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We Enable Science

Regulated Pharmaceutical Instrumental Analysis
Complete solutions from EMD Millipore

Expert advice to keep you informed

We are committed to supporting our customers in Regulated Pharmaceutical Instrumental Analysis through combining premium products with expert advice. One of our most valuable guides is our new Monograph Method Compendium. In addition to experimental data, the compendium offers up-to-date information about the United States Pharmacopeia (USP), including upcoming changes.

Stay a step ahead

To give you a preview of our compendium, this document provides details of some of the monograph methods for four selected blockbuster molecules that have recently come off patent, or will do so by 2016.

Selected molecules and monograph method examples

The methods presented here demonstrate the advantages of our products for Regulated Pharmaceutical Instrumental Analysis, exemplified by HPLC, FTIR, Karl Fischer Titration, AAS and ICP methods for the analysis of different types of drugs. Our proven track record in product quality, regulatory compliance and technical expertise makes EMD Millipore your preferred partner in regulated instrumental analysis.

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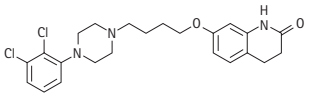
Aripiprazole



FTIR

Fourier transform infrared spectroscopy

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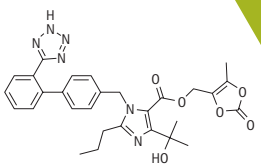
Olmesartan medoxomil



KF

Karl Fischer titration

AAS

Atomic absorption spectroscopy

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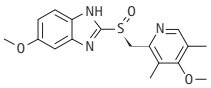
Esomeprazole (API)



ICP

Inductively coupled plasma spectroscopy (MS and OES)

HPLC

High performance liquid chromatography

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Esomeprazole (Capsule)

Expert Advice

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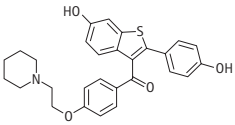
Raloxifene



Regulated Pharmaceutical Instrumental Analysis

All you need ...

Premium products

Quality is critical to your work. Ours, too. That's why we manufacture, test, and certify all our products in our own state-of-the-art, accredited labs using the latest technologies to ensure their reliability and consistency. So whether you need high purity solvents and HPLC columns for assay determinations, or certified standards for ICP, AAS or Karl Fischer titration, we deliver nothing short of excellence for instrumental analysis.

Expert advice

Is this the right grade of chemical for the analysis? Can the method be optimized or changed? Is there a faster technique? Our dedicated team of experienced application scientists understands your need to innovate. We work around the world and across all aspects of regulated instrumental analysis to support you in achieving your individual goals.

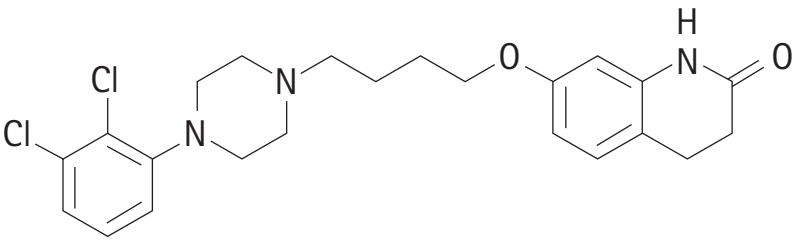
We share our insights with you through our growing collection of application compilations and our new Monograph Method Compendium. If you have an analytical challenge, we want to help you solve it.

Regulatory compliance

Compliance with national and international guidelines is one of the most challenging aspects of pharmaceutical work. We can help – in more ways than one. We comply with numerous global standards, such as ISO, ACS, USP and Reag. Ph Eur. We offer products with an unrivaled range of specifications and accreditations. And, we provide comprehensive quality documentation to streamline your accreditation and audits. We don't just promise secure quality. We put it in writing.

... from one trusted source.

Aripiprazole (USP)



Aripiprazole is an atypical antipsychotic, and a partial dopamine agonist. It is primarily used in the treatment of schizophrenia, bipolar disorder, major depressive disorder, tic disorders, and irritability associated with autism.

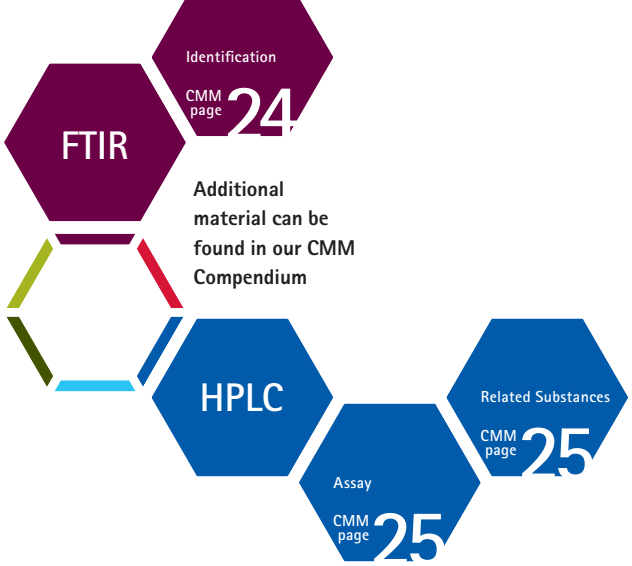
Common commercial brand names: **Abilify and Aripiprex.**

Aripiprazole was developed by Otsuka in Japan; in the United States, Otsuka America markets it jointly with Bristol-Myers Squibb. Patent expires in 2015.

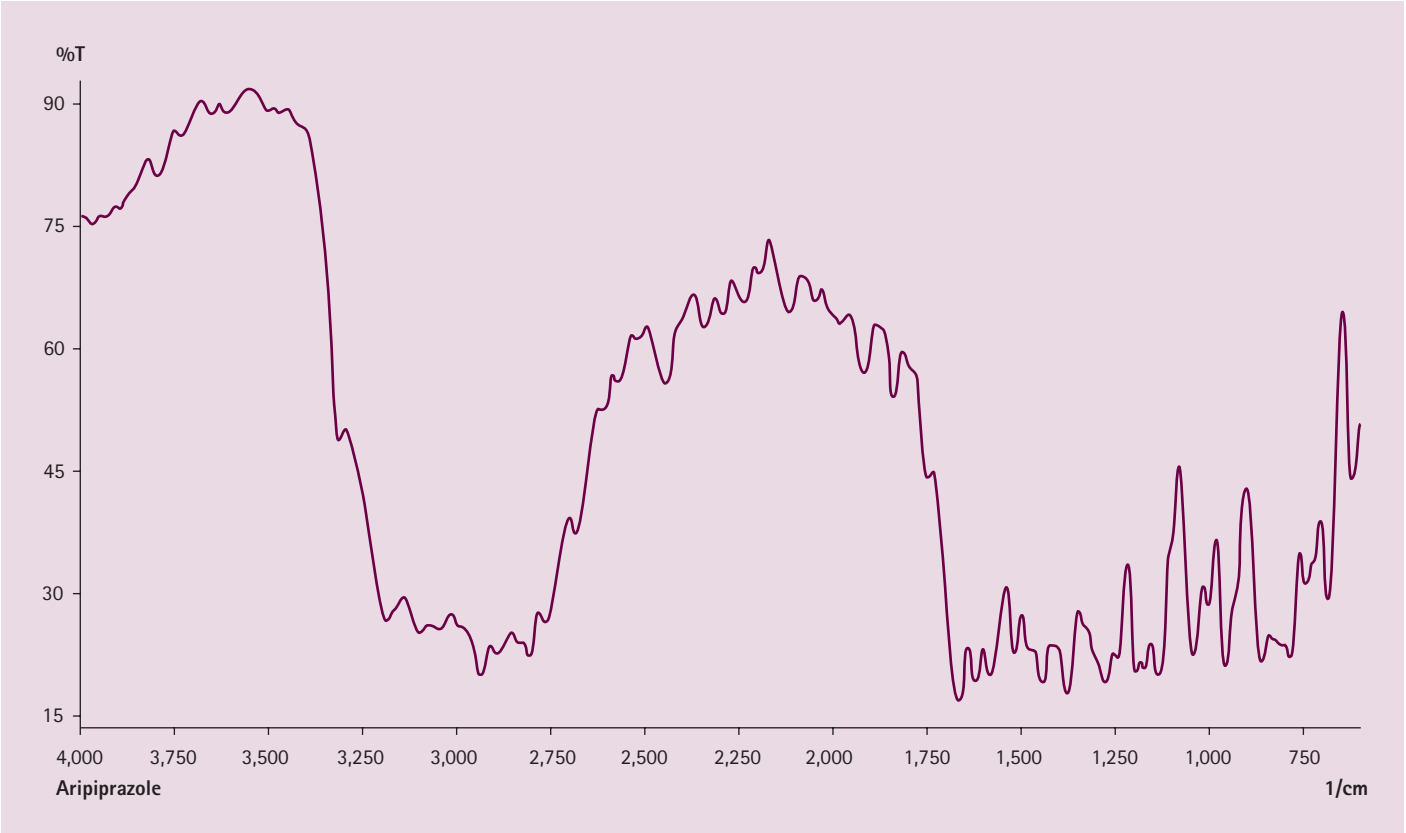
Details shown in this document	Identification – FTIR (197K)
Details shown in the Complete Monograph Method (CMM) Compendium	Assay – HPLC (gradient method – non scalable)
	Related Substances – HPLC (gradient method – non-scalable)

Products for Aripiprazole – FTIR

Products	VWR Cat. No.
Potassium bromide for analysis Uvasol® ACS, Reag. Ph Eur	EM1.04907.0100

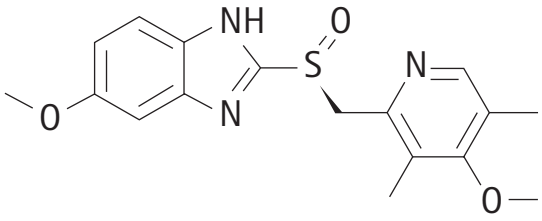


Aripiprazole (USP)
FTIR Analysis



Did you know?
When determining the pH of your HPLC mobile phase it is important to keep your pH-meter well calibrated. Single-use pH buffer sachets guarantee reliability and ease of use.

Esomeprazole (USP)



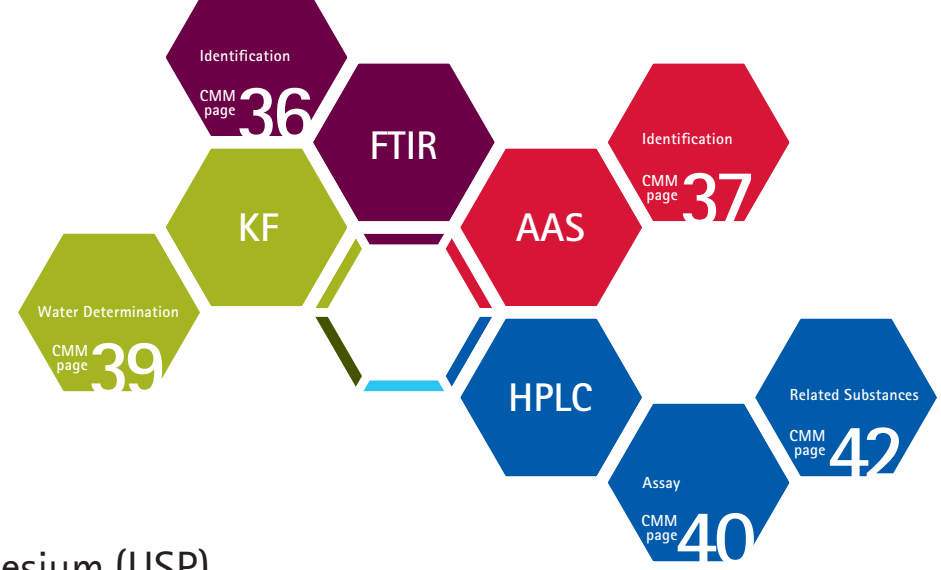
Esomeprazole is a proton pump inhibitor, and the S-enantiomer of omeprazole. It is used in the treatment of dyspepsia, peptic ulcer disease, and gastroesophageal reflux disease.

Common commercial brand names: **Nexium, Essocam, Esomezol.**
Esomeprazole was developed by AstraZeneca. Patent expired in 2014.

Identification tests were performed with FTIR; magnesium content was determined using AAS; assay and Related Substances (RS) as well as dissolution testing were carried out with HPLC using RP-8 and RP-18 endcapped columns; and water content in the API was determined using Karl Fischer (KF) titration.

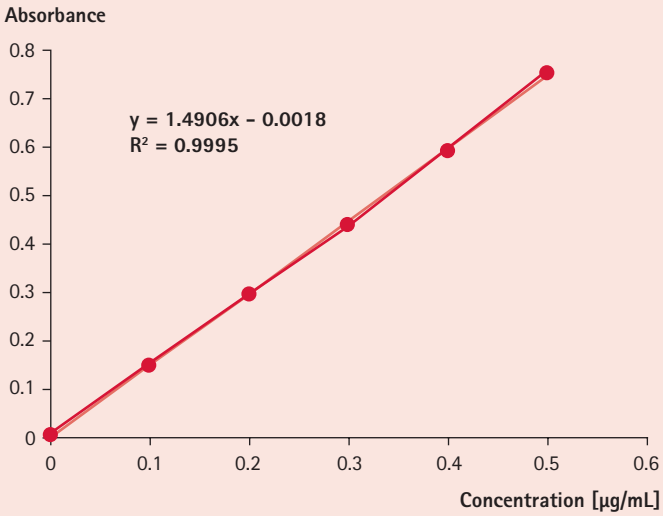
Details shown in the CMM Compendium	Identification – FTIR
Details shown in this document	Identification – Magnesium content – AAS
Details shown in the Complete Monograph Method (CMM) Compendium	Assay – HPLC and UHPLC (isocratic – scalable)
	Related Substances – HPLC and UHPLC (isocratic – scalable)
	Water Determination – Karl Fischer titration

Content of magnesium	**Atomic absorption spectroscopy (AAS)**
Sample solution	Transfer 250 mg esomeprazole magnesium to a 100 mL volumetric flask, add 20 mL of 1 N hydrochloric acid, swirl until dissolved, and dilute with water to volume. Allow to stand for 30 min. Transfer 10 mL of this solution to a 200 mL volumetric flask, and dilute with water to volume. Transfer 10 mL of the solution to another 100 mL volumetric flask, add 4 mL lanthanum solution, and dilute with water to volume.
	Absorption at 285.2 –> 0.563
Lanthanum solution	Transfer 58.7 g lanthanum oxide to a 1,000 mL volumetric flask, wet the substance with some water, and dissolve by cautious addition of 250 mL hydrochloric acid in 20 to 30 mL portions, cooling between additions. Add water while stirring, cool to room temperature, and dilute with water to volume.
Standard stock solution	1,000 µg/mL magnesium in water, from a commercially prepared atomic absorption standard solution.
Result	(CS / CU) x (100 / (100-F)) x 100 = (0.3896/12.516) x (100/ (100 – 8.121)) x 100 = 3.39 % The obtained value is within the acceptance criteria: 3.30 – 3.55 %, on anhydrous basis



Esomeprazole (API) Magnesium (USP) Monograph Flow Charts – AAS

	Solution A	Lanthanum oxide solution	Dilution	Final standard concentration
Standard Solution B	5.0 mL	4.0 mL	100 mL	0.1 µg/mL
Standard Solution C	10.0 mL	4.0 mL	100 mL	0.2 µg/mL
Standard Solution D	15.0 mL	4.0 mL	100 mL	0.3 µg/mL
Standard Solution E	20.0 mL	4.0 mL	100 mL	0.4 µg/mL
Standard Solution F	25.0 mL	4.0 mL	100 mL	0.5 µg/mL

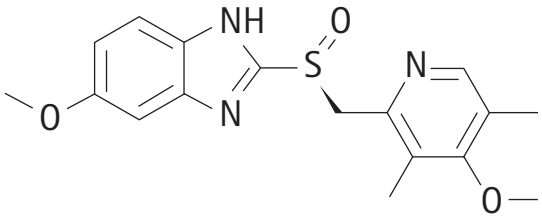


Concentration	Absorbance
0 µg/mL	0.003
0.1 µg/mL	0.148
0.2 µg/mL	0.294
0.3 µg/mL	0.437
0.4 µg/mL	0.591
0.5 µg/mL	0.752
Absorbance of sample	**0.563**
Calculated concentration of sample	0.390 µg/mL

Products for Esomeprazole API – AAS

Products	VWR Cat. No.
Lanthanum (III) oxide for atomic absorption spectroscopy	EM1.10982.0025
Hydrochloric acid Ultrapur®	EM1.01514.0500
Magnesium ICP standard traceable to SRM from NIST $Mg(NO_3)_2$ in HNO_3 2 – 3 % 1,000 mg/L | Mg Certipur®	EM1.70331.0100

Esomeprazole (USP)



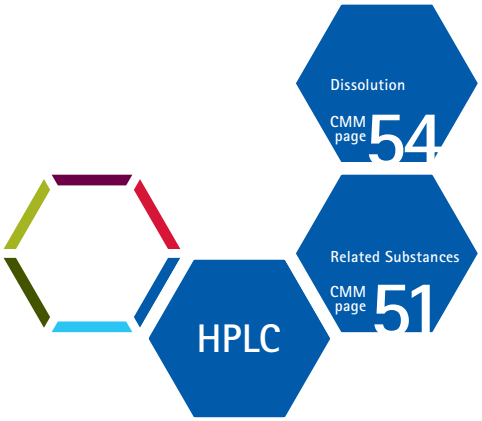
Esomeprazole is a proton pump inhibitor, and the S-enantiomer of omeprazole. It is used in the treatment of dyspepsia, peptic ulcer disease, and gastroesophageal reflux disease.

Common commercial brand names: **Nexium, Essocam, Esomezol.**
Esomeprazole was developed by AstraZeneca. Patent expired in 2014.

Details shown in the CMM Compendium	Related Substances – HPLC (gradient method – non-scalable)
Details shown in this document	Dissolution – chromatography as in assay method (scalable)

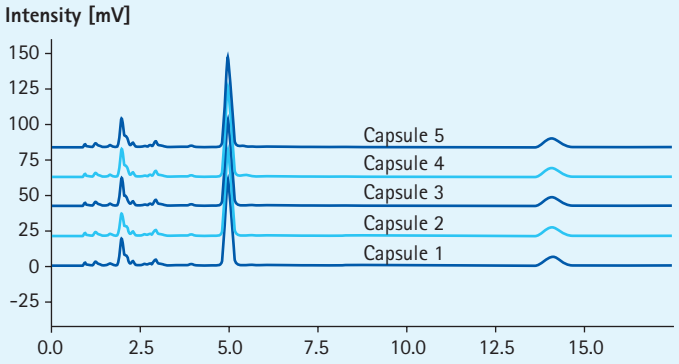
Products for Esomeprazole Capsule – Dissolution Testing

Products	VWR Cat. No.
Hydrochloric acid, fuming 37 % for analysis EMSURE® ACS, ISO, Reag. Ph Eur	EM1.00317.1000
Sodium dihydrogen phosphate dihydrate for analysis EMSURE® Reag. Ph Eur	EM1.06342.1000
di-Sodium hydrogen phosphate dihydrate for analysis EMSURE®	EM1.06580.5000
Sodium hydroxide solution 50 % for analysis EMSURE®	EM1.58793.1000
LiChrosolv® Water LC-MS grade (or water from a Milli-Q® system)	EM1.15333.1000
Acetonitrile isocratic grade for liquid chromatography LiChrosolv®	EM1.14291.5000
Purospher® STAR RP-18 endcapped (5 µm) 150 x 4.6 mm	48219-812
Chromolith® HighResolution RP-18 endcapped 100 x 4.6 mm	EM1.52022.0001

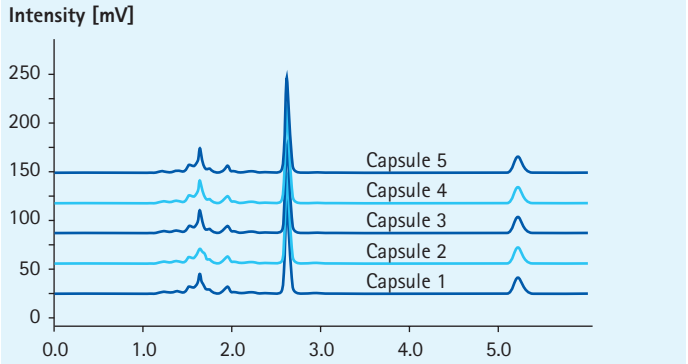


Additional material can be found in our CMM Compendium

Esomeprazole (Delayed-Release Capsules) Magnesium (USP) – Dissolution (Assay)



Chromatographic conditions	
Column	**Purospher® STAR RP-18 endcapped (5 µm) 150 x 4.6 mm (VWR Cat. No. 48219-812)**
Injection	**20 µL**
Detection	UV 302 nm
Cell	10 µL
Flow Rate	1.0 mL/min
Medium	0.1 N hydrochloric acid; 300 mL. After 2 h, continue with a pH 6.8 phosphate buffer as follows: To the vessel, add 700 mL of 0.086 M dibasic sodium phosphate, and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide if necessary, to pH 6.8 ± 0.05.
Apparatus 2	100 rpm
Mobile Phase	Buffer: Prepare a pH 7.3 phosphate buffer by mixing 10.5 mL of 1.0 M monobasic sodium phosphate buffer and 60 mL of 0.5 M dibasic sodium phosphate buffer, and diluting with water to 1,000 mL. Mix 350 mL of acetonitrile and 500 mL of the buffer. Dilute with water to 1,000 mL.
Temperature	25 °C
Diluent	Dissolve 5.24 g of tribasic sodium phosphate dodecahydrate in water. Add 110 mL of 0.5 M dibasic sodium phosphate solution, and dilute with water to 1,000 mL.
Standard Solution	Transfer 10 mg of USP Omeprazole RS to a 250 mL volumetric flask, and dissolve in about 10 mL alcohol. Add 40 mL diluent, and dilute with water to volume.
Sample Solution	After 30 min in pH 6.8 phosphate buffer, pass a portion of the solution under test through a suitable filter. Transfer 5.0 mL of the filtrate to a suitable glassware containing 1.0 mL of 0.25 M sodium hydroxide. Mix well. Protect from light.
Pressure Drop	**149 Bar (2,160 psi)**



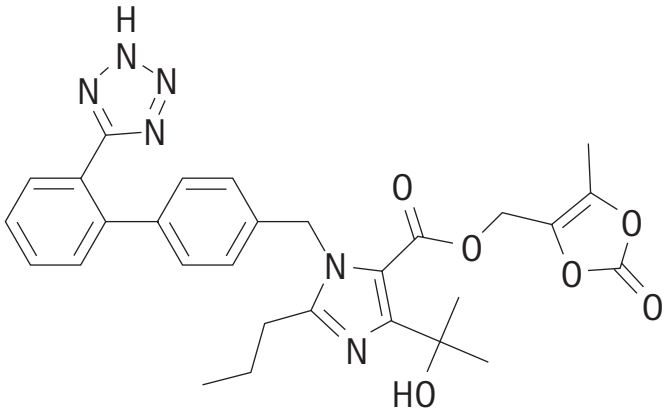
Chromatographic conditions	
Column	**Chromolith® HighResolution RP-18 endcapped 100 x 4.6 mm (VWR Cat. No. EM1.52022.0001)**
Injection	**5 µL**
Detection	UV 302 nm
Cell	10 µL
Flow Rate	1.0 mL/min
Medium	0.1 N hydrochloric acid; 300 mL. After 2 h, continue with a pH 6.8 phosphate buffer as follows: To the vessel, add 700 mL of 0.086 M dibasic sodium phosphate, and adjust with 2 N hydrochloric acid or 2 N sodium hydroxide if necessary, to pH 6.8 ± 0.05.
Apparatus 2	100 rpm
Mobile Phase	Buffer: Prepare a pH 7.3 phosphate buffer by mixing 10.5 mL of 1.0 M monobasic sodium phosphate buffer and 60 mL of 0.5 M dibasic sodium phosphate buffer, and diluting with water to 1,000 mL. Mix 350 mL of acetonitrile and 500 mL of the buffer. Dilute with water to 1,000 mL.
Temperature	25 °C
Diluent	Dissolve 5.24 g of tribasic sodium phosphate dodecahydrate in water. Add 110 mL of 0.5 M dibasic sodium phosphate solution, and dilute with water to 1,000 mL.
Standard Solution	Transfer 10 mg of USP Omeprazole RS to a 250 mL volumetric flask, and dissolve in about 10 mL alcohol. Add 40 mL of diluent, and dilute with water to volume.
Sample Solution	After 30 min in pH 6.8 phosphate buffer, pass a portion of the solution under test through a suitable filter. Transfer 5.0 mL of the filtrate to a suitable glassware containing 1.0 mL of 0.25 M sodium hydroxide. Mix well. Protect from light.
Pressure Drop	**75 Bar (1,080 psi)**

Result for both	**Percentage of esomeprazole dissolved (n=5) = (rU/rS) × (CS/L) × V × 100 = 90 %** **Acceptance criteria: NLT 75 % of the claimed esomeprazole ($C_{17}H_{19}N_3O_3S$) is dissolved.**

The new method with Chromolith® HighResolution RP-18 endcapped is:

3x faster, has improved chromatographic resolution, lower column backpressure, and is still meeting all method performance criteria.

Olmesartan medoxomil (USP)



Olmesartan medoxomil is an angiotensin II receptor antagonist. It is an ester prodrug that is completely and rapidly hydrolyzed to the active acid form, olmesartan. It is used to treat high blood pressure.

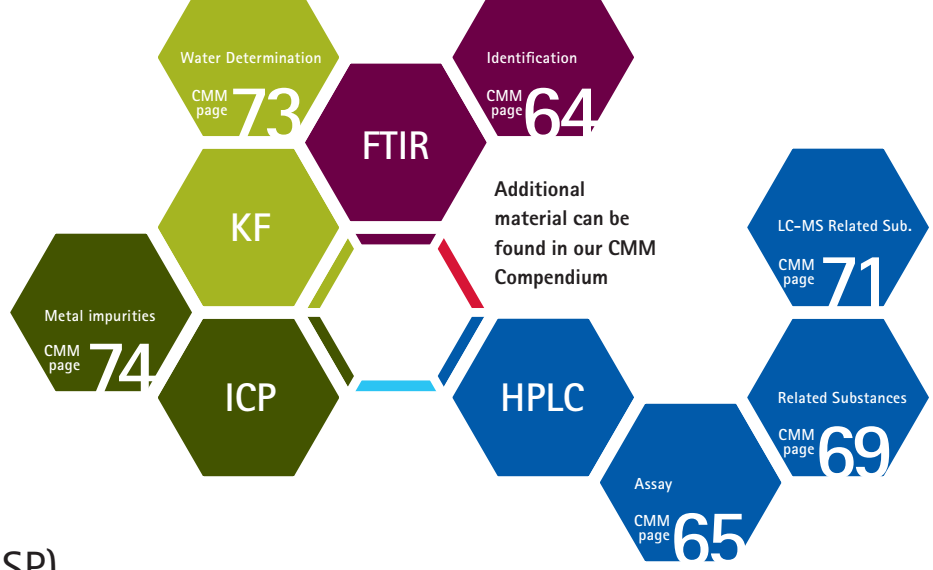
Common commercial brand names: **Benicar** (US), **Olmetec** (EU, Canada and Japan), **WinBP, Olsar, Golme** (India), etc. **Olmesartan medoxomil** was developed by Daiichi Sankyo in 1995. Patent expires 2016.

Identification tests were carried out with FTIR; assay was performed using HPLC and scaled to UHPLC; Related Substances (RS) testing was carried out with HPLC; water content was determined using Karl Fischer (KF) titration; and elemental impurities were measured by ICP.

Details shown in the Complete Monograph Method (CMM) Compendium	Identification – FTIR
	Assay – HPLC and UHPLC (isocratic – scalable)
	Related Substances – HPLC (gradient method – non-scalable)
	Related Substances – LC-MS (NEW proposal / in-house method)
Details shown in this document	Water Determination – coulometric Karl Fischer titration
Details shown in the CMM Compendium	Metal impurities – ICP (NEW proposal ICP-MS USP 232/233)

New Procedures

Due to the upcoming USP changes regarding heavy metal analysis and improved impurity profiling methods, we have developed two new procedures:
Heavy metals: NEW proposal following USP 232/233
Related substances: NEW proposal using LC–MS conditions (in-house method)



Olmesartan medoxomil (USP) Monograph Flow Chart – KF Titration

Water Determination <USP 921>

Pharmaceutical products typically feature complex formulations. Difficulties observed during Karl Fischer determination are often caused by limited solubility. In some cases, side reactions should also be considered. Depending on the formulation's composition and properties, various measures are necessary for secure Karl Fischer determination.

In the case of olmesartan medoxomil, water determination can be performed without problems according to standard methods.
In pharmaceutical guidelines (USP, Ph Eur, DAB), Karl Fischer titration is described as a common method for water determination. For some substances, special procedures are proposed. However, the determination of mass loss as a method for water determination is not recommended.

Titration (one-component system)

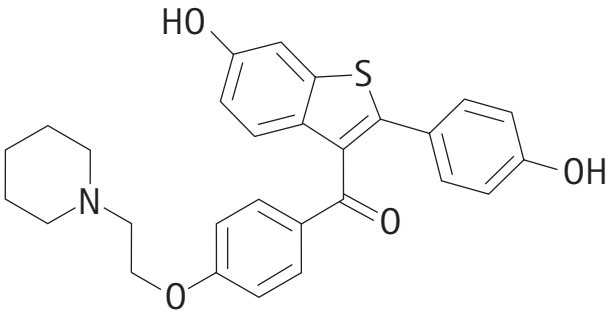
Working medium: Apura® CombiCoulomat fritless coulometric KF reagent for cells with or without diaphragm; 100 mL (VWR Cat. No. EM1.09257.0500)

Titration parameters	Stirring time: 60 s Default coulometer settings for cell without diaphragm: End point indication, e.g.: I(pol) = 5 – 10 µA, U(EP) = 50 – 100 mV Stop criterion for fast titration: Drift <20 µg/min Sample size: 0.4 g (we used olmesartan medoxomil RS)
Procedure	The Karl Fischer reagent is placed in the titration cell without a diaphragm. The coulometer is started and the solvent is titrated dry. After preliminary titration and stabilization of drift, the sample is added into the titration cell with a weighing boat (exact sample weight determination by weighing of weighing boat before and after injection), and water determination is started. For complete sample dissolution, a stirring time of 60 seconds is recommended.
Result	Measured water content in olmesartan: 0.054% USP requirement: <0.5%

Products for Olmesartan – KF Titration

Products	VWR Cat. No.
Apura® CombiTitrant one-component reagent for volumetric Karl Fischer titration	89423-864
Working Medium: Apura® CombiCoulomat fritless Karl Fischer reagent for coulometric water determination for cells with and without diaphragm; 100 mL	EM1.09257.0500

Raloxifene (USP)



Raloxifene is an oral selective estrogen receptor modulator (SERM) that has estrogenic actions on bone and anti-estrogenic actions on the uterus and breasts. It is used for the prevention of osteoporosis in postmenopausal women.

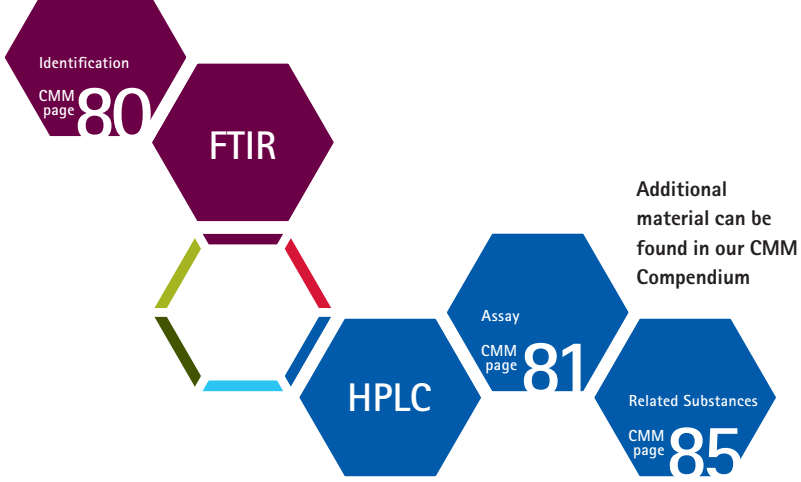
Common commercial brand name: **Evista.**
Raloxifene was developed by Eli Lilly and Company. Patent expired in 2014.

Identification tests were carried out with FTIR; assay was performed using HPLC and scaled to UHPLC; and Related Substances (RS) testing was carried out with HPLC.

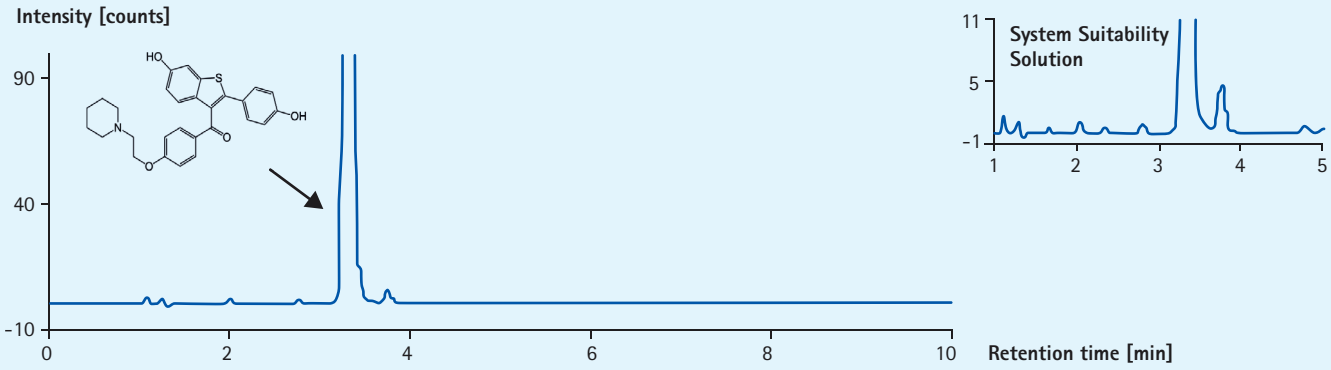
Details shown in the CMM Compendium	Identification – FTIR
Details shown in this document	Assay – HPLC and UHPLC (isocratic method – scalable)
Details shown in the CMM Compendium	Related Substances – HPLC (gradient method – non-scalable)

Products for Raloxifene – HPLC

Products	VWR Cat. No.
Potassium dihydrogen phosphate for analysis (<= 0.005 % Na) EMSURE® ACS, ISO, Reag. Ph Eur	EM1.04877.9025
Water: LiChrosolv® LC-MS grade (or water from a Milli-Q® system)	EM1.15333.1000
Ortho-phosphoric acid 85 % for analysis EMSURE® ACS, ISO, Reag. Ph Eur	EM1.00573.2510
Potassium hydroxide solution 47 % for analysis EMSURE®	EM1.05545.9025
Acetonitrile isocratic grade for liquid chromatography LiChrosolv®	EM1.14291.5000
Purospher® STAR RP-8 endcapped (3 µm) 150 x 4.6 mm	10143-350
and scaled to Purospher® STAR RP-8 endcapped (2 µm) 100 x 2.1 mm	10811-818



Raloxifene Hydrochloride (USP) Monograph Flow Chart – HPLC Assay



Chromatographic conditions

Column	Purospher® STAR RP-8 endcapped (3 µm) 150 x 4.6 mm (VWR Cat. No. 10143-350)
Injection	10 µL
Detection	UV 280 nm
Cell	11 µL
Flow Rate	1.5 mL/min
Mobile Phase	Dissolve 7.2 g monobasic potassium phosphate in 1,000 mL water. Add 1.3 mL phosphoric acid, and adjust with phosphoric acid or potassium hydroxide solution to pH 2.5 ± 0.1. Mix acetonitrile and buffer (33:67 v/v).
Temperature	35 °C
Diluent	Mix 11 mL of 0.25 M tribasic sodium phosphate with 22 mL of 0.5 M dibasic sodium phosphate, and dilute with water to 100 mL.
Samples	**Standard solution:** 0.05 mg/mL USP raloxifene hydrochloride RS in mobile phase. **Sample solution:** 0.05 mg/mL raloxifene hydrochloride in mobile phase. **System suitability solution:** Transfer 15 mg USP raloxifene hydrochloride RS to a 50 mL volumetric flask, add 1.0 mL raloxifene related compound C solution, and dilute with Diluent A to volume.
Pressure Drop	172 Bar (2,494 psi)

System suitability criteria	**Resolution:** NLT 2.0 between raloxifene and raloxifene RS C **Tailing factor:** NMT 2.0 for raloxifene
Specificity	Determined by injection of SST solution, and determination of the retention time and relative retention time for raloxifene HCl and raloxifene RS C.
Linearity, Limit of Detection (LOD) and Limit of Quantitation (LOQ)	Determined by injecting six (6) concentration levels from 100 – 10,000 ppm of raloxifene HCl, and six (6) concentration levels ranging from 1.5 – 150 ppm of raloxifene RS C.

We provide information and advice to our customers to the best of our knowledge and ability, but without obligation or liability. Existing laws and regulations are to be observed in all cases by our customers. This also applies in respect to any rights of third parties. Our information and advice do not relieve our customers of their own responsibility for checking the suitability of our products for the envisaged purpose.

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