ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight containers.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP 6-Hydroxynicotinic Acid RS
  USP Niacin RS■2S *(USP35)*

Nystatin Vaginal Inserts

DEFINITION
Nystatin Vaginal Inserts are composed of Nystatin with suitable binders, diluents, and lubricants. Vaginal Inserts contain NLT 90.0% and NMT 140.0% of the labeled amount of USP Nystatin Units.

ASSAY
- **NYSTATIN**
  (See *Antibiotics—Microbial Assays* ⟨81⟩.)
  Sample stock solution: 400 USP Nystatin Units/mL in dimethylformamide prepared as follows. Blend NLT 5 Vaginal Inserts for 3–5 min in a high-speed blender with a sufficient volume of dimethylformamide to obtain a solution of suitable concentration. Dilute a portion of this solution with dimethylformamide.
  Test dilution: Dilute a volume of the *Sample stock solution* with *Buffer No. 6* to obtain a nystatin concentration assumed to be equal to the median dose level of the standard.
  Acceptance criteria: 90.0%–140.0% of the labeled amount of USP Nystatin Units

PERFORMANCE TESTS

Change to read:

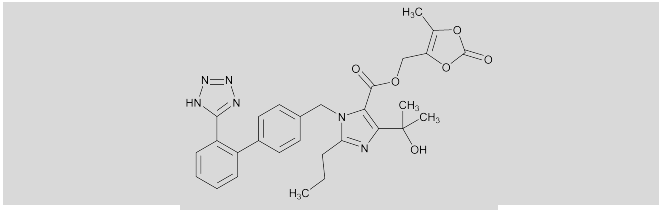
- **DISINTEGRATION** ⟨701⟩
  Time: 60 min
  ■**Analysis:** Use the *Procedure* for *Uncoated Tablets* in the chapter.■2S *(USP35)*
  Acceptance criteria: Meets the requirements

SPECIFIC TESTS
- **LOSS ON DRYING** ⟨731⟩**:** Dry 100 mg of powdered Vaginal Inserts in a capillary-stoppered bottle in vacuum at a pressure not exceeding 5 mm of mercury at 60° for 3 h: it loses NMT 5.0% of its weight.

ADDITIONAL REQUIREMENTS
- **PACKAGING AND STORAGE:** Preserve in tight, light-resistant containers and, where so specified in the labeling, in a refrigerator.
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Nystatin RS

Add the following:

■Olmesartan Medoxomil



$C_{29}H_{30}N_6O_6$ 558.59

1*H*-Imidazole-5-carboxylic acid, 4-(1-hydroxy-1-methylethyl)-2-propyl-1-[[2′-(1*H*-tetrazol-5-yl) [1,1′-biphenyl] -4-yl]methyl]-, (5-methyl-2-oxo-1,3-dioxol-4-yl)methyl ester [144689-63-4].

DEFINITION
Olmesartan Medoxomil contains NLT 98.5% and NMT 101.5% of $C_{29}H_{30}N_6O_6$, calculated on the anhydrous and solvent-free basis.

IDENTIFICATION
- **A. INFRARED ABSORPTION** ⟨197K⟩
- **B.** The ratio of the retention time of the major peak to that of the internal standard of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY
- **PROCEDURE**
  [NOTE—The *Standard solution* and *Sample solution* are stable for 24 h at 5°.]
  Diluted phosphoric acid: 0.2% phosphoric acid
  Buffer: 0.015 M monobasic potassium phosphate. Adjust the solution with *Diluted phosphoric acid* (w/v) to a pH of 3.4.
  Mobile phase: Acetonitrile and *Buffer* (17:33)
  Diluent 1: Acetonitrile and water (4:1)
  Diluent 2: Acetonitrile and water (2:3)
  Internal standard solution: 0.5 mg/mL of 4-hydroxybenzoic acid isobutyl ester in *Diluent 2*. [NOTE—This solution is stable for 1 month at room temperature.]
  Standard stock solution: 1 mg/mL of USP Olmesartan Medoxomil RS in *Diluent 1*
  Standard solution: 0.05 mg/mL of USP Olmesartan Medoxomil RS from the *Standard stock solution* and 0.025 mg/mL of *p*-hydroxybenzoic acid isobutyl ester from the *Internal standard solution* in *Diluent 2*
  Sample stock solution: 1 mg/mL of Olmesartan Medoxomil in *Diluent 1*
  Sample solution: 0.05 mg/mL of Olmesartan Medoxomil from the *Sample stock solution* and 0.025 mg/mL of *p*-hydroxybenzoic acid isobutyl ester from the *Internal standard solution* in *Diluent 2*
  Chromatographic system
  (See *Chromatography* ⟨621⟩*, System Suitability*.)
  Mode: LC
  Detector: UV 250 nm
  Column: 4.6-mm × 15-cm; 5-µm packing L1
  Column temperature: 40°
  Flow rate: 1 mL/min
  Injection size: 10 µL
  System suitability
  Sample: *Standard solution*
  Suitability requirements
  Resolution: NLT 4 between olmesartan medoxomil and *p*-hydroxybenzoic acid isobutyl ester

Relative standard deviation: NMT 0.5% for the peak ratio of olmesartan medoxomil and the internal standard

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of olmesartan medoxomil in the portion taken:

$$\text{Result} = (R_U/R_S) \times (C_S/C_U) \times 100$$

R_U = ratio of the peak areas of olmesartan medoxomil and *p*-hydroxybenzoic acid isobutyl ester from the *Sample solution*

R_S = ratio of the peak areas of olmesartan medoxomil and *p*-hydroxybenzoic acid isobutyl ester from the *Standard solution*

C_S = concentration of USP Olmesartan Medoxomil RS in the *Standard solution* (mg/mL)

C_U = concentration of Olmesartan Medoxomil in the *Sample solution* (mg/mL)

Acceptance criteria: 98.5%–101.5% on the anhydrous and solvent-free basis

IMPURITIES

Inorganic Impurities

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%. [NOTE—The ignition temperature range is 450° to 550°.]

• **HEAVY METALS,** *Method II* ⟨**231**⟩**:** NMT 10 ppm

Organic Impurities

• **PROCEDURE**

Buffer: Prepare as directed in the *Assay*.

Solution A: Acetonitrile and *Buffer* (1:4)

Solution B: Acetonitrile and *Buffer* (4:1)

Mobile phase: See the gradient table below.

Time (min)	Solution A (%)	Solution B (%)
0	75	25
10	75	25
35	0	100
45	0	100

System suitability solution: 0.01 mg/mL each of USP Olmesartan Medoxomil RS and USP Olmesartan Medoxomil Related Compound A RS in acetonitrile

Standard solution: 0.01 mg/mL of USP Olmesartan Medoxomil RS in acetonitrile

Sample solution: 1 mg/mL of Olmesartan Medoxomil in acetonitrile

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

[NOTE—A guard column of 4.6-mm × 5-cm of packing L7 may be used.]

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm × 10-cm; 3.5-µm packing L7

Column temperature: 40°

Flow rate: 1 mL/min

Injection size: 10 µL

System suitability

Suitability requirements

Sample: *System suitability solution*

Resolution: NLT 5 between olmesartan medoxomil and olmesartan medoxomil related compound A

Relative standard deviation: NMT 2.0% for the olmesartan medoxomil peak

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Olmesartan Medoxomil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*

r_S = peak response of olmesartan medoxomil from the *Standard solution*

C_S = concentration of USP Olmesartan Medoxomil RS in the *Standard solution* (mg/mL)

C_U = concentration of Olmesartan Medoxomil in the *Sample solution* (mg/mL)

F = relative response factor (see the *Impurity Table*)

Acceptance criteria

Individual impurities: See the *Impurity Table*.

Total impurities: NMT 1.3%. [NOTE—Disregard any peak below 0.05%.]

Impurity Table

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Olmesartan[a]	0.2	1.0	0.5
Olmesartan medoxomil related compound A[b]	0.7	1.6	0.1
Olmesartan medoxomil	1.0	1.0	—
Olefinic impurity[c]	1.6	1.0	0.6
N-alkyl impurity[d]	3.4	0.7	0.1
Any other individual unidentified impurity	—	1.0	0.1

[a] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-2-yl)-2-propyl-1*H*-imidazole-5-carboxylic acid.

[b] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1*H*-furo[3,4-d]imidazol-6(4*H*)-one.

[c] (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-((2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-4-(prop-1-en-2-yl)-2-propyl-1*H*-imidazole-5-carboxylate.

[d] ((5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2′-(1-trityl-1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-1*H*-imidazole-5-carboxylate.

SPECIFIC TESTS

• **LIMIT OF ACETONE (IF PRESENT)**

Internal standard solution: 1% solution of 1-butanol in dimethyl sulfoxide. [NOTE—This solution is stable for 1 month at room temperature.]

Standard solution: 0.37 µL/mL of acetone and 2 µL/mL of 1-butanol from the *Internal standard solution* in dimethylsulfoxide. [NOTE—This solution is stable for 8 h at room temperature.]

Sample solution: 25 mg/mL of Olmesartan Medoxomil and 2 µL/mL of 1-butanol from the *Internal standard solution* in dimethylsulfoxide. [NOTE—This solution is stable for 8 h at room temperature.]

Chromatographic system

(See *Chromatography* ⟨621⟩*, System Suitability*.)

Mode: GC

Detector: Flame ionization

Column: 30-m × 0.53-mm column bonded with a 1-µm film of phase G14

Column temperature: See the temperature program table below.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
50	0	50	5
50	10	180	5

Injection port temperature: 200°
Detector temperature: 200°
Autosampler temperature: 80°
Carrier gas: Helium
Flow rate: 4 mL/min. [NOTE—Adjust the flow rate so that the retention time of acetone is 2.5 min.]
Injection size: 1 mL
Split ratio: 5:1
System suitability
Sample: *Standard solution*. [NOTE—Allow the samples to stand for 30 min in the autosampler at 80°.]
Suitability requirements
Resolution: NLT 60 between the acetone and 1-butanol peaks
Relative standard deviation: NMT 5.0% for the peak area ratio of acetone and 1-butanol
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of acetone in the portion of Olmesartan Medoxomil taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of acetone from the *Sample solution*
r_S = peak response of acetone from the *Standard solution*
C_S = concentration of acetone in the *Standard solution* (mg/mL)
C_U = concentration of Olmesartan Medoxomil in the *Sample solution* (mg/mL)

Acceptance criteria: NMT 0.6%

• **WATER DETERMINATION,** *Method Ic* ⟨**921**⟩**:** NMT 0.5%

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in well-closed containers, protect from moisture, and store below 25°.

• **USP REFERENCE STANDARDS** ⟨**11**⟩
USP Olmesartan Medoxomil RS
USP Olmesartan Medoxomil Related Compound A RS
1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1*H*-furo[3,4-*d*]imidazol-6(4*H*)-one.
$C_{24}H_{24}N_6O_2$ · 428.49 ■2S *(USP35)*

Olopatadine Hydrochloride Ophthalmic Solution

DEFINITION

Olopatadine Hydrochloride Ophthalmic Solution is a sterile aqueous solution of Olopatadine Hydrochloride. It contains NLT 90.0% and NMT 110.0% of the labeled amount of olopatadine ($C_{21}H_{23}NO_3$). It may contain suitable antimicrobial agents.

IDENTIFICATION

• **A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

• **PROCEDURE**
[NOTE—Protect solutions from light.]
Buffer: Dissolve 13.6 g of monobasic potassium phosphate in 1 L of water, add 1 mL of triethylamine, and mix. Adjust with phosphoric acid to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (28:72)
Standard solution: 0.1 mg/mL of USP Olopatadine Hydrochloride RS in *Mobile phase*
Sample solution: Equivalent to 0.1 mg/mL of olopatadine in *Mobile phase*, from Ophthalmic Solution
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 299 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 30 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Column efficiency: NLT 2000 theoretical plates
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of olopatadine ($C_{21}H_{23}NO_3$) in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of the *Sample solution*
r_S = peak response of the *Standard solution*
C_S = concentration of USP Olopatadine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of olopatadine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of olopatadine, 337.41
M_{r2} = molecular weight of olopatadine hydrochloride, 373.87

Acceptance criteria: 90.0%–110.0%

IMPURITIES

• **LIMIT OF EARLY ELUTING IMPURITIES**
[NOTE—Protect solutions from light.]
Mobile phase: Proceed as directed in the *Assay*.
Blank solution: *Mobile phase*
System suitability solution: 0.2 mg/mL of USP Olopatadine Hydrochloride RS and 0.02 mg/mL of USP Olopatadine Related Compound B RS in *Mobile phase*
Standard solution: 0.2 mg/mL of USP Olopatadine Hydrochloride RS in *Mobile phase*
Sample solution: Equivalent to 0.2 mg/mL of olopatadine in *Mobile phase*, from Ophthalmic Solution
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 299 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Flow rate: 1 mL/min
Injection volume: 30 µL
Run time: At least 1.6 times the retention time of the major peak
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between olopatadine and olopatadine related compound B, *System suitability solution*
Column efficiency: NLT 2000 theoretical plates, *Standard solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each impurity in the portion of Ophthalmic Solution taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of each impurity from the *Sample solution*
r_S = peak response of olopatadine from the *Standard solution*