Promethazine Hydrochloride Injection

Type of Posting	Revision Bulletin
Posting Date	26–May–2017
Official Date	01–Jun–2017
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 ($C_{17}H_{20}N_2S \cdot HCl$).

[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 1

Time (min)	Solution A (%)	Acetonitrile (%)
0	100	0
10	60	40
18	60	40
18.1	100	0
25	100	0

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 *System suitability solution*, *Standard solution*, and *Sample solution*.]
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 254 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Column: 30°
Autosampler: 4°
Flow rate: 1.4 mL/min
Injection volume: 15 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for promethazine and promethazine related compound B are 1.0 and 1.3, respectively.]
Suitability requirements
Resolution: NLT 5.0 between the promethazine and promethazine related compound B peaks, *System suitability solution*
Tailing factor: NMT 2.0, *Standard solution*
Relative standard deviation: NMT 1.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of promethazine hydrochloride ($C_{17}H_{20}N_2S \cdot HCl$) in the portion of Injection 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 Promethazine Hydrochloride RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of promethazine hydrochloride in the *Sample solution* (mg/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 *Standard solution* and *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:

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

r_U = peak response of each degradation product from the *Sample solution*
r_S = peak response of promethazine from the *Standard solution*
C_S = concentration of USP Promethazine Hydrochloride RS in the *Standard solution* (µg/mL)
C_U = 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%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Promethazine sulfoxide[a]	0.3	0.29	•2.6• (RB 1-Jun-2017)
Desmethyl promethazine[b]	0.7	1.1	0.2
Promethazine	1.0	—	—
Promethazine related compound B[c]	1.3	—	—
Phenothiazine[d]	1.7	2.3	0.2
Any individual unspecified degradation product	—	1.0	0.1
Total degradation products	—	—	•2.8• (RB 1-Jun-2017)

[a] *N,N*-Dimethyl-1-(10*H*-phenothiazin-10-yl)propan-2-amine sulfoxide.
[b] *N*-Methyl-1-(10*H*-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] 10*H*-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-(10*H*-phenothiazin-10-yl)propan-1-amine hydrochloride.
  $C_{17}H_{20}N_2S \cdot HCl$ 320.88• (ERR 1-Feb-2017)