GPO COPY No. 3

THE GOVERNMENT PHARMACEUTICAL ORGANIZATION

RAW MATERIAL SPECIFICATION

Title: Chlorpromazine Hydrochloride USP (For injection dosage form) (Item No. 41031420)	**Spec. No.** : SP-AK30-C24/1
Reference(s) : USP 41 p. 906	**Rev. No.** : 05
Other Requirements : GPO Specification	**Page** : 1/2

USP 41

Test Items	Specification
Description	White or slightly creamy white, odorless, crystalline powder.
Solubility	Very soluble in water, freely soluble in alcohol and in chloroform; insoluble in ether and in benzene.
Identification A. Infrared absorption <197K> B. Thin layer chromatography C. Chloride Test	 Conforms to IR standard spectrum. The principal spot found in the test for *Other alkylated phenothiazines* corresponds in R_f to the spot from the Standard solution. A white, curdy precipitate is formed which is insoluble in nitric acid but is soluble in a slight excess of ammonia.
Melting range	Between 195 °C and 198 °C.
Loss on drying	Not more than 0.5%.
Residue on ignition	Not more than 0.1%.
Other alkylated phenothiazines	The area and intensity of any spot, other than the principal spot, from the solution of Chlorpromazine Hydrochloride are not greater than those of the spot from the Diluted standard solution (0.5%).
Assay	98.0 – 101.5% of $C_{17}H_{19}ClN_2S \cdot HCl$, calculated on the dried basis.

GPO Specification

Test Items	Specification
Bacterial endotoxin	Not more than 6.9 USP Endotoxin Units per mg of Chlorpromazine HCl.

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ใช้ในการจัดซื้อ

Prepared by :		Reviewed by :			Approved by :	Eff. Date
Suwannee, 25/07/19 Head of Raw Material Standard Section I	Benjawan Ubonklee, 26/07/19 Head of Microbiological Analysis Section I	26/07/19 Director of Raw Material Standard Division	19/08/19 Director of Microbiological Analysis Division	19/08/19 Director of Regulatory Compliance and Documentation Division	20/08/19 Director of Quality Assurance Department (Acting)	30/10/19

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Product Information

Approved source (s)	Refer to current version of Approved Vendor List of Chlorpromazine Hydrochloride USP (For injection dosage form) (Item No. 41031420).
Sampling plan	1. N Plan ($\sqrt{N}+1$) : for other tests. 2. 100% Identification.
Testing procedure	Tests to be performed as per current version of WI-AK30-C24/1.
Storage condition	Preserve in tight, light-resistant containers.
Retest period	1 year after first testing date.

History of changes

Rev. No.	Description	Effective date
03	อ้างอิง spec. เป็น BP 2011	17/10/11
04	Update spec. เป็น BP 2016 อ้างอิง CR No. AN80-59089 เนื่องจากเอกสารมีอายุมากกว่า 3 ปี จึงต้องทบทวน	24/05/16
05	Update spec. เป็น USP 41 อ้างอิงมติที่ประชุม Site transfer	30/10/19

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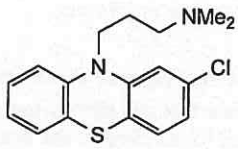
ใช้ในการจัดซื้อ

Prepared by :		Reviewed by :			Approved by :	Eff. Date
25/07/19	26/07/19	20/09/19	16/08/19	19/8/19	30/08/19	30/10/19
Head of Raw Material Standard Section I	Head of Microbiological Analysis Section I	Director of Raw Material Standard Division	Director of Microbiological Analysis Division	Director of Regulatory Compliance and Documentation Division	Director of Quality Assurance Department	

Chlorpromazine



$C_{17}H_{19}ClN_2S$ 318.9 *50-53-3*

Action and use
Dopamine receptor antagonist; neuroleptic.

Preparation
Chlorpromazine Suppositories

DEFINITION
Chlorpromazine is [3-(2-chlorophenothiazin-10-yl)propyl]-dimethylamine. It contains not less than 99.0% and not more than 101.0% of $C_{17}H_{19}ClN_2S$, calculated with reference to the dried substance.

CHARACTERISTICS
A white or creamy white powder or waxy solid.

Practically insoluble in *water*; freely soluble in *ethanol (96%)* and in *ether*.

IDENTIFICATION
A. The *infrared absorption spectrum*, Appendix II A, is concordant with the *reference spectrum* of chlorpromazine *(RS 056)*.

B. Complies with the test for *identification of phenothiazines*, Appendix III A, using *chlorpromazine hydrochloride BPCRS* to prepare reference solution.

TESTS
Melting point
56° to 58°, Appendix V A.

Related substances
Complies with the test for *related substances in phenothiazines*, Appendix III A, using *mobile phase A*.

Loss on drying
When dried to constant weight over *phosphorus pentoxide* at a pressure not exceeding 0.7 kPa, loses not more than 0.5% of its weight. Use 1 g.

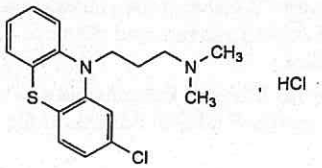
Sulfated ash
Not more than 0.1%, Appendix IX A.

ASSAY
Dissolve 0.8 g in 300 mL of *acetone* and carry out Method I for *non-aqueous titration*, Appendix VIII A, using 3 mL of a saturated solution of *methyl orange* in *acetone* as indicator. Each mL of 0.1M *perchloric acid VS* is equivalent to 31.89 mg of $C_{17}H_{19}ClN_2S$.

STORAGE
Chlorpromazine should be protected from light.

Chlorpromazine Hydrochloride

(Ph. Eur. monograph 0475)



$C_{17}H_{20}Cl_2N_2S$ 355.3 69-09-0

Action and use
Dopamine receptor antagonist; neuroleptic.

Preparations
Chlorpromazine Injection
Chlorpromazine Oral Solution
Chlorpromazine Tablets

Ph Eur

DEFINITION
3-(2-Chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine hydrochloride.

Content
99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS
Appearance
White or almost white, crystalline powder.

Solubility
Very soluble in water, freely soluble in ethanol (96 per cent).

It decomposes on exposure to air and light.

It shows polymorphism (*5.9*).

IDENTIFICATION
First identification B, D.

Second identification A, C, D.

A. Ultraviolet and visible absorption spectrophotometry (*2.2.25*). *Prepare the solutions protected from bright light and measure the absorbances immediately.*

Test solution Dissolve 50.0 mg in a 10.3 g/L solution of *hydrochloric acid R* and dilute to 500.0 mL with the same solution. Dilute 5.0 mL of the solution to 100.0 mL with a 10.3 g/L solution of *hydrochloric acid R*.

Spectral range 230-340 nm.

Absorption maxima At 254 nm and 306 nm.

Specific absorbance at the absorption maximum at 254 nm 890 to 960.

✓ B. Infrared absorption spectrophotometry (*2.2.24*).

Preparation 60 g/L solutions in *methylene chloride R* using a 0.1 mm cell.

Comparison chlorpromazine hydrochloride CRS.

C. Identification of phenothiazines by thin-layer chromatography (*2.3.3*): use *chlorpromazine hydrochloride CRS* to prepare the reference solution.

✓ D. It gives reaction (b) of chlorides (*2.3.1*).

TESTS
pH (*2.2.3*)
3.5 to 4.5. *Carry out the test protected from light and use freshly prepared solutions.*

Dissolve 1.0 g in *carbon dioxide-free water R* and dilute to 10 mL with the same solvent.

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Impurity F

Thin-layer chromatography (*2.2.27*). *Prepare the solutions immediately before use and protect from light.*

Solvent mixture diethylamine R, methanol R (5:95 *V/V*).

Test solution Dissolve 0.100 g of the substance to be examined in the solvent mixture and dilute to 5.0 mL with the solvent mixture.

Reference solution (a) Dissolve the contents of a vial of *chlorpromazine impurity F CRS* in 2.0 mL of the solvent mixture.

Reference solution (b) Dilute 300 µL of reference solution (a) to 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 0.10 g of the substance to be examined in the solvent mixture, add 1.0 mL of reference solution (a) and dilute to 5.0 mL with the solvent mixture.

Plate TLC silica gel F_{254} plate R.

Mobile phase acetone R, diethylamine R, cyclohexane R (10:10:80 *V/V/V*).

Application 10 µL of the test solution and reference solutions (b) and (c).

Development Over 3/4 of the plate.

Drying In air.

Detection Examine in ultraviolet light at 254 nm.

Retardation factors Impurity F = about 0.5; chlorpromazine = about 0.6.

System suitability: reference solution (c):
— the chromatogram shows 2 clearly separated spots due to impurity F and chlorpromazine.

Limit:
— *impurity F*: any spot due to impurity F is not more intense than the spot in the chromatogram obtained with reference solution (b) (0.15 per cent).

Related substances

Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use and protect from light.*

Test solution Dissolve 40.0 mg of the substance to be examined in the mobile phase and dilute to 100.0 mL with the mobile phase.

Reference solution (a) Dissolve 4 mg of *chlorpromazine impurity D CRS* in the mobile phase and dilute to 10.0 mL with the mobile phase. To 1 mL of the solution add 1 mL of the test solution and dilute to 100.0 mL with the mobile phase.

Reference solution (b) Dilute 1.0 mL of the test solution to 20.0 mL with the mobile phase. Dilute 1.0 mL of this solution to 10.0 mL with the mobile phase.

Reference solution (c) Dissolve 4.0 mg of *chlorpromazine impurity A CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Reference solution (d) Dissolve 4 mg of *promazine hydrochloride CRS* (impurity C) and 4.0 mg of *chlorpromazine impurity E CRS* in the mobile phase and dilute to 100.0 mL with the mobile phase. Dilute 1.0 mL of the solution to 100.0 mL with the mobile phase.

Column:
— *size*: l = 0.25 m, Ø = 4.0 mm;
— *stationary phase*: *base-deactivated octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase Mix 0.2 volumes of *thiodiethylene glycol R* with 50 volumes of *acetonitrile R* and 50 volumes of a 0.5 per cent *V/V* solution of *trifluoroacetic acid R* previously adjusted to pH 5.3 with *tetramethylethylenediamine R*.

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 254 nm.

Injection 10 µL.

Run time 4 times the retention time of chlorpromazine.

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (d) to identify the peaks due to impurities C and E; use the chromatogram obtained with reference solution (a) to identify the peak due to impurity D.

Relative retention With reference to chlorpromazine (retention time = about 8 min): impurity A = about 0.4; impurity B = about 0.5; impurity C = about 0.7; impurity D = about 0.9; impurity E = about 3.4.

System suitability: reference solution (a):
— *resolution*: minimum 2.0 between the peaks due to impurity D and chlorpromazine.

Limits:
— *impurities B, C, D*: for each impurity, not more than 0.6 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent);
— *impurity A*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (c) (0.15 per cent);
— *impurity E*: not more than 1.5 times the area of the corresponding peak in the chromatogram obtained with reference solution (d) (0.15 per cent);
— *unspecified impurities*: for each impurity, not more than 0.2 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.10 per cent);
— *total*: maximum 1.0 per cent;
— *disregard limit*: 0.1 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

Heavy metals (*2.4.8*)

Maximum 10 ppm.

Solvent water R.

0.25 g complies with test H. Prepare the reference solution using 0.25 mL of *lead standard solution (10 ppm Pb) R.*

Loss on drying (*2.2.32*)

Maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 5.0 mL of *0.1 M hydrochloric acid* and 50 mL of *ethanol (96 per cent) R*. Carry out a potentiometric titration (*2.2.20*), using *0.1 M sodium hydroxide*. Read the volume added between the 2 points of inflexion.

1 mL of *0.1 M sodium hydroxide* is equivalent to 35.53 mg of $C_{17}H_{20}Cl_2N_2S$.

STORAGE

In an airtight container, protected from light.

IMPURITIES

Specified impurities A, B, C, D, E, F

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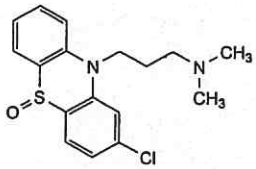
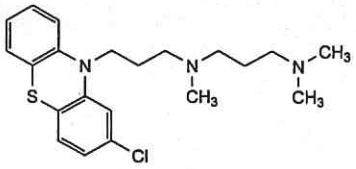
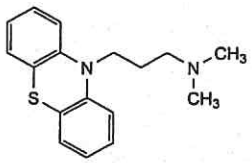


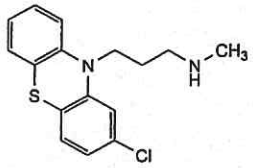
A. 3-(2-chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine *S*-oxide (chlorpromazine sulfoxide),



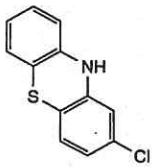
B. *N*-[3-(2-chloro-10*H*-phenothiazin-10-yl)propyl]-*N*,*N*′,*N*′-trimethylpropane-1,3-diamine,



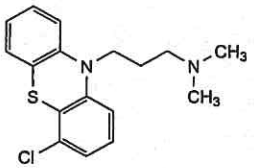
C. 3-(10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine (promazine),



D. 3-(2-chloro-10*H*-phenothiazin-10-yl)-*N*-methylpropan-1-amine (desmethylchlorpromazine),



E. 2-chloro-10*H*-phenothiazine,

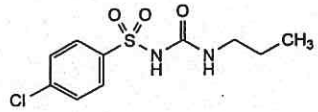


F. 3-(4-chloro-10*H*-phenothiazin-10-yl)-*N*,*N*-dimethylpropan-1-amine.

Ph Eur

Chlorpropamide

(Ph. Eur. monograph 1087)



$C_{10}H_{13}ClN_2O_3S$ 276.7 94-20-2

Action and use
Inhibition of ATP-dependent potassium channels (sulfonylurea); treatment of diabetes mellitus.

Preparation
Chlorpropamide Tablets

Ph Eur

DEFINITION

Chlorpropamide contains not less than 99.0 per cent and not more than the equivalent of 101.0 per cent of 1-[(4-chlorophenyl)sulfonyl]-3-propylurea, calculated with reference to the dried substance.

CHARACTERS

A white or almost white, crystalline powder, practically insoluble in water, freely soluble in acetone and in methylene chloride, soluble in alcohol. It dissolves in dilute solutions of alkali hydroxides.

It shows polymorphism (*5.9*).

IDENTIFICATION

First identification C, D

Second identification A, B, D

A. Melting point (*2.2.14*): 126 °C to 130 °C.

B. Dissolve 0.10 g in *methanol R* and dilute to 50.0 mL with the same solvent. Dilute 5.0 mL of the solution to 100.0 mL with *0.01 M hydrochloric acid*. Dilute 10.0 mL of the solution to 100.0 mL with *0.01 M hydrochloric acid*. Examined between 220 nm and 350 nm (*2.2.25*), the solution shows an absorption maximum at 232 nm. The specific absorption at the maximum is 570 to 630.

C. Examine by infrared absorption spectrophotometry (*2.2.24*), comparing with the spectrum obtained with *chlorpropamide CRS*. Examine the substances prepared as discs. If the spectra obtained show differences, dissolve the substance to be examined and the reference substance in *methylene chloride R*, evaporate to dryness and record the new spectra using the residues.

D. Heat 0.1 g with 2 g of *anhydrous sodium carbonate R* until a dull red colour appears for 10 min. Allow to cool, extract the residue with about 5 mL of *water R*, dilute to 10 mL with *water R* and filter. The solution gives the reaction (a) of chloride (*2.3.1*).

TESTS

Related substances

Examine by thin-layer chromatography (*2.2.27*), using a suitable silica gel as the coating substance.

Test solution Dissolve 0.50 g of the substance to be examined in *acetone R* and dilute to 10 mL with the same solvent.

Reference solution (a) Dissolve 15 mg of *4-chlorobenzenesulfonamide R* (chlorpropamide impurity A) in *acetone R* and dilute to 100 mL with the same solvent.

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