Promethazine Hydrochloride Injection

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Expert Committee: Chemical Medicines Monographs 5
Reason for Revision: Compliance

In accordance with the Rules and Procedures of the 2015-2020 Council of Experts, the Chemical Medicines Monographs 5 Expert Committee has revised the Promethazine Hydrochloride Injection monograph. The purpose for the revision is to widen the limit of Promethazine sulfoxide and the Total impurities based on FDA approval.

Additionally, minor editorial changes have been made to update the monograph to current USP style.

The Promethazine Hydrochloride Injection Revision Bulletin supersedes the currently official Promethazine Hydrochloride Injection monograph. The Revision Bulletin will be incorporated into the USP 41–NF 36.

Should you have any questions, please contact Ren-Hwa Yeh, Ph.D., Senior Scientific Liaison, (301–998–6818 or rhy@usp.org).
Promethazine Hydrochloride Injection

DEFINITION
Promethazine Hydrochloride Injection is a sterile solution of Promethazine Hydrochloride in Water for Injection. It contains NLT 95.0% and NMT 110.0% of the labeled amount of promethazine hydrochloride (C_{17}H_{20}N_{2}S \cdot HCl).

NOTE—Throughout the following procedures, protect the samples, the Reference Standards, and the solutions containing them, by conducting the procedures without delay under subdued light or using low-actinic glassware.

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.

B. The UV spectrum of the major peak of the Sample solution corresponds to that of the Standard solution, as obtained in the Assay.

ASSAY

PROCEDURE

Buffer: 3.7 g/L of ammonium acetate in water
Solution A: Acetonitrile and Buffer (30:70)
Mobile phase: See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Acetonitrile (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>18.1</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>18.1</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>100</td>
<td>0</td>
</tr>
</tbody>
</table>

Diluent: 0.1% triethylamine in methanol
System suitability solution: 1.0 µg/mL each of USP Promethazine Hydrochloride RS and USP Promethazine Related Compound B RS in Diluent
Standard solution: 0.05 mg/mL of USP Promethazine Hydrochloride RS in Diluent
Sample solution: Nominally 0.05 mg/mL of promethazine hydrochloride from a volume of Injection in Diluent

NOTE—Sonication may be used in the preparation of the Sample solution.

System suitability
Sample: Standard solution
NOTE—See Table 2 for the relative retention times.
Suitability requirements
Resolution: NLT 5.0 between the promethazine and promethazine related compound B peaks.
Relative standard deviation: NMT 2.0% for promethazine

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of each degradation product in the portion of Injection taken:

Result = \left( \frac{r_0}{r_u} \right) \times \left( \frac{C_u}{C_0} \right) \times 100

r_0 = peak response from the Sample solution
r_u = peak response from the Standard solution
C_u = concentration of USP Promethazine Hydrochloride RS in the Standard solution (µg/mL)
C_0 = nominal concentration of promethazine hydrochloride in the Sample solution (µg/mL)

Acceptance criteria: 95.0%–110.0%

IMPURITIES

Change to read:

- Organic Impurities

Mobile phase, Diluent, and Chromatographic system: Proceed as directed in the Assay.

Standard solution: 1.0 µg/mL each of USP Promethazine Hydrochloride RS and USP Promethazine Related Compound B RS in Diluent
Sample solution: Nominally 500 µg/mL of promethazine hydrochloride from a volume of Injection in Diluent

NOTE—Sonication may be used in the preparation of the Sample solution.

System suitability
Sample: Standard solution
NOTE—See Table 2 for the relative retention times.
Suitability requirements
Resolution: NLT 5.0 between the promethazine and promethazine related compound B peaks.
Relative standard deviation: NMT 2.0% for promethazine

Analysis

Samples: Standard solution and Sample solution
Calculate the percentage of each degradation product in the portion of Injection taken:

Result = \left( \frac{r_0/r_u} \right) \times \left( \frac{C_u/C_0} \right) \times (1/F) \times 100

r_0 = peak response of each degradation product from the Sample solution
r_u = peak response of promethazine from the Standard solution
C_u = concentration of USP Promethazine Hydrochloride RS in the Standard solution (µg/mL)
C_0 = nominal concentration of promethazine hydrochloride in the Sample solution (µg/mL)
F = relative response factor (see Table 2)

Acceptance criteria: See Table 2. Disregard peaks less than 0.05%.

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Table 2

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promethazine sulfoxide*</td>
<td>0.3</td>
<td>0.29</td>
<td>2.6 (RB 1-Jun-2017)</td>
</tr>
<tr>
<td>Desmethyl promethazineb</td>
<td>0.7</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Promethazine</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Promethazine related compound Bc</td>
<td>1.3</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phenothiazine*</td>
<td>1.7</td>
<td>2.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>2.8 (RB 1-Jun-2017)</td>
</tr>
</tbody>
</table>

* N,N-Dimethyl-1-(10H-phenothiazin-10-yl)propan-2-amine sulfoxide.

b N-Methyl-1-(10H-phenothiazin-10-yl)propan-2-amine.

c This is a process impurity that is controlled in the drug substance and is included for identification only.

d 10H-Phenothiazine.

**SPECIFIC TESTS**

- **BACTERIAL ENDOTOXINS TEST (85):** NMT 5.0 USP Endotoxin Units/mg of promethazine hydrochloride

- **PH (791):** 4.0–5.5
- **OTHER REQUIREMENTS:** It meets the requirements in *Injections and Implanted Drug Products* (1).

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

**Change to read:**

- **USP REFERENCE STANDARDS** (11)
  - USP Endotoxin RS
  - USP Promethazine Hydrochloride RS
  - USP Promethazine Related Compound B RS
  - Isopromethazine hydrochloride; N,N-Dimethyl-2-(10H-phenothiazin-10-yl)propan-1-amine hydrochloride.
  - C17H20N2S.HCl 320.88 (ERR 1-Feb-2017)