## Moexipril Hydrochloride

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| **Type of Posting** | Revision Bulletin |
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| **Expert Committee** | Chemical Medicines Monographs 2 |
| **Reason for Revision** | Compliance |

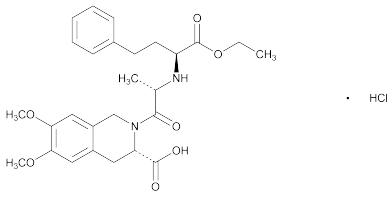
In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Moexipril Hydrochloride monograph. The purpose for the revision is to widen the disregard limit from NMT 0.02% to NMT 0.05% and the total impurities from NMT 1.00% to NMT 1.0% to be consistent with the FDA approved drug product.

Minor editorial changes have been made to update the monograph to the current *USP* style.

The Moexipril Hydrochloride Revision Bulletin supersedes the currently official Moexipril Hydrochloride monograph. The Revision Bulletin will be incorporated in the *USP 40–NF 35.*

Should you have any questions, please contact Sujatha Ramakrishna, Ph.D., MBA. Senior Scientific Liaison (301–816–8349 or sxr@usp.org).

# Moexipril Hydrochloride



$C_{27}H_{34}N_2O_7 \cdot HCl$ 535.03

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-, monohydrochloride, [3*S*-[2[*R**(*R**)],3*R**]]-; (3*S*)-2-[(2*S*)-*N*-[(1*S*)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, 2-ethyl ester, monohydrochloride [82586-52-5].

## DEFINITION

Moexipril Hydrochloride contains NLT 98.0% and NMT 102.0% of moexipril hydrochloride ($C_{27}H_{34}N_2O_7 \cdot HCl$), calculated on the anhydrous basis.

## IDENTIFICATION

- **A. Infrared Absorption** ⟨197K⟩
- **B.** The relative retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
- **C. Identification Tests—General** ⟨191⟩**,** *Chloride***:** Meets the requirements

## ASSAY

- **Procedure**

**Buffer:** 1.32 g/L of dibasic ammonium phosphate. Adjust with diluted phosphoric acid to a pH of 7.5.
**Solution A:** Acetonitrile and tetrahydrofuran (95:5)
**Mobile phase:** *Solution A* and *Buffer* (30:70)
**Standard solution:** 0.1 mg/mL of USP Moexipril Hydrochloride RS in *Mobile phase*. [NOTE—Sonication may be necessary for complete dissolution.]
**Sample solution:** 0.1 mg/mL of Moexipril Hydrochloride in *Mobile phase*. [NOTE—Sonication may be necessary for complete dissolution.]
**Chromatographic system**
(See *Chromatography* ⟨621⟩*, System Suitability*.)
**Mode:** LC
**Detector:** UV 215 nm
**Column:** 4.6-mm × 25-cm; 5-µm packing L1
**Column temperature:** 35°
**Flow rate:** 1 mL/min
**Injection volume:** 10 µL
**Run time:** NLT 3.2 times the retention time of moexipril
**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Relative standard deviation:** NMT 2.0%
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of moexipril hydrochloride ($C_{27}H_{34}N_2O_7 \cdot HCl$) in the portion of Moexipril Hydrochloride taken:

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

$r_U$ = peak response from the *Sample solution*
$r_S$ = peak response from the *Standard solution*
$C_S$ = concentration of USP Moexipril Hydrochloride RS in the *Standard solution* (mg/mL)
$C_U$ = concentration of Moexipril Hydrochloride in the *Sample solution* (mg/mL)
**Acceptance criteria:** 98.0%–102.0% on the anhydrous basis

## IMPURITIES

***Delete the following:***

•• **Heavy Metals,** *Method II* ⟨231⟩**:** NMT 10 ppm
• (Official 1-Jan-2018)
• **Residue on Ignition** ⟨281⟩**:** NMT 0.20%

***Change to read:***

- **Organic Impurities**

[NOTE—Use freshly prepared samples for analysis.]
**Solution A** and **Chromatographic system:** Proceed as directed in the *Assay*.
**Solution B:** Proceed as directed for the *Buffer* in the *Assay*.
**Diluent:** *Solution A* and *Solution B* (20:80)
**Mobile phase:** See *Table 1*.

**Table 1**

| Time (min) | Solution A (%) | Solution B (%) |
|---|---|---|
| 0 | 20 | 80 |
| 5 | 20 | 80 |
| 35 | 55 | 45 |
| 65 | 55 | 45 |
| 70 | 20 | 80 |
| 80 | 20 | 80 |

**Standard solution 1:** 4 µg/mL of USP Moexipril Hydrochloride RS in *Diluent*. [NOTE—Sonication may be necessary for complete dissolution.]
**Standard solution 2:** 2 mg/mL of USP Moexipril Hydrochloride RS and 3 µg/mL each of USP Moexipril Related Compound A RS, USP Moexipril Related Compound B RS, USP Moexipril Related Compound C RS, USP Moexipril Related Compound D RS, USP Moexipril Related Compound E RS, USP Moexipril Related Compound F RS, and USP Moexipril Related Compound G RS in *Diluent*. [NOTE—Sonication may be necessary for complete dissolution.]
**Sample solution:** 2 mg/mL of Moexipril Hydrochloride in *Diluent*. [NOTE—Sonication may be necessary for complete dissolution.]
**System suitability**
**Samples:** *Standard solution 1* and *Standard solution 2*
**Suitability requirements**
**Resolution:** NLT 3.5 between moexipril related compound A and moexipril related compound E; NLT 2.5 between moexipril and moexipril related compound G, *Standard solution 2*
**Relative standard deviation:** NMT 5.0% for moexipril, *Standard solution 1*
**Analysis**
**Samples:** *Standard solution 1*, *Standard solution 2*, and *Sample solution*
Calculate the percentage of each specified impurity in the portion of Moexipril Hydrochloride taken:

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

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

$r_S$ = peak response of the corresponding Reference Standard from *Standard solution 2*
$C_S$ = concentration of each specified impurity in *Standard solution 2* (mg/mL)
$C_U$ = concentration of Moexipril Hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any other individual unspecified impurity in the portion of Moexipril Hydrochloride taken:

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

$r_U$ = peak response of each individual unspecified impurity from the *Sample solution*
$r_S$ = peak response of moexipril from *Standard solution 1*
$C_S$ = concentration of USP Moexipril Hydrochloride RS in *Standard solution 1* (mg/mL)
$C_U$ = concentration of Moexipril Hydrochloride in the *Sample solution* (mg/mL)

**Acceptance criteria:** See *Table 2*. Disregard peaks less than •0.05%.• (RB 1-Jun-2016)

**Table 2**

| Name | Relative Retention Time | Acceptance Criteria, NMT (%) |
|---|---|---|
| Moexipril related compound E[a] | 0.14 | 0.15 |
| Moexipril related compound A[b] | 0.28 | 0.2 |
| Moexipril related compound F[c] | 0.62 | 0.15 |
| Moexipril related compound G[d] | 0.90 | 0.15 |
| Moexipril | 1.00 | — |
| Moexipril related compound D[e] | 1.28 | 0.15 |
| Moexipril related compound B[f] | 1.62 | 0.2 |
| Moexipril related compound C[g] | 2.26 | 0.15 |
| Any other individual unspecified impurity | — | 0.10 |
| Total impurities[h] | — | •1.0• (RB 1-Jun-2016) |

[a] (*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
[b] (3*S*)-2-{(2*S*)-*N*-[(1*S*)-1-Carboxy-3-phenylpropyl]alanyl}-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid.
[c] (*S*)-2-[(*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-ylamino]propanoic acid.
[d] (*S*)-6,7-Dimethoxy-2-{(*S*)-2-[(*S*)-1-methoxy-1-oxo-4-phenylbutan-2-ylamino]propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
[e] (*S*)-2-{(*S*)-2-[(*S*)-4-Cyclohexyl-1-ethoxy-1-oxobutan-2-ylamino]propanoyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
[f] (*S*)-Ethyl 2-{(3*S*,11a*S*)-8,9-dimethoxy-3-methyl-1,4-dioxo-3,4-dihydro-1*H*-pyrazino[1,2-*b*]isoquinolin-2(6*H*,11*H*,11a*H*)-yl}-4-phenylbutanoate.
[g] (*S*)-*tert*-Butyl 2-{(*S*)-2-[(*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino]propanoyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.
[h] Sum of all specified and unspecified impurities.

- **CONTENT OF IMIDAZOLE**

**Mobile phase:** Hexane, isopropyl alcohol, and diethyl amine (52: 48: 0.025)
**Standard solution:** 0.01 mg/mL of USP Imidazole RS in *Mobile phase*. [NOTE—Sonication may be necessary for complete dissolution.]
**Sample solution:** 2 mg/mL of Moexipril Hydrochloride in *Mobile phase*. [NOTE—Sonication may be necessary for complete dissolution. Use freshly prepared *Sample solution* for analysis.]
**Chromatographic system**
(See *Chromatography* ⟨621⟩, *System Suitability*.)
**Mode:** LC
**Detector:** UV 215 nm
**Column:** 4.6-mm × 25-cm; 5-µm packing L3
**Flow rate:** 1 mL/min
**Injection volume:** 20 µL
**Run time:** NLT 3.3 times the retention time of imidazole
**System suitability**
**Sample:** *Standard solution*
**Suitability requirements**
**Relative standard deviation:** NMT 5.0%
**Analysis**
**Samples:** *Standard solution* and *Sample solution*
Calculate the percentage of imidazole in the portion of Moexipril Hydrochloride taken:

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

$r_U$ = peak response of imidazole from the *Sample solution*
$r_S$ = peak response of imidazole from the *Standard solution*
$C_S$ = concentration of USP Imidazole RS in the *Standard solution* (mg/mL)
$C_U$ = concentration of Moexipril Hydrochloride in the *Sample solution* (mg/mL)

**Acceptance criteria:** NMT 0.03%

## SPECIFIC TESTS

- **WATER DETERMINATION ⟨921⟩,** *Method I, Method Ia*: NMT 1.5%
- **OPTICAL ROTATION ⟨781S⟩,** *Procedures, Specific Rotation*
**Sample solution:** 0.011 g/mL of Moexipril Hydrochloride in alcohol. Sonicate to dissolve the sample.
**Acceptance criteria:** +30.0° to +38.0°

## ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight containers, protected from moisture. Store at room temperature.
- **USP REFERENCE STANDARDS ⟨11⟩**

USP Imidazole RS
USP Moexipril Hydrochloride RS
USP Moexipril Related Compound A RS
(3*S*)-2-{(2*S*)-*N*-[(1*S*)-1-Carboxy-3-phenylpropyl]alanyl}-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid.
$C_{25}H_{30}N_2O_7$ 470.51
USP Moexipril Related Compound B RS
(*S*)-Ethyl 2-{(3*S*,11a*S*)-8,9-dimethoxy-3-methyl-1,4-dioxo-3,4-dihydro-1*H*-pyrazino[1,2-*b*]isoquinolin-2(6*H*,11*H*,11a*H*)-yl}-4-phenylbutanoate.
$C_{27}H_{32}N_2O_6$ 480.55
USP Moexipril Related Compound C RS
(*S*)-*tert*-Butyl 2-{(*S*)-2-[(*S*)-1-ethoxy-1-oxo-4-phenylbutan-2-ylamino]propanoyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate.
$C_{31}H_{42}N_2O_7$ 554.67
USP Moexipril Related Compound D RS
(*S*)-2-{(*S*)-2-[(*S*)-4-Cyclohexyl-1-ethoxy-1-oxobutan-2-ylamino]propanoyl}-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
$C_{27}H_{40}N_2O_7$ 504.62
USP Moexipril Related Compound E RS
(*S*)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.
$C_{12}H_{15}NO_4$ 237.25
USP Moexipril Related Compound F RS
(*S*)-2-[(*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-ylamino]propanoic acid.
$C_{15}H_{21}NO_4$ 279.33

| | | |
|---|---|---|
| USP Moexipril Related Compound G RS<br>(*S*)-6,7-Dimethoxy-2-{(*S*)-2-[(*S*)-1-methoxy-1-oxo-4-phenylbutan-2-ylamino]propanoyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid. | $C_{26}H_{32}N_2O_7$ | 484.54 |