

1 **Esomeprazole Magnesium Delayed-release** 2 **Capsules**

3 エソメプラゾールマグネシウム腸溶カプセル

5 Esomeprazole Magnesium Delayed-release Cap-
6 sules contain not less than 90.0% and not more
7 than 105.0% of the labeled amount of Esomeprazole
8 ($C_{17}H_{19}N_3O_3S$; 345.42).

9 **Method of preparation** Prepare as directed under Cap-
10 sules, with Esomeprazole Magnesium Hydrate.

11 **Identification** Take out the contents of Esomeprazole
12 Magnesium Delayed-release Capsules, equivalent to 20 mg
13 of esomeprazole ($C_{17}H_{19}N_3O_3S$), add about 120 mL of the
14 dissolving solution, and shake for 20 minutes. Then, add 40
15 mL of ethanol (95) and sonicate to dissolve. To this solution
16 add the dissolving solution to make 200 mL. Filter this solu-
17 tion through a membrane filter with a pore size not exceeding
18 $1\ \mu\text{m}$, to 5 mL of the filtrate add water to make 50 mL, and
19 use this solution as the sample solution. Separately, dissolve
20 20 mg of Omeprazole RS in 20 mL of ethanol (95), and add
21 the dissolving solution to make 100 mL. To 5 mL of this so-
22 lution add water to make 50 mL, and use this solution as the
23 standard solution. Perform the test with 20 μL of the sample
24 solution and standard solution as directed under Liquid Chroma-
25 tography <2.01> according to the following conditions: the
26 retention times of the principal peak obtained from the sam-
27 ple solution and the peak that elutes late of the two principal
28 peaks from the standard solution are the same.

29 Dissolving solution: Dissolve 5.24 g trisodium phosphate
30 dodecahydrate in 110 mL of 0.5 mol/L disodium hydrogen
31 phosphate TS and water to make 1000 mL. If necessary, ad-
32 just to pH 11.0 ± 0.2 with sodium hydroxide TS or a solution
33 of phosphoric acid (17 in 250).

34 **Operating conditions**—

35 Detector: An ultraviolet absorption photometer (wave-
36 length: 302 nm).

37 Column: A stainless steel column 4 mm in inside diameter
38 and 10 cm in length, packed with α_1 -acid glycoprotein bind-
39 ing silica gel for liquid chromatography ($5\ \mu\text{m}$ in particle di-
40 ameter).

41 Column temperature: A constant temperature of about
42 22°C .

43 Mobile phase: Dissolve 21.2 g of anhydrous disodium hy-
44 drogen phosphate and 62.4 g of sodium dihydrogen phos-
45 phate dihydrate in water to make 1000 mL, and, if necessary,
46 adjust to pH 6.0 with sodium hydroxide TS or a solution of
47 phosphoric acid (17 in 250). To 85 mL of this solution add
48 150 mL of acetonitrile and water to make 1000 mL.

49 Flow rate: Adjust so that the retention time of esomepra-
50 zole is about 3 minutes.

51 **System suitability**—

52 System performance: When the procedure is run with 20
53 μL of the standard solution under the above operating condi-
54 tions, the resolution between the two principal peaks is not
55 less than 1.5.

56 **Purity** Related substances—Conduct this procedure with-
57 out exposure to light within 2 hours after preparation of the
58 sample solution, using a light-resistant vessels. Take out the
59 contents of Esomeprazole Magnesium Delayed-release Cap-
60 sules, and powder. To a portion of the powder, equivalent to
61 20 mg of esomeprazole ($C_{17}H_{19}N_3O_3S$), add 20 mL of meth-
62 anol, shake for 30 seconds, add 40 mL of the dissolving so-
63 lution, shake for 30 seconds, then sonicate to dissolve, and
64 add water to make 200 mL. Filter this solution through a
65 membrane filter with a pore size not exceeding $0.45\ \mu\text{m}$, dis-
66 card the first 3 mL of the filtrate and use the subsequent fil-
67 trate as the sample solution. Perform the test with 20 μL of
68 the sample solution as directed under Liquid Chromatog-
69 raphy <2.01> according to the following conditions. Deter-
70 mine each peak area by the automatic integration method,
71 and calculate their amounts by the area percentage method:
72 the amounts of the peaks of related substance D having the
73 relative retention time of about 0.9 to esomeprazole, related
74 substance G having the retention time of about 0.2 and related
75 substance H having the retention time of about 0.3 are not
76 more than 0.5%, respectively, and the amount of the peak
77 other than esomeprazole and the peaks mentioned above is
78 not more than 0.2%. Furthermore, the total amount of the
79 peaks other than esomeprazole is not more than 2%.

80 Dissolving solution: Dissolve 5.24 g of trisodium phos-
81 phate dodecahydrate in 110 mL of 0.5 mol/L disodium hy-
82 drogen phosphate TS and water to make 1000 mL. If neces-
83 sary, adjust to pH 11.0 ± 0.2 with sodium hydroxide TS or a
84 solution of phosphoric acid (17 in 250).

85 **Operating conditions**—

86 Detector: An ultraviolet absorption photometer (wave-
87 length: 302 nm).

88 Column: A stainless steel column 4.6 mm in inside diam-
89 eter and 10 cm in length, packed with octadecylsilanized sil-
90 ica gel for liquid chromatography ($3\ \mu\text{m}$ in particle diameter).

91 Column temperature: A constant temperature of about
92 22°C .

93 Mobile phase A: To 5.2 mL of a solution of sodium dihy-
94 drogen phosphate dihydrate (39 in 250) and 63 mL of 0.5
95 mol/L disodium hydrogen phosphate TS add water to make
96 1000 mL, and, if necessary, adjust to pH 7.6 with sodium hy-
97 droxide TS or a solution of phosphoric acid (17 in 250). To
98 100 mL of this solution and 100 mL of acetonitrile add water
99 to make 1000 mL.

100 Mobile phase B: To 5.2 mL of a solution of sodium dihy-
101 drogen phosphate dihydrate (39 in 250) and 63 mL of 0.5
102 mol/L disodium hydrogen phosphate TS add water to make

1000 mL, and, if necessary, adjust to pH 7.6 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250). To 10 mL of this solution and 800 mL of acetonitrile add water to make 1000 mL.

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 — 10	100 → 80	0 → 20
10 — 30	80 → 0	20 → 100

Flow rate: 1.0 mL per minute.

Time span of measurement: About 2 times as long as the retention time of omeprazole, beginning after the solvent peak.

System suitability—

Test for required detectability: Dissolve 5 mg of Omeprazole RS in 5 mL of methanol, and add 10 mL of the dissolving solution and water to make 50 mL. To 2 mL of this solution, add a mixture of water, the dissolving solution and methanol (7:2:1) to make 100 mL. To 2.5 mL of this solution, add a mixture of water, the dissolving solution and methanol (7:2:1) to make 100 mL. When the procedure is run with 20 μ L of this solution under the above operating conditions, the SN ratio of the peak of omeprazole is not less than 10.

System performance: Dissolve 5 mg each of Omeprazole RS and omeprazole sulfone in 5 mL each of methanol, add 10 mL of the dissolving solution and water to make 50 mL. To 1 mL each of these solutions add 20 mL of the dissolving solution and water to make 100 mL. When the procedure is run with 20 μ L of this solution under the above operating conditions, omeprazole sulfone and omeprazole are eluted in this order with the resolution between these peaks being not less than 2.5.

Uniformity of dosage units <6.02> Perform the Mass variation test, or the Content uniformity test according to the following method: it meets the requirement.

Take out the content of 1 capsule of Esomeprazole Magnesium Delayed-release Capsules, add 60 mL of the dissolving solution, shake for 20 minutes, if necessary, sonicate to disintegrate, then add 20 mL of ethanol (95), sonicate to dissolve, and add the dissolving solution to make exactly 100 mL. Filter this solution through a membrane filter with a pore size not exceeding 1 μ m, discard the first 3 mL of the filtrate, pipet 10 mL of the subsequent filtrate, add water to make exactly V mL so that each mL contains about 40 μ g of esomeprazole ($C_{17}H_{19}N_3O_3S$), and use this solution as the sample solution. Then, proceed as directed in the Assay.

$$\begin{aligned} &\text{Amount (mg) of esomeprazole (C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S)} \\ &= M_S \times A_T / A_S \times V / 50 \end{aligned}$$

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

Dissolving solution: Dissolve 5.24 g of trisodium phosphate dodecahydrate in 110 mL of 0.5 mol/L disodium hydrogen phosphate TS and water to make 1000 mL. If necessary, adjust to pH 11.0 ± 0.2 with sodium hydroxide TS or a solution of phosphoric acid (17 in 250).

Dissolution <6.10> After stirring at 100 revolutions per minute according to the Paddle method for 2 hours, using 300 mL of 0.1 mol/L hydrochloric acid TS as the dissolution medium, subsequently add 700 mL of a solution prepared by dissolving 12.21 g of anhydrous disodium hydrogen phosphate in water to make 1000 mL, and then the test is performed at 100 revolutions per minute according to the Paddle method, the values Q in 30 minutes of a 10-mg capsule and a 20-mg capsule are 75%.

Start the test with 1 capsule of Esomeprazole Magnesium Delayed-release Capsules, withdraw not less than 10 mL of the medium at the specified minute after starting the test, and filter through a membrane filter with a pore size not exceeding 1 μ m. Discard not less than 2 mL of the first filtrate, pipet 5 mL of the subsequent filtrate, add exactly 1 mL of 0.25 mol/L sodium hydroxide TS, and use this solution as the sample solution. Separately, weigh accurately about 20 mg of Omeprazole RS (separately determine the Loss on drying <2.41> in vacuum at 50°C for 2 hours using phosphorous (V) oxide as a desiccant, using 1 g of Omeprazole RS), dissolve in 10 mL of ethanol (95), and add the dissolving solution to make exactly 100 mL. Dilute this solution as follows.

10-mg capsule: pipet 5 mL of this solution, and immediately add the dissolving solution to make exactly 100 mL.

20-mg capsules: pipet 5 mL of this solution, and immediately add the dissolving solution to make exactly 50 mL. Immediately pipet 5 mL of this solution, immediately add exactly 1 mL of 0.25 mol/L sodium hydroxide TS, and use this solution as the standard solution. Perform the test with exactly 20 μ L each of the sample solution and standard solution as directed under Liquid Chromatography <2.01> according to the following conditions, and determine the peak area, A_T , of esomeprazole in the sample solution and the peak area, A_S , of omeprazole in the standard solution.

Dissolution rate (%) with respect to the labeled amount of esomeprazole ($C_{17}H_{19}N_3O_3S$)

$$= M_S \times A_T / A_S \times 1 / V \times 1 / C \times 5000$$

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

C : Labeled amount (mg) of esomeprazole ($C_{17}H_{19}N_3O_3S$) in 1 capsule

V : 100 for a 10-mg capsule and 50 for a 20-mg capsule

199 Dissolving solution: Dissolve 12.21 g of anhydrous diso-
200 dium hydrogen phosphate in water to make 1000 mL. To 700
201 mL of this solution add 300 mL of 0.1 mol/L hydrochloric
202 acid TS.

203 *Operating conditions—*

204 Proceed as directed in the operating conditions in the As-
205 say.

206 *System suitability—*

207 Proceed as directed in the system suitability in the Assay.

208 **Assay** Take out the contents of not less than 20 Esomepra-
209 zole Magnesium Delayed-release Capsules, weigh accurately
210 the mass of the contents, and mix uniformly. Weigh accu-
211 rately an amount, equivalent to about 20 mg of esomeprazole
212 ($C_{17}H_{19}N_3O_3S$), add 60 mL of the dissolving solution, shake
213 for 20 minutes, and, if necessary, sonicate to disintegrate.
214 Then, add 20 mL of ethanol (95), sonicate to dissolve, and
215 add the dissolving solution to make exactly 100 mL. Filter
216 this solution through a membrane filter with a pore size not
217 exceeding 1 μ m, discard the first 3 mL of the filtrate, pipet 5
218 mL of the subsequent filtrate, add water to make exactly 25
219 mL, and use this solution as the sample solution. Separately,
220 weigh accurately about 20 mg of Omeprazole RS (separately
221 determine the Loss on drying <2.41> in vacuum at 50°C for 2
222 hours using phosphorous (V) oxide as a desiccant, using 1 g
223 of Omeprazole RS), dissolve in 20 mL of ethanol (95), and
224 add the dissolving solution to make exactly 100 mL. Pipet 5
225 mL of this solution, add water to make exactly 25 mL, and
226 use this solution as the standard solution. Perform the test
227 with exactly 20 μ L of the sample solution and standard solu-
228 tion as directed under Liquid Chromatography <2.01> accord-
229 ing to the following conditions, and determine the peak area,
230 A_T of esomeprazole in the sample solution and the peak area,
231 A_S , of omeprazole in the standard solution.

$$\begin{aligned} 232 & \text{Amount (mg) of esomeprazole (C}_{17}\text{H}_{19}\text{N}_3\text{O}_3\text{S)} \\ 233 & = M_S \times A_T / A_S \end{aligned}$$

234 M_S : Amount (mg) of Omeprazole RS taken, calculated on
235 the dried basis

236 Dissolving solution: Dissolve 5.24 g of trisodium phos-
237 phate dodecahydrate in 110 mL of 0.5 mol/L disodium hy-
238 drogen phosphate TS and water to make 1000 mL. If neces-
239 sary, adjust to pH 11.0 ± 0.2 with sodium hydroxide TS or a
240 solution of phosphoric acid (17 in 250).

241 *Operating conditions—*

242 Detector: An ultraviolet absorption photometer (wave-
243 length: 302 nm).

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

247 Column temperature: A constant temperature of about
248 22°C.

249 Mobile phase: To 10.5 mL of a solution of sodium dihy-
250 drogen phosphate dihydrate (39 in 250) add 60 mL of
251 0.5mol/L disodium hydrogen phosphate TS and water to
252 make 1000 mL, and, if necessary, adjust to pH 7.3 with so-
253 dium hydroxide TS or a solution of phosphoric acid (17 in
254 250). To 500 mL of this solution add 350 mL of acetonitrile
255 and water to make 1000 mL.

256 Flow rate: 1.0 mL per minute.

257 *System suitability—*

258 System performance: When the procedure is run with 20
259 μ L of the standard solution under the above operating condi-
260 tions, the number of theoretical plates and the symmetry fac-
261 tor of the peak of omeprazole are not less than 2000 and not
262 more than 1.5, respectively.

263 System repeatability: When the test is repeated 6 times
264 with 20 μ L of the standard solution under the above operating
265 conditions, the relative standard deviation of the peak area of
266 omeprazole is not more than 1.0%.

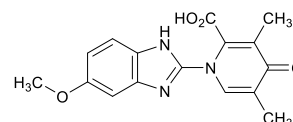
267 **Containers and storage** Containers—Tight containers.

268 **Others**

269 Related substances D: Refer to it described in Esomeprazole
270 Magnesium Hydrate.

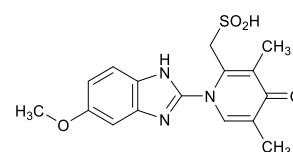
271 Related substances G:

272 1-(5-Methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-
273 4-oxo-1,4-dihydropyridine-2-carboxylic acid



275 Related substances H:

276 [1-(5-Methoxy-1*H*-benzimidazol-2-yl)-3,5-dimethyl-4-
277 oxo-1,4-dihydropyridin-2-yl]methanesulfinic acid



279 **9.01 Add the following to Reference**
280 **Standards (1) section.**

281 Omeprazole RS

282 **Add the following to 9.41 Reagents, Test**
283 **Solutions:**

284 **Omeprazole sulfone** $C_{17}H_{19}N_3O_4S$: 361.42

285 *Description*—It occurs as a white to brown powder.

286 *Identification*—Determine the ^1H spectrum of a solution of
287 Omeprazole sulfone in deuterated dimethyl sulfoxide for nu-
288 clear magnetic resonance spectroscopy (1 in 100) as directed
289 under Nuclear Magnetic Resonance Spectroscopy <2.21>, us-
290 ing tetramethylsilane for nuclear magnetic resonance spec-
291 troscopy as an internal reference compound: it exhibits a sin-
292 glet signal A at around δ 2.17 ppm, a singlet signal B at
293 around δ 2.20 ppm, a singlet signal C at around δ 3.68 ppm,
294 a singlet signal D at around δ 3.82 ppm, a singlet signal E at
295 around δ 5.01 ppm, a broad singlet signal F at around δ 7.61
296 ppm, and a singlet signal G at around δ 8.04 ppm. The ratio
297 of the integrated intensity of each signal, A:B:C:D:E:F:G is
298 about 3:3:3:3:2:1:1(When the frequency is 500 MHz).

299 **0.25 mol/L Sodium hydroxide TS** To 50 mL of 0.5
300 mol/L sodium hydroxide TS add water to make 100 mL.