## Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules

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| **Type of Posting** | Notice of Intent to Revise |
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| **Expert Committee** | Small Molecules 4 |

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 4 Expert Committee intends to revise the Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to accommodate drug products with different dissolution conditions and tolerances than the existing dissolution test. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

- *Dissolution Test 2* was validated using an Accucore XL C18 brand of column with L1 packing. The typical retention times for clidinium and chlordiazepoxide are about 2.3 and 5.4 min, respectively.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Mary P. Koleck, Principal Scientist (301-230-7420 or mpk@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

*Notice of Intent to Revise*
Official: To Be Determined

# Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules

## DEFINITION

Chlordiazepoxide Hydrochloride and Clidinium Bromide Capsules contain NLT 90.0% and NMT 110.0% of the labeled amounts of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) and clidinium bromide ($C_{22}H_{26}BrNO_3$).

## IDENTIFICATION

● **A.** The retention times of the major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

## ASSAY

● **Procedure**

[Note—Use low-actinic glassware.]

**Buffer:** Dissolve 1.92 g of sodium 1-pentanesulfonate in 900 mL of water in a 1-L volumetric flask. Adjust with 1 N sulfuric acid to a pH of 3.8 ± 0.1. Dilute with water to volume.

**Mobile phase:** Methanol, tetrahydrofuran, and *Buffer* (6:24:70)

**Diluent:** Methanol and water (1:1)

**Standard solution:** 0.1 mg/mL of USP Chlordiazepoxide Hydrochloride RS and 0.05 mg/mL of USP Clidinium Bromide RS in *Diluent*

**Sample solution:** Weigh the contents of NLT 20 Capsules, and calculate the average weight per Capsule. Mix the combined contents of the Capsules, and transfer an amount equivalent to about 5 mg of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$ ) to a 50-mL volumetric flask. Add about 25 mL of *Diluent*, sonicate for 5 min, and shake by mechanical means for 10 min. Dilute with *Diluent* to volume, and filter, discarding the first 20 mL of the filtrate.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 212 nm

**Column:** 8-mm × 10-cm; packing L1

**Flow rate:** 3 mL/min

**Injection size:** 20 µL

**System suitability**

**Sample:** *Standard solution*

[Note—The relative retention times for clidinium bromide and chlordiazepoxide hydrochloride are about 0.5 and 1.0, respectively.]

**Suitability requirements**

**Resolution:** NLT 5.0 between the clidinium bromide and chlordiazepoxide hydrochloride peaks

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) in the portion of Capsules taken:

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

$r_U$ = peak response of chlordiazepoxide hydrochloride from the *Sample solution*

$r_S$ = peak response of chlordiazepoxide hydrochloride from the *Standard solution*

$C_S$ = concentration of USP Chlordiazepoxide Hydrochloride RS in the *Standard solution* (mg/mL)

$C_U$ = nominal concentration of chlordiazepoxide hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of the labeled amount of clidinium bromide ($C_{22}H_{26}BrNO_3$) in the portion of Capsules taken:

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

$r_U$ = peak response of clidinium bromide from the *Sample solution*

$r_S$ = peak response of clidinium bromide from the *Standard solution*

$C_S$ = concentration of USP Clidinium Bromide RS in the *Standard solution* (mg/mL)

$C_U$ = nominal concentration of clidinium bromide in the *Sample solution* (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

***Change to read:***

● **Dissolution**

▲▲ (TBD)

⟨711⟩

▲**Test 1:** Use *Dissolution* ⟨711⟩*, Procedure, Apparatus 1 and Apparatus 2, Immediate-release dosage forms, Procedure for a pooled sample for immediate-release dosage forms.*▲ (TBD)

**Medium:** Water; 900 mL

**Apparatus 1:** 100 rpm

**Time:** 30 min

**Buffer:** Dissolve 1.92 g of sodium 1-pentanesulfonate in 900 mL of water in a 1-L volumetric flask. Adjust with dilute sulfuric acid to a pH of 3.8 ± 0.1. Dilute with water to volume.

**Mobile phase:** Methanol, tetrahydrofuran, and *Buffer* (6:18:75)

**Standard solution:** Prepare a solution having known concentrations of USP Chlordiazepoxide Hydrochloride RS and USP Clidinium Bromide RS in *Medium*.

**Sample solution:** Pass a portion of the solution under test through a suitable filter. Combine equal volumes of the filtered solutions and use the pooled sample for the analysis. Dilute with *Medium* to a concentration that is similar to that of the *Standard solution*, if necessary.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 212 nm

**Column:** 4-mm × 25-cm; packing L1

**Flow rate:** 2 mL/min

**Injection size:** 100 µL

**System suitability**

**Sample:** *Standard solution*

[NOTE—The relative retention times for clidinium bromide and chlordiazepoxide hydrochloride are about 0.6 and 1.0, respectively.]

**Suitability requirements**

**Resolution:** NLT 5.0 between the clidinium bromide and chlordiazepoxide hydrochloride peaks

**Relative standard deviation:** NMT 2.0%

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the average percentage of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) or clidinium bromide ($C_{22}H_{26}BrNO_3$) dissolved:

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

$r_U$ = peak response of chlordiazepoxide hydrochloride or clidinium bromide from the *Sample solution*

$r_S$ = peak response of chlordiazepoxide hydrochloride or clidinium bromide from the *Standard solution*

$C_S$ = concentration of USP Chlordiazepoxide Hydrochloride RS or USP Clidinium Bromide RS in the *Standard solution* (mg/mL)

$L$ = chlordiazepoxide hydrochloride or clidinium bromide label claim (mg)

$V$ = volume of *Medium* (mL), 900

**Tolerances:** NLT 75% ($Q$) each of the labeled amounts of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) and clidinium bromide ($C_{22}H_{26}BrNO_3$) are dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Protect the *Standard stock solution*, *Standard solution*, and *Sample solution* from light.

**Medium:** 0.1N hydrochloric acid; 500 mL

**Apparatus 1:** 100 rpm

**Time:** 30 min

**Buffer:** Transfer 1.36 g of monobasic potassium phosphate to 1000 mL of water. Add 1.0 mL of triethylamine and adjust with 25% phosphoric acid to a pH of 3.6.

**Mobile phase:** Acetonitrile, methanol, and *Buffer* (25:10:65)

**Standard stock solution:** 0.32 mg/mL of USP Chlordiazepoxide Hydrochloride RS and 0.16 mg/mL of USP Clidinium Bromide RS in methanol. Sonicate to dissolve.

**Standard solution:** 0.01 mg/mL of USP Chlordiazepoxide Hydrochloride RS and 0.005 mg/mL of USP Clidinium Bromide RS from the *Standard stock solution*, in *Medium*. Store at 5°.

**Sample solution:** Pass a portion of the solution under test through a suitable PVDF filter of 0.45-µm pore size, discarding the first 5 mL of filtrate. Store at 5°.

**Chromatographic system**

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

**Mode:** LC

**Detector:** UV 212 nm

**Column:** 4.6-mm × 15-cm; 4.0-µm packing L1

**Temperatures**

**Autosampler:** 5°

**Column:** 50°

**Flow rate:** 1 mL/min

**Injection volume:** 25 µL

**Run time:** NLT 2 times the retention time of chlordiazepoxide

**System suitability**

**Sample:** *Standard solution*

[NOTE—The relative retention times for clidinium and chlordiazepoxide are about 0.43 and 1.0, respectively.]

**Suitability requirements**

**Resolution:** NLT 5.0 between clidinium and chlordiazepoxide

**Tailing factor:** NMT 2.0 for clidinium and chlordiazepoxide

**Relative standard deviation:** NMT 2.0% for clidinium and chlordiazepoxide

**Analysis**

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) and clidinium bromide ($C_{22}H_{26}BrNO_3$) dissolved:

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

$r_U$ = peak response of chlordiazepoxide or clidinium from the *Sample solution*

$r_S$ = peak response of chlordiazepoxide or clidinium from the *Standard solution*

$C_S$ = concentration of USP Chlordiazepoxide Hydrochloride RS or USP Clidinium Bromide RS in the *Standard solution* (mg/mL)

$V$ = volume of *Medium*, 500 mL

$L$ = label claim for chlordiazepoxide hydrochloride or clidinium bromide (mg/Capsule)

**Tolerances:** NLT 80% ($Q$) each of the labeled amount of chlordiazepoxide hydrochloride ($C_{16}H_{14}ClN_3O \cdot HCl$) and clidinium bromide ($C_{22}H_{26}BrNO_3$) is dissolved. ▲ (TBD)

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

**IMPURITIES**

- **LIMIT OF CHLORDIAZEPOXIDE RELATED COMPOUND A AND 2-AMINO-5-CHLOROBENZOPHENONE**

**Standard solution A:** 1 mg/mL of USP Chlordiazepoxide Related Compound A RS in acetone

**Standard solution B:** 50 µg/mL of USP 2-Amino-5-chlorobenzophenone RS in acetone

**Sample solution:** Transfer an amount equivalent to 25 mg of chlordiazepoxide hydrochloride from Capsule contents to a 10-mL conical flask, add 2.5 mL of acetone, and shake. Allow any undissolved particles to settle, and use the supernatant.

**Chromatographic system**

(See *Chromatography* ⟨621⟩*, General Procedures, Thin-Layer Chromatography*.)

**Adsorbent:** 0.25-mm layer ofchromatographic silica gel

**Application volume:** 50 µL for the *Sample solution*, 15 µL for *Standard solution A*, and 10 µL for *Standard solution B*

**Developing solvent system:** Ethyl acetate

**Spray reagent:** 2 N sulfuric acid

**Analysis**

**Samples:** *Standard solutions* and *Sample solution*

Proceed as directed in the chapter. Develop the chromatogram in a chromatographic chamber (not previously saturated with the developing solvent) in the *Developing solvent system* until the solvent front has moved three-fourths of the length of the plate. Remove the plate from the developing chamber, mark the solvent front, and allow the solvent to evaporate. Locate the spots on the plate by lightly spraying with *Spray reagent*. Dry at 105° for 15 min, and then spray in succession with sodium nitrite solution (1 in 1000), ammonium sulfamate solution (1 in 200), and *N*-(1-naphthyl)ethylenediamine dihydrochloride solution (1 in 1000).

**Acceptance criteria:** Any spots from the *Sample solution* are not greater in size or intensity than the spots at the respective $R_F$ values produced by the *Standard solutions*, corresponding to NMT 3.0% of chlordiazepoxide related compound A and to NMT 0.1% of 2-amino-5-chlorobenzophenone.

- **Limit of Clidinium Bromide Related Compound A**

**Extracting solvent mixture:** Dehydrated alcohol and cyclohexane (1:1)

**Identification solution:** Dissolve 50 mg of USP Clidinium Bromide RS in 1 mL of 0.1 N methanolic hydrochloric acid. To this solution add 20 µL of a solution of 25 mg/mL of USP Clidinium Bromide Related Compound A RS in methanol. Prepare this solution at the time of use.

**Standard solution:** 50 mg/mL of USP Clidinium Bromide RS in 0.1 N methanolic hydrochloric acid. [Note—Prepare this solution at the time of use.]

**Sample solution:** Empty a number of Capsules, equivalent to 25 mg of clidinium bromide, into a glass-stoppered centrifuge tube, and add 5 mL of the *Extracting solvent mixture*. Heat the tube gently, with shaking, to 50°, centrifuge, and decant the clear supernatant into a second tube. Repeat the addition of *Extracting solvent mixture* twice, heating, centrifuging, and decanting as before, and combine the three extracts in a single tube. Gently heating, evaporate the combined extracts under a stream of nitrogen to dryness. Dissolve the residue in 0.5 mL of methanol.

**Chromatographic system**

(See *Chromatography* ⟨621⟩*, General Procedures, Thin-Layer Chromatography*.)

**Adsorbent:** 0.25-mm layer of chromatographic silica gel mixture

**Application volume:** 20 µL

**Developing solvent system:** Acetone, methanol, water, andhydrochloric acid (70:20:5:5)

**Spray reagent:** Dissolve 850 mg of bismuth subnitrate in a mixture of 10 mL of glacial acetic acid and 40 mL of water. In a separate container, dissolve 20 g of potassium iodide in 50 mL of water. Mix the two solutions, and dilute with dilute sulfuric acid (1 in 10) to 500 mL. Add 7.5 ± 2.5 g of iodine, and mix until solution is complete.

**Chromatographic plates:** Predevelop suitable thin-layer chromatographic plates by placing in a chromatographic chamber saturated with *Developing solvent system*, and allow the *Developing solvent system* to move 15 cm. Remove the plates from the chamber, dry at 105° for 15 min, and cool.

**Analysis**

**Samples:** *Identification solution*, *Standard solution*, and *Sample solution*

Proceed as directed in the chapter. Place the plates in an unsaturated chromatographic chamber containing freshly prepared *Developing solvent system*, and develop the chromatogram until the solvent front has moved 15 cm. Remove the plates, and dry at 105° for 10 min. Cool to room temperature, and spray with *Spray reagent*. Any spot in the chromatogram of the *Sample solution* occurring at an $R_F$ value of 0.4 is not greater in size or intensity than the corresponding spot in the chromatogram of the *Identification solution*; and the *Standard solution* shows no spot at the $R_F$ value corresponding to that of clidinium bromide related compound A.

**Acceptance criteria:** NMT 1.0% of clidinium bromide related compound A

**ADDITIONAL REQUIREMENTS**

- **Packaging and Storage:** Preserve in tight, light-resistant containers.

***Add the following:***

▲● **Labeling:** When more than one *Dissolution* test is used, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (TBD)

- **USP Reference Standards** ⟨11⟩

USP 2-Amino-5-chlorobenzophenone RS

2-Amino-5-chlorobenzophenone.

$C_{13}H_{10}ClNO$ 231.68

USP Chlordiazepoxide Hydrochloride RS

USP Chlordiazepoxide Related Compound A RS

7-Chloro-1,3-dihydro-5-phenyl-2*H*-1,4-benzodiazepin-2-one 4-oxide.

$C_{15}H_{11}ClN_2O_2$ 286.72

USP Clidinium Bromide RS

USP Clidinium Bromide Related Compound A RS

3-Hydroxy-1-methylquinuclidinium bromide.

$C_8H_{16}BrNO$ 222.13

**Page Information:**

Not Applicable

**Current DocID:**