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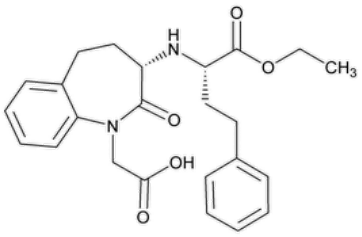
Benazepril Hydrochloride



· HCl

$C_{24}H_{28}N_2O_5 \cdot HCl$ 460.95

1*H*-1-Benzazepine-1-acetic acid, 3-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-, monohydrochloride, [*S*-(*R**,*R**)]-. (3*S*)-3-[[(1*S*)-1-Carboxy-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, 3-ethyl ester, monohydrochloride CAS RN®: 86541-74-4; UNII: N1SN99T69T.

» Benazepril Hydrochloride contains not less than 98.0 percent and not more than 102.0 percent of $C_{24}H_{28}N_2O_5 \cdot HCl$, calculated on the dried basis.

Packaging and storage—Preserve in well-closed containers, and store at a temperature below 30°, preferably between 15° and 30°.

Change to read:

USP Reference standards ⟨11⟩—

USP Benazepril Hydrochloride RS

USP Benazepril Related Compound A RS

▲2-[(*R*)-3-{[(*R*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl]acetic acid hydrochloride;

Also known as▲ (ERR 1-Jul-2021) (3*R*) 3-[[(1*R*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, monohydrochloride.

$C_{24}H_{28}N_2O_5 \cdot HCl$ 460.95

USP Benazepril Related Compound B RS

▲2-[(*S*)-3-{[(*R*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]amino}-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl]acetic acid hydrochloride;

Also known as▲ (ERR 1-Jul-2021) (3*S*) 3-[[(1*R*)-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, monohydrochloride.

$C_{24}H_{28}N_2O_5 \cdot HCl$ 460.95

USP Benazepril Related Compound C RS

▲(*S*)-2-{[(*S*)-1-(Carboxymethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl]amino}-4-phenylbutanoic acid;

Also known as▲ (ERR 1-Jul-2021) 3-(1-Carboxy-3-phenyl-1(*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid.

$C_{22}H_{24}N_2O_5$ 396.44

USP Benazepril Related Compound D RS

▲2-[(*S*)-3-{[(*S*)-4-Cyclohexyl-1-ethoxy-1-oxobutan-2-yl]amino}-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl]acetic acid hydrochloride;

Also known as▲ (ERR 1-Jul-2021) (3-(1-Ethoxycarbonyl-3-cyclohexyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid, monohydrochloride.

$C_{24}H_{34}N_2O_5 \cdot HCl$ 467.00

USP Benazepril Related Compound E RS

▲(*S*)-2-(3-Amino-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)acetic acid hydrochloride;

Also known as▲ (ERR 1-Jul-2021) 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid ▲monohydrochloride.

$C_{12}H_{14}N_2O_3 \cdot HCl$ 270.71▲ (ERR 1-Jul-2021)

USP Benazepril Related Compound F RS

▲*tert*-Butyl (*S*)-2-(3-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl)acetate;

Also known as▲ (ERR 1-Jul-2021) *tert*-Butyl-3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid.

▲$C_{16}H_{22}N_2O_3$ 290.36▲ (ERR 1-Jul-2021)

USP Benazepril Related Compound G RS

▲Ethyl (*S*)-2-{[(*S*)-1-(2-ethoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-3-yl]amino}-4-phenylbutanoate;

Also known as▲ (ERR 1-Jul-2021) (3-(1-Ethoxycarbonyl-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid ethyl ester.

▲$C_{26}H_{32}N_2O_5$ 452.55▲ (ERR 1-Jul-2021)

Identification—

A: *Spectroscopic Identification Tests ⟨197⟩, Infrared Spectroscopy: 197M.*

B: The retention time of the major peak in the chromatogram of the *Assay preparation* corresponds to that in the chromatogram of the *Standard preparation,* as obtained in the *Assay.*

C: It responds to the test for *Chloride ⟨191⟩.*

Absorbance of solution—The absorbance of a 1 in 100 solution of it in methanol, determined in a 1-cm cell at 420 nm, is not more than 0.015, methanol being used as the blank.

Absorptivity—

Test preparation—Dissolve an accurately weighed quantity of Benazepril Hydrochloride in methanol, and dilute quantitatively, and stepwise if necessary, to obtain a solution having a known concentration of about 0.025 mg per mL.

Procedure—Proceed as directed under *Ultraviolet-Visible Spectroscopy ⟨857⟩,* and measure the absorbance at 238 nm: the absorptivity is between 21.0 and 23.2.

Loss on drying ⟨731⟩—Dry it at 105° for 3 hours: it loses not more than 1.5% of its weight.

Residue on ignition ⟨281⟩—Ignite at 600°. Not more than 0.1% residue is found.

Related compounds—

TEST 1 (FOR BENAZEPRIL RELATED COMPOUND A)—

pH 6.0 Phosphate buffer—Dissolve 9.66 g of monobasic potassium phosphate and 2.68 g of dibasic sodium phosphate, heptahydrate in about 900 mL of water, and dilute with water to 1000 mL.

Mobile phase—Prepare a filtered and degassed mixture of *pH 6.0 Phosphate buffer* and methanol (80:20). Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

Resolution solution—Dissolve accurately weighed quantities of USP Benazepril Hydrochloride RS and USP Benazepril Related Compound A RS in *Mobile phase,* and dilute quantitatively, and stepwise if necessary, with *Mobile phase* to obtain a solution having known concentrations of about 1.0 mg per mL and 0.005 mg per mL, respectively.

Standard stock solution—Dissolve an accurately weighed quantity of USP Benazepril Related Compound A RS in *Mobile phase* to obtain a solution having a known concentration of about 0.05 mg per mL.

Standard solution—Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 5 µg per mL.

Dilute standard solution—Dilute a suitable portion of *Standard stock solution,* accurately measured, with *Mobile phase* to obtain a solution having a known concentration of about 1 µg per mL.

Test solution—Transfer about 50 mg of Benazepril Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see Chromatography ⟨621⟩)—The liquid chromatograph is equipped with a 240-nm detector and a 4.0-mm × 10-cm column that contains packing L41. The flow rate is about 0.9 mL per minute. The column temperature is maintained at 30°. Chromatograph the *Resolution solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between benazepril hydrochloride and benazepril related compound A is not less than 2.0. Chromatograph the *Dilute standard solution,* and record the peak responses as directed for *Procedure:* the signal-to-noise ratio is not less than 10:1. Chromatograph the *Standard solution:* the relative standard deviation for replicate injections determined from the benazepril related compound A peak is not more than 10%.

Procedure—Separately inject equal volumes (about 50 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the area for the benazepril related compound A peak. Calculate the percentage of benazepril related compound A in the portion of Benazepril Hydrochloride taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of USP Benazepril Related Compound A RS in the *Standard solution;* C_T is the concentration, in mg per mL, of Benazepril Hydrochloride in the *Test solution;* r_U is the peak response for benazepril related compound A obtained from the *Test solution;* and r_S is the peak response for benazepril related compound A obtained from the *Standard solution:* The limit of benazepril related compound A is given in the table below.

Benazepril Related Compound	Relative Retention Time	Limit (%)
A[1]	2.3	0.1

[1] ((3*R*)-3-[[(1*R*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, monohydrochloride

TEST 2 (FOR BENAZEPRIL RELATED COMPOUNDS B, C, D, E, F, AND G)—

Tetrabutylammonium bromide solution, Mobile phase, System suitability solution, and *Chromatographic system*— Proceed as directed in the *Assay.*

Standard solution—Dissolve accurately weighed quantities of USP Benazepril Hydrochloride RS, USP Benazepril Related Compound B RS, USP Benazepril Related Compound C RS, USP Benazepril Related Compound D RS, USP Benazepril Related Compound E RS, USP Benazepril Related Compound F RS, and USP Benazepril Related Compound G RS in *Mobile phase* to obtain a solution having known concentrations of about 1 µg of USP Benazepril Hydrochloride RS per mL and 10 µg of each related compound per mL.

Test solution—Transfer about 50 mg of Benazepril Hydrochloride, accurately weighed, to a 50-mL volumetric flask, dissolve in and dilute with *Mobile phase* to volume, and mix.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the areas for all the peaks. Calculate the percentage of benazepril related compounds in the portion of Benazepril Hydrochloride taken by the formula:

$$100(C_S/C_T)(r_U/r_S)$$

in which C_S is the concentration, in mg per mL, of the relevant USP Reference Standard in the *Standard solution;* C_T is the concentration, in mg per mL, of benazepril hydrochloride in the *Test solution;* r_U is the peak response for the relevant benazepril related compound obtained from the *Test solution;* and r_S is the peak response for the relevant benazepril related compound obtained from the *Standard solution* (see *Table 1* for values).

Table 1

Benazepril Related Compound	Relative Retention Time	Limit (%)
E[1]	0.4	0.2
F[2]	0.5	0.2
C[3]	0.6	0.3
B[4]	1.5	0.5
D[5]	1.7	0.2
G[6]	2.0	0.2

[1] 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid

[2] *t*-Butyl-3-amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid

[3] 3-(1-Carboxy-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid

[4] Mixture of diastereoisomers (3-(1-ethoxycarbonyl-3-phenyl-(1*R*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid and (3-(1-ethoxycarbonyl-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*R*)-benzazepine)-1-acetic acid

[5] 3-(1-Ethoxycarbonyl-3-cyclohexyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid monohydrochloride

[6] 3-(1-Ethoxycarbonyl-3-phenyl-(1*S*)-propyl)amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine)-1-acetic acid ethyl ester

In addition to not exceeding the limits for benazepril related compounds in *Table 1,* not more than 0.1% of any other single impurity is found; [NOTE—For calculating any other single unspecified impurity, C_S is the concentration of the USP Benazepril Hydrochloride RS in the *Standard solution.*] and not more than 2.0% of total impurities (excluding benazepril related compound A from *Test 1*) is found.

Assay—

Tetrabutylammonium bromide solution—Dissolve 0.81 g of tetrabutylammonium bromide in 360 mL of water containing 0.2 mL of glacial acetic acid.

Mobile phase—Prepare a filtered and degassed mixture of methanol and *Tetrabutylammonium bromide solution* (64:36). Make adjustments if necessary (see *System Suitability* under *Chromatography ⟨621⟩*).

System suitability solution—Dissolve accurately weighed quantities of USP Benazepril Hydrochloride RS and USP Benazepril Related Compound B RS in *Mobile phase* to obtain a solution having known concentrations of about 0.4 mg of each per mL.

Standard preparation—Dissolve an accurately weighed quantity of USP Benazepril Hydrochloride RS in *Mobile phase* to obtain a solution having a known concentration of about 0.2 mg per mL.

Assay preparation—Transfer about 10.0 mL of the *Test solution* (from either *Test 1* or *Test 2*), prepared as directed in the test for *Related compounds,* to a 50-mL volumetric flask, dilute with *Mobile phase* to volume, and mix.

Chromatographic system (see *CHROMATOGRAPHY ⟨621⟩*)—The liquid chromatograph is equipped with a 240-nm detector and a 4.6-mm × 3-cm guard column that contains packing L1 connected to a 3.9-mm × 30-cm column that contains packing L1. The flow rate is about 1 mL per

minute. Chromatograph the *System suitability solution,* and record the peak responses as directed for *Procedure:* the resolution, *R,* between benazepril hydrochloride and benazepril related compound B is not less than 1.7; and the relative standard deviation for replicate injections determined from benazepril hydrochloride and benazepril related compound B is not more than 2.0% for each.

Procedure—Separately inject equal volumes (about 25 µL) of the *Standard preparation* and the *Assay preparation* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the quantity, in mg, of $C_{24}H_{28}N_2O_5 \cdot HCl$ in the portion of Benazepril Hydrochloride taken by the formula:

$$250C(r_U/r_S)$$

in which C is the concentration, in mg per mL, of USP Benazepril Hydrochloride RS in the *Standard preparation;* and r_U and r_S are the peak responses obtained from the *Assay preparation* and the *Standard preparation,* respectively.

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
BENAZEPRIL HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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