

1 Febuxostat Tablets

2 フェブキシソスタット錠

4 Febuxostat Tablets contain not less than 95.0% and
5 not more than 105.0% of the labeled amount of febuxo-
6 stat ($C_{16}H_{16}N_2O_3S$: 316.37).

7 **Method of preparation** Prepare as directed under Tablets,
8 with Febuxostat.

9 **Identification** Perform the test with 20 μ L each of the sam-
10 ple solution and standard solution obtained in the Assay as
11 directed under Liquid Chromatography <2.01>, according to
12 the following conditions: the retention times of the principal
13 peaks in the chromatograms obtained from the sample solu-
14 tion and standard solution are the same, and both absorption
15 spectra of these peaks exhibit similar intensities of absorption
16 at the same wavelengths.

17 *Operating conditions*—

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

20 Detector: A photodiode array detector (wavelength: 317
21 nm, spectrum range of measurement: 210 – 350 nm).

22 *System suitability*—

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

25 **Purity** Related substances—To 5 tablets of Febuxostat
26 Tablets add 3V/4 mL of a mixture of acetonitrile and water
27 (3:2), shake vigorously for 30 minutes until the tablets com-
28 pletely disintegrated, then add a mixture of acetonitrile and
29 water (3:2) to make exactly V mL so that each mL contains
30 about 1 mg of febuxostat ($C_{16}H_{16}N_2O_3S$). Centrifuge this so-
31 lution, filter the supernatant liquid, and use the filtrate as the
32 sample solution. Pipet 1 mL of the sample solution, add a
33 mixture of acetonitrile and water (3:2) to make exactly 100
34 mL, and use this solution as the standard solution. Perform
35 the test with exactly 40 μ L each of the sample solution and stand-
36 ard solution as directed under Liquid Chromatography <2.01> ac-
37 cording to the following conditions, and determine each peak
38 area by the automatic integration method: The area of the
39 peaks other than the related substance TA, having the relative
40 retention time of about 0.4 to the related substance A ob-
41 served in the solution for system suitability test, and febuxo-
42 stat obtained from the sample solution are not larger than 1/5
43 times the peak area of febuxostat from the standard solution,
44 respectively. Furthermore, the total area of the peaks other
45 than febuxostat from the sample solution is not larger than
46 1/2 times the peak area of febuxostat from the standard solu-
47 tion.

48 *Operating conditions*—

49 Detector: An ultraviolet absorption photometer (wave-
50 length: 217 nm).

51 Column: A stainless steel column 4.6 mm in inside diam-
52 eter and 25 cm in length, packed with octadecylsilanized sil-
53 ica gel for liquid chromatography (5 μ m in particle diameter).

54 Column temperature: A constant temperature of about
55 40°C.

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

57 Mobile phase B: A solution of acetic acid (100) in metha-
58 nol (1 in 5000).

59 Flowing of mobile phase: Control the gradient by mixing
60 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
40 – 60	0	100

61 Flow rate: 0.7 mL per minute.

62 Time span of measurement: For 60 minutes after injection.

63 *System suitability*—

64 Test for required detectability: Pipet 2mL of the standard
65 solution, and add a mixture of acetonitrile and water (3:2) to
66 make exactly 10 mL. Confirm that the peak area of febuxostat
67 obtained with 40 μ L of this solution is equivalent to 14 to
68 26% of that with 40 μ L of the standard solution.

69 System performance: Dissolve 1 mg of Febuxostat Related
70 Substance A for System Suitability RS in a mixture of ace-
71 tonitrile and water (3:2) to make 100 mL. To 1 mL of this
72 solution, add 10 mg of Febuxostat RS, add a mixture of ace-
73 tonitrile and water (3:2) to make 10 mL, and use this solution
74 as the solution for system suitability test. When the procedure
75 is run with 40 μ L of the solution for system suitability test
76 under the above operating conditions, febuxostat and the re-
77 lated substance A are eluted in this order with the resolution
78 between these peaks being not less than 2.0.

79 System repeatability: When the test is repeated 6 times
80 with 40 μ L of the standard solution under the above operating
81 conditions, the relative standard deviation of the peak area of
82 febuxostat is not more than 2.0%.

83 **Uniformity of dosage units** <6.02> Perform the test ac-
84 cording to the following method: it meets the requirement of
85 the Content uniformity test.

86 To 1 tablet of Febuxostat Tablets add 3V/4 mL of a mixture
87 of acetonitrile and water (3:2), shake vigorously for 30
88 minutes until the tablets are completely disintegrated, then
89 add a mixture of acetonitrile and water (3:2) to make exactly
90 V mL. Centrifuge this solution, pipet a volume of the super-
91 natant liquid, equivalent to about 4 mg of febuxostat
92 ($C_{16}H_{16}N_2O_3S$), add a mixture of acetonitrile and water (3:2)
93 to make exactly 50 mL. Then pipet 2.5 mL of this solution,
94 add a mixture of acetonitrile and water (3:2) to make exactly
95 20 mL, filter this solution, and use the filtrate as the sample
96 solution. Then, proceed as directed in the Assay.

97 Amount (mg) of febuxostat ($C_{16}H_{16}N_2O_3S$)
 98 $=M_S \times A_T/A_S \times C/10$

99 M_S : Amount (mg) of Febuxostat RS taken
 100 C: Labeled amount (mg) of febuxostat($C_{16}H_{16}N_2O_3S$) in
 101 1 tablet.

102 **Dissolution** <6.10> When the test is performed at 50 revo-
 103 lutions per minute according to the Paddle method, using 900
 104 mL of disodium hydrogen phosphate-citric acid buffer solu-
 105 tion (pH 5.5) as the dissolution medium for 10-mg and 20-
 106 mg tablets and 900 mL of 0.05 mol/L disodium hydrogen
 107 phosphate-citric acid buffer solution (pH 6.0) as the dissolu-
 108 tion medium for a 40-mg tablet, the dissolution rates in 30
 109 minutes of 10-mg and 40-mg tablets are not less than 80%,
 110 and that in 60 minutes of a 20-mg tablet is not less than 75%.

111 Start the test with 1 tablet of Febuxostat Tablets, withdraw
 112 not less than 20 mL of the medium at the specified minute
 113 after starting the test, and filter through a membrane filter
 114 with a pore size not exceeding 0.45 μ m. Discard not less than
 115 10 mL of the first filtrate, pipet V mL of the subsequent fil-
 116 trate, add 2nd fluid for disintegration test to make exactly V'
 117 mL so that each mL contains about 11 μ g of febuxostat
 118 ($C_{16}H_{16}N_2O_3S$), and use this solution as the sample solution.
 119 Separately, weigh accurately about 11 mg of Febuxostat RS,
 120 and dissolve in 2nd fluid for disintegration test to make ex-
 121 actly 50 mL. Pipet 5 mL of this solution, add 2nd fluid for
 122 disintegration test to make exactly 100 mL, and use this so-
 123 lution as the standard solution. Determine the absorbances,
 124 A_T and A_S , of the sample solution and standard solution at 317
 125 nm as directed under Ultraviolet-visible Spectrophotometry
 126 <2.24>

127 Dissolution rate (%) with respect to the labeled amount of
 128 febuxostat ($C_{16}H_{16}N_2O_3S$)
 129 $=M_S \times A_T/A_S \times V'/V \times 1/C \times 90$

130 M_S : Amount (mg) of Febuxostat RS taken
 131 C: Labeled amount (mg) of febuxostat($C_{16}H_{16}N_2O_3S$)
 132 in 1 tablet.

133 **Assay** To 10 tablets of Febuxostat Tablets add 3V/4 mL of
 134 a mixture of acetonitrile and water (3:2), shake vigorously for
 135 30 minutes until the tablets are completely disintegrated, then
 136 add a mixture of acetonitrile and water (3:2) to make exactly
 137 V mL. Centrifuge this solution, pipet a volume of the super-
 138 natant liquid, equivalent to about 4 mg of febuxostat
 139 ($C_{16}H_{16}N_2O_3S$), add a mixture of acetonitrile and water (3:2)
 140 to make exactly 50 mL. Then pipet 2.5 mL of this solution,
 141 add a mixture of acetonitrile and water (3:2) to make exactly
 142 20 mL, filter this solution, and use the filtrate as the sample
 143 solution. Separately, weigh accurately about 10 mg of Febux-
 144 ostat RS, dissolve in a mixture of a solution of acetonitrile
 145 and water (3:2) to make exactly 200 mL. Pipet 5 mL of this
 146 solution, add a mixture of acetonitrile and water (3:2) to make

147 exactly 25 mL, and use this solution as the standard solution.
 148 Perform the test with 20 μ L each of the sample solution and
 149 standard solution as directed under Liquid chromatography
 150 <2.01> according to the following conditions, and determine
 151 the peak areas, A_T and A_S , of febuxostat in each solution.

152 Amount (mg) of febuxostat ($C_{16}H_{16}N_2O_3S$)
 153 $=M_S \times A_T/A_S \times C/10$

154 M_S : Amount (mg) of Febuxostat RS taken
 155 C: Labeled amount (mg) of febuxostat($C_{16}H_{16}N_2O_3S$)
 156 in 1 tablet.

157 **Operating conditions**—

158 Detector: An ultraviolet absorption photometer (wave-
 159 length: 317 nm).

160 Column: A stainless steel column 4.6 mm in inside diam-
 161 eter and 15 cm in length, packed with octadecylsilanized sil-
 162 ica gel for liquid chromatography (5 μ m in particle diameter).

163 Column temperature: A constant temperature of about
 164 40°C.

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

168 Flow rate: Adjust so that the retention time of febuxostat
 169 is about 6 minutes.

170 **System suitability**—

171 System performance: When the procedure is run with 20
 172 μ L of the standard solution under the above operating condi-
 173 tions, the theoretical plates and the symmetry factor of the
 174 peak of febuxostat are not less than 1500 and 0.9 to 1.4, re-
 175 spectively.

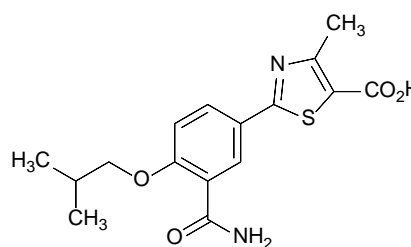
176 System repeatability: When the test is repeated 6 times
 177 with 20 μ L of the standard solution under the above operating
 178 conditions, the relative standard deviation of the ratio of the
 179 peak area of febuxostat is not more than 1.0%.

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

181 **Others**

182 Related substance TA:

183 2-[3-Carbamoyl-4-(2-methylpropoxy)phenyl]-4-methyl-1,3-
 184 thiazole-5-carboxylic acid



185

186 *Add the following to 9.01 (1) Reference*

187 *Standards:*

188 Febuxostat RS

189 Febuxostat Related Substance A for System Suitability RS