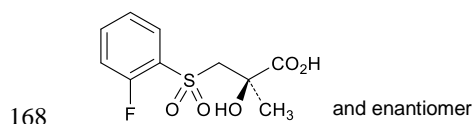
161 (2*RS*)-3-[(*SR*)-(4-Fluorophenyl)sulfinyl]-2-hydroxy-2-
162 methylpropanoic acid



164

165 Related substance I:

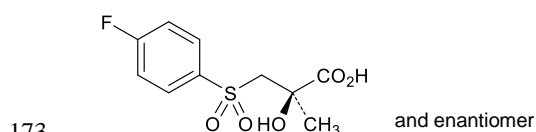
166 (2*RS*)-3-[(2-Fluorophenyl)sulfonyl]-2-hydroxy-2-
167 methylpropanoic acid



169

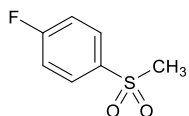
170 Related substance M:

171 (2*RS*)-3-[(4-Fluorophenyl)sulfonyl]-2-hydroxy-2-
172 methylpropanoic acid



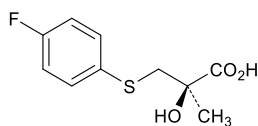
174

- 175 Related substance N:
176 1-Fluoro-4-(methylsulfonyl)benzene



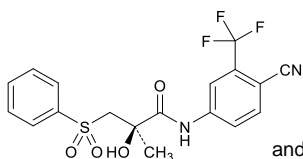
177

- 178
179 Related substance O:
180 (2*RS*)-3-[(4-Fluorophenyl)sulfonyl]-2-hydroxy-2-
181 methylpropanoic acid



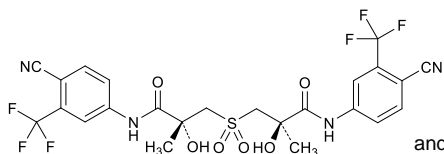
182 and enantiomer

- 183
184 Related substance A:
185 (2*RS*)-*N*-[4-Cyano-3-(trifluoromethyl)phenyl]-2-hydroxy-
186 2-methyl-3-(phenylsulfonyl)propanamide



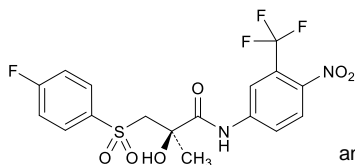
187 and enantiomer

- 188
189 Related substance L:
190 (2*RS*,2'*RS*)-3,3'-Sulfonyl bis {*N*-[4-cyano-3-(trifluorome-
191 thyl) phenyl]-2-hydroxy-2-methylpropanamide }



192 and enantiomer

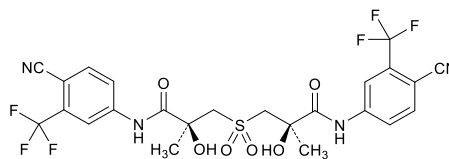
- 193
194 Related substance P:
195 (2*RS*)-3-[(4-Fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-
196 *N*-[4-nitro-3-(trifluoromethyl)phenyl]propanamide



197 and enantiomer

- 198
199 Related substance K:

- 200 (2*R*,2'*S*)-3,3'-Sulfonyl bis {*N*-[4-cyano-3-(trifluoromethyl)
201 phenyl]-2-hydroxy-2-methylpropanamide }



202

203

- 204 **Add the following to 9.01 Reference**
205 **Standards (1) :**

206 **Bicalutamide RS**

207

208

209

210