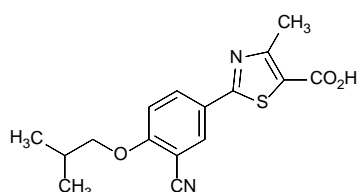


# 1 Febuxostat

2 フェブキシソスタット



3

4  $C_{16}H_{16}N_2O_3S$ : 316.37

5 2-[3-Cyano-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-thiazole-5-

6 carboxylic acid

7 [144060-53-7]

8

9 Febuxostat contains not less than 98.0% and not  
10 more than 102.0% of febuxostat ( $C_{16}H_{16}N_2O_3S$ ).

11 **Description** Febuxostat occurs as white, crystals or crys-  
12 talline powder.

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

15 Melting point: about 209°C (with decomposition, after  
16 drying).

17 It shows crystal polymorphism.

18 **Identification** (1) Determine the absorption spectrum of  
19 a solution of Febuxostat in ethanol (99.5) (1 in 100,000) as  
20 directed under Ultraviolet-visible Spectrophotometry <2.24>,  
21 and compare the spectrum with the Reference Spectrum or  
22 the spectrum of a solution of Febuxostat RS prepared in the  
23 same manner as the sample solution: both spectra exhibit  
24 similar intensities of absorption at the same wavelengths.

25 (2) Determine the infrared absorption spectrum of  
26 Febuxostat as directed in the potassium bromide disk method  
27 under Infrared Spectrophotometry <2.25>, and compare the  
28 spectrum with the Reference Spectrum or the spectrum of  
29 Febuxostat RS: both spectra exhibit similar intensities of ab-  
30 sorption at the same wave numbers. If any difference appears  
31 between the spectra, recrystallize the sample and the Refer-  
32 ence Standard according to the method otherwise specified,  
33 filter and dry the crystals, and perform the test with the crys-  
34 tals.

35 **Purity** Related substances—(i) Weigh accurately about  
36 50 mg of Febuxostat, dissolve in acetonitrile to make exactly  
37 50 mL, and use this solution as the sample solution. Sepa-  
38 rately, weigh accurately about 50 mg of Febuxostat RS, dis-  
39 solve in acetonitrile to make exactly 50 mL. Pipet 10 mL of  
40 this solution, add acetonitrile to make exactly 100 mL, then  
41 pipet 10 mL of this solution, add acetonitrile to make exactly  
42 200 mL, and use this solution as the standard solution. Per-  
43 form the test with exactly 40  $\mu$ L each of the sample solution

44 and standard solution as directed under Liquid Chromatog-  
45 raphy <2.01> according to the following conditions. Deter-  
46 mine each peak area,  $A_T$ , of related substances obtained from  
47 the sample solution and the peak area,  $A_S$ , of febuxostat from  
48 the standard solution by the automatic integration method,  
49 and calculate the amount of each related substance by the fol-  
50 lowing equation. For the peak area of the related substance A  
51 having the relative retention time of about 1.2 to febuxostat,  
52 multiply the correction factor 1.8.

$$53 \quad \text{Amount of the related substance (\%)} \\ 54 \quad = M_S / M_T \times A_T / A_S \times 1 / 2$$

55  $M_S$ : Amount (mg) of Febuxostat RS taken

56  $M_T$ : Amount (mg) of Febuxostat

57 **Operating conditions**—

58 Detector: An ultraviolet absorption photometer (wave-  
59 length: 217 nm).

60 Column: A stainless steel column 4.6 mm in inside diam-  
61 eter and 25 cm in length, packed with octadecylsilanized sil-  
62 ica gel for liquid chromatography (5  $\mu$ m in particle diameter).

63 Column temperature: A constant temperature of about  
64 40°C.

65 Mobile phase A: Diluted acetic acid (100) (1 in 5000).

66 Mobile phase B: A solution of acetic acid (100) in acetoni-  
67 trile for liquid chromatography (1 in 5000).

68 Flowing of mobile phase: Control the gradient by mixing  
69 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 — 40	60 → 0	40 → 100

70 Flow rate: 0.7 mL per minute.

71 Time span of measurement: For 40 minutes after injection.

72 **System suitability**—

73 Test for required detectability: Pipet 1 mL of the standard  
74 solution, and add acetonitrile to make exactly 10 mL. Con-  
75 firm that the peak area of febuxostat obtained with 40  $\mu$ L of  
76 this solution is equivalent to 7 to 13% of that with 40  $\mu$ L of  
77 the standard solution.

78 System performance: Dissolve 1 mg of Febuxostat Related  
79 Substance A for System Suitability RS in acetonitrile to make  
80 100 mL. To 1 mL of this solution add 10 mg of Febuxostat  
81 RS, and add acetonitrile to make 10 mL. When the procedure  
82 is run with 40  $\mu$ L of this solution under the above operating  
83 conditions, febuxostat and the related substance A are eluted  
84 in this order with the resolution between these peaks being  
85 not less than 2.5.

86 System repeatability: When the test is repeated 6 times  
87 with 40  $\mu$ L of the standard solution under the above operating  
88 conditions, the relative standard deviation of the peak area of  
89 febuxostat is not more than 2.0%.

90 (ii) Weigh accurately about 50 mg of Febuxostat, dis-  
 91 solve in acetonitrile to make exactly 50 mL. Pipet 10 mL of  
 92 this solution, add 40 mmol/L ammonium acetate TS to make  
 93 exactly 100 mL, and use this solution as the sample solution.  
 94 Separately, weigh accurately about 50 mg of Febuxostat RS,  
 95 add acetonitrile to make exactly 50 mL. Pipet 10 mL of this  
 96 solution, add acetonitrile to make exactly 100 mL, and use  
 97 this solution as the febuxostat stock solution. Pipet 10 mL of  
 98 the febuxostat stock solution, and add acetonitrile to make  
 99 exactly 200 mL. Then, pipet 10 mL of this solution, add 40  
 100 mmol/L ammonium acetate TS to make exactly 100 mL, and  
 101 use this solution as the standard solution. Perform the test  
 102 with exactly 20  $\mu$ L each of the sample solution and standard  
 103 solution as directed under Liquid Chromatography <2.01> ac-  
 104 cording to the following conditions. Determine the peak area  
 105  $A_T$  of the related substance B, having the relative retention  
 106 time of about 1.1 to febuxostat, obtained from the sample so-  
 107 lution and the peak area  $A_S$  of febuxostat from the standard  
 108 solution by the automatic integration method, and calculate  
 109 the amount of the related substance B by the following equa-  
 110 tion.

$$\begin{aligned} & \text{Amount of the related substance B (\%)} \\ & = M_S / M_T \times A_T / A_S \times 1 / 2 \end{aligned}$$

113  $M_S$ : Amount of Febuxostat RS taken

114  $M_T$ : Amount of Febuxostat taken

115 *Operating conditions—*

116 Detector: An ultraviolet absorption photometer (wave-  
 117 length: 317 nm).

118 Column: A stainless steel column 4.6 mm in inside diam-  
 119 eter and 15 cm in length, packed with triacontylsilanized sil-  
 120 ica gel for liquid chromatography (3  $\mu$ m in particle diameter).

121 Column temperature: A constant temperature of about  
 122 15°C.

123 Mobile phase: A mixture of diluted trifluoroacetic acid (1  
 124 in 2000) and a solution of trifluoroacetic acid in acetonitrile  
 125 for liquid chromatography (1 in 2000) (11:9).

126 Flow rate: Adjust so that the retention time of febuxostat  
 127 is about 47 minutes.

128 *System suitability—*

129 Test for required detectability: Weigh accurately 1 mg of  
 130 Febuxostat Related Substance B for System Suitability RS,  
 131 dissolve in acetonitrile to make exactly 100 mL, and use this  
 132 solution as the related substance B solution. Pipet 2 mL of  
 133 the febuxostat stock solution, add acetonitrile to make ex-  
 134 actly 20 mL, and use this solution as the febuxostat 10 times  
 135 dilution solution. Pipet 1 mL each of febuxostat 10 times di-  
 136 lution solution and the related substance B solution, add ace-  
 137 tonitrile to make exactly 20 mL. Pipet 2 mL of this solution,  
 138 and add 40 mmol/L ammonium acetate TS to make exactly  
 139 20 mL. Confirm that the peak areas of febuxostat and the re-  
 140 lated substance B obtained with 20  $\mu$ L of this solution are

141 equivalent to 7 to 13% of those with 20  $\mu$ L of the solution for  
 142 system suitability test.

143 System performance: Pipet 2.5 mL each of febuxostat 10  
 144 times dilution solution and the related substance B solution,  
 145 add 40 mmol/L ammonium acetate TS to make exactly 50 mL,  
 146 and use this solution as the solution for system suitability test.

147 When the procedure is run with 20  $\mu$ L of the solution for sys-  
 148 tem suitability test under the above operating conditions,  
 149 febuxostat and the related substance B are eluted in this order  
 150 with the resolution between these peaks being not less than 3.

151 System repeatability: When the test is repeated 6 times  
 152 with 20  $\mu$ L of the standard solution under the above operating  
 153 conditions, the relative standard deviation of the peak area of  
 154 febuxostat is not more than 2.0%.

155 (iii) Each amount of the related substances determined in  
 156 (i) and (ii) is not more than 0.10%, and the total amount of  
 157 the related substances is not more than 0.5%.

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

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

161 **Assay** Weigh accurately about 50 mg of Febuxostat, dis-  
 162 solve in acetonitrile to make exactly 50 mL. Pipet 10 mL of  
 163 this solution, add acetonitrile to make exactly 100 mL. Pipet  
 164 25 mL of this solution and 10 mL of the internal standard  
 165 solution, add acetonitrile to make exactly 100 mL, and use  
 166 this solution as the sample solution. Separately, weigh accu-  
 167 rately about 50 mg of Febuxostat RS, dissolve in acetonitrile  
 168 to make exactly 50 mL. Then, proceed as in the same manner  
 169 as the sample solution, and use the solution so obtained as the  
 170 standard solution. Perform the test with 20  $\mu$ L each of the  
 171 sample solution and standard solution as directed under Liq-  
 172 uid Chromatography <2.01> according to the following con-  
 173 ditions, and calculate the ratios,  $Q_T$  and  $Q_S$  of the peak area  
 174 of febuxostat to that of the internal standard.

$$\begin{aligned} & \text{Amount (mg) of febuxostat (C}_{16}\text{H}_{16}\text{N}_2\text{O}_3\text{S)} \\ & = M_S \times Q_T / Q_S \end{aligned}$$

177  $M_S$ : Amount (mg) of Febuxostat RS taken

178 *Internal standard solution* — A solution of diphenyl in ace-  
 179 tonitrile (1 in 2500).

180 *Operating conditions—*

181 Detector: An ultraviolet absorption photometer (wave-  
 182 length: 217 nm).

183 Column: A stainless steel column 4.6 mm in inside diam-  
 184 eter and 15 cm in length, packed with octadecylsilanized sil-  
 185 ica gel for liquid chromatography (5  $\mu$ m in particle diameter).

186 Column temperature: A constant temperature of about  
 187 40°C.

188 Mobile phase: A mixture of a solution of acetic acid (100)  
 189 in acetonitrile for liquid chromatography (1 in 500) and di-  
 190 luted acetic acid (100) (1 in 500) (3:2).

191 Flow rate: Adjust so that the retention time of febuxostat  
 192 is about 7 minutes.

193 *System suitability*—

194 System performance: When the procedure is run with 20  
 195  $\mu\text{L}$  of the standard solution under the above operating condi-  
 196 tions, febuxostat and the internal standard are eluted in this  
 197 order with the resolution being not less than 10.

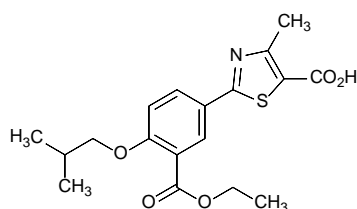
198 System repeatability: When the test is repeated 6 times  
 199 with 20  $\mu\text{L}$  of the standard solution under the above operating  
 200 conditions, the relative standard deviation of the ratio of the  
 201 peak area of febuxostat to that of the internal standard is not  
 202 more than 1.0%.

203 **Containers and storage** Containers— Tight containers.

204 **Others**

205 Related substance A:

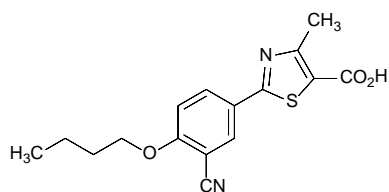
206 2-[3-Ethoxycarbonyl-4-(2-methylpropoxy)phenyl]-4-methyl-  
 207 1,3-thiazole-5-carboxylic acid



208

209 Related substance B:

210 2-(4-Butoxy-3-cyanophenyl)-4-methyl-1,3-thiazole-5-  
 211 carboxylic acid



212

213 **Add the following to 9.01 Reference**

214 **Standards (1):**

215 Febuxostat RS

216 Febuxostat Related Substance A for System Suitability RS

217 Febuxostat Related Substance B for System Suitability RS

218 **Add the following to 9.41 Reagents, Test**

219 **Solutions:**

220 **40 mmol/L ammonium acetate TS** Dissolve 3.08 g of  
 221 ammonium acetate in water to make 1000 mL.