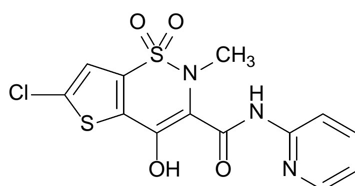
Lornoxicam

ロルノキシカム



$C_{13}H_{10}ClN_3O_4S_2$: 371.82
6-Chloro-4-hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide 1,1-dioxide
[*70374-39-9*]

Lornoxicam contains not less than 98.0% and not more than 102.0% of lornoxicam ($C_{13}H_{10}ClN_3O_4S_2$), calculated on the dried basis.

Description Lornoxicam occurs as a yellow crystalline powder.

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

Melting point: about 207°C (with decomposition).

It shows crystal polymorphism.

Identification **(1)** Dissolve 5 mg of Lornoxicam in 1000 mL of a solution of hydrochloric acid in methanol (9 in 10000). Determine the absorption spectrum of this solution as directed under Ultraviolet-visible Spectrophotometry *<2.24>*, and compare the spectrum with the Reference Spectrum or the spectrum of a solution of Lornoxicam 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 Lornoxicam, previously dried, 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 dried Lornoxicam RS: both spectra exhibit similar intensities of absorption at the same wave numbers. If any difference appears between the spectra, to 0.2 g of Lornoxicam add 2 mL of methanol, and stir at 55 – 60°C for 1 hour. Cool to room temperature while stirring, then collect the crystals formed, dry at 120°C for 2 hours, and perform the test with the crystals.

Purity Related substances—Dissolve 20 mg of Lornoxicam in 100 mL of a mixture of acetonitrile and methanol (1:1), and use this solution as the sample solution. Pipet 2 mL of the sample solution, add a mixture of acetonitrile and methanol (1:1) to make exactly 20 mL. Then pipet 1 mL of this solution, add a mixture of acetonitrile and methanol (1:1) to make exactly 20 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 area of related substance A, having the relative retention time of about 0.3 to lornoxicam, obtained from the sample solution is not larger than the peak area of lornoxicam from the standard solution, the peak area of the related substance B having the relative retention time of about 0.8 from the sample solution is not larger than 2/25 times the peak area of lornoxicam from the standard solution, and the peak area of the related substance C having the relative retention time of about 1.1 from the sample solution is not larger than 19/50 times the peak area of lornoxicam from the standard solution, the peak area of the related substance D having the relative retention time of about 1.4 from the sample solution is not larger than 3/10 times the peak area of lornoxicam from the standard solution, and the area of the peak other than the peak of lornoxicam and the peaks mentioned above from the sample solution is not larger than 1/5 times the peak area of lornoxicam from the standard solution. Furthermore, the total area of the peaks other than the peak of lornoxicam and the peaks mentioned above from the sample solution is not larger than the peak area of lornoxicam from the standard solution. For the peak areas of the related substances B, C and D, multiply their correction factors, 0.4, 1.9 and 1.5, respectively.

Operating conditions—

Detector: An ultraviolet absorption photometer (wavelength: 295 nm).

Column: A stainless steel column 4 mm in inside diameter and 15 cm in length, packed with octadecylsilanized silica gel for liquid chromatography (5 μm in particle diameter).

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

Mobile phase A: A mixture of a solution of sodium lauryl sulfate (1 in 2500) and phosphoric acid (1000:1).

Mobile phase B: A mixture of a solution of sodium lauryl sulfate in methanol (1 in 2500) and phosphoric acid (1000:1).

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 – 15	59	41
15 – 30	59 → 30	41 → 70
30 – 35	30	70

Flow rate: 1.0 mL per minute (the retention time of lornoxicam is about 20 minutes).

Time span of measurement: For 35 minutes after injection, beginning after the solvent peak.

System suitability－

Test for required detectability: Pipet 2 mL of the standard solution, and add a mixture of acetonitrile and methanol (1:1) to make exactly 20 mL. Confirm that the peak area of lornoxicam obtained with 10 μL of this solution is equivalent to 7 to 13% of that with 10 μL of the standard solution.

System performance: To 2 mL of the sample solution add 1 mL of a solution of 2-aminopyridine in a solution of a mixture of acetonitrile and methanol (1:1) (1 in 12500), then add a mixture of acetonitrile and methanol (1:1) to make 20 mL. To 1 mL of this solution add a mixture of acetonitrile and methanol (1:1) to make 20 mL. When the procedure is run with 10 μL of this solution under the above operating conditions, 2-aminopyridine and lornoxicam are eluted in this order with the resolution between these peaks being not less than 3.

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 lornoxicam is not more than 2.0%.

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

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

Assay Weigh accurately about 20 mg of Lornoxicam and Lornoxicam RS, both previously dried, add exactly 1 mL each of the internal standard solution, then dissolve in acetonitrile to make exactly 100 mL, and use these solutions as the sample solution and the standard solution, respectively. Perform the test with exactly 5 μL each of the sample solution and standard solution as directed under Liquid Chromatography <*2.01*> according to the following conditions, and calculate the ratios, Q_T and Q_S, of the peak area of lornoxicam to that of the internal standard.

Amount (mg) of lornoxicam ($C_{13}H_{10}ClN_3O_4S_2$)
$$= M_S \times Q_T / Q_S$$

M_S: Amount (mg) of Lornoxicam RS taken

Internal standard solution—A solution of diphenylamine in acetonitrile (1 in 160).

Operating conditions－

Detector: An ultraviolet absorption photometer (wavelength: 295 nm).

Column: A stainless steel column 4.6 mm in inside diameter and 10 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 methanol, a solution of sodium lauryl sulfate (2 in 175) and phosphoric acid (650:350:1).

Flow rate: Adjust so that the retention time of lornoxicam is about 3 minutes.

System suitability－

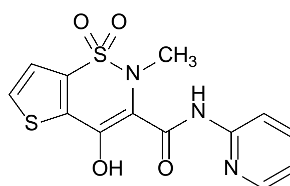
System performance: When the procedure is run with 5 μL of the standard solution under the above operating conditions, lornoxicam and the internal standard are eluted in this order with the resolution between these peaks being not less than 8.

System repeatability: When the test is repeated 6 times with 5 μL of the standard solution under the above operating conditions, the relative standard deviation of the peak area of lornoxicam is not more than 1.0%.

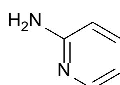
Containers and storage Containers－Well-closed containers.

Others

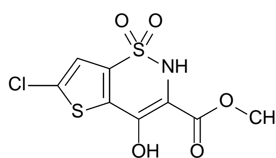
Related substance A:
4-Hydroxy-2-methyl-*N*-(pyridin-2-yl)-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide 1,1-dioxide



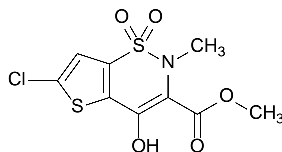
Related substance B:
Pyridin-2-amine



Related substance C:
Methyl 6-chloro-4-hydroxy-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxylate 1,1-dioxide



Related substance D:
Methyl 6-chloro-4-hydroxy-2-methyl-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxylate 1,1-dioxide

166 

167 ***Add the following to 9.01 Reference***
168 ***Standards (1):***

169 Lornoxicam RS

170 ***Add the following to 9.41 Reagents, Test***
171 ***Solutions:***

172 **2-Aminopyridine** $C_5H_6N_2$ White to light yellow, or
173 light brown, crystals, powder or masses.
174 *Melting point* <*2.60*>: 56 – 62℃
175 *Identification*—Determine the absorption spectrum of a
176 solution of 2-aminopyridine in ethanol (95) (1 in 250,000) as
177 directed under Ultraviolet-visible Spectrophotometry <*2.24*>:
178 it exhibits maxima between 232 nm and 236 nm, and between
179 294 nm and 298 nm.
180 *Content*: not less than 98.0%. *Assay*—Dissolve 1 g of 2-
181 aminopyridine in 10 mL of acetone. Perform the test with 1
182 μL of this solution as directed under Gas Chromatography
183 <*2.02*> according to the following conditions, and determine
184 the peak area of each component by the automatic integration
185 method.

186 $$\text{Content (\%)} = \frac{\text{peak area of 2-aminopyridine}}{\text{total of peak areas of components}} \times 100$$

187 Operating *conditions*
188 Detector: A hydrogen flame-ionization detector.
189 Column: A fused silica column 0.25 mm in inside diameter
190 and 30 m in length, with the inside surface coated with poly-
191 ethylene glycol 20M for gas chromatography 0.25 μm in
192 thickness.
193 Column temperature: A constant temperature of about
194 170°C.
195 Injection port temperature: A constant temperature of
196 about 260°C.
197 Detector temperature: A constant temperature of about
198 250°C.
199 Carrier gas: Helium.
200 Flow rate: Adjust so that the retention time of 2-amino-
201 pyridine is about 4 minutes.
202 Split ratio: 1:100.
203 Time span of measurement: About 5 times as long as the
204 retention time of 2-aminopyridine beginning after the solvent
205 peak.