# Phenytoin Injection

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Manufacturers, regulatory authorities, health authorities, researchers, and other stakeholders are invited to provide their feedback and comments on this draft proposal. Comments and samples received after the last date will not be considered by the IPC before finalizing the monograph.

**Please send any comments you may have on this draft document to lab.ipc@gov.in, with a copy to Dr. Gaurav Pratap Singh (email: gpsingh.ipc@gov.in) before the last date for comments.**

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# Phenytoin Injection

Phenytoin sodium Injection

Phenytoin Injection is a sterile solution of Phenytoin Sodium with propylene glycol and alcohol in water for injections.

Phenytoin Injection contains not less than 95.0 per cent and not more than 105.0 per cent of the stated amount of phenytoin sodium, $C_{15}H_{11}N_2NaO_2$.

**Usual strength**. 50 mg per ml.

**Description**. A colourless solution.

## Identification

A. Transfer a suitable volume of the injection containing 0.25 g of Phenytoin sodium to a separator containing 25 ml of *water*. Extract first with 50 ml of *ethyl acetate* and then with two additional 30 ml of portions of *ethyl acetate*. Wash each extract with two 20 ml portions of 1 per cent w/v solution of *sodium acetate*. Evaporate the combine ethyl acetate extracts and dry the residue of phenytoin at 105° to constant weight. On the residue, determine by infrared absorption spectrophotometry (2.4.6). Compare the spectrum with that obtained with *phenytoin IPRS* or with the reference spectrum of phenytoin.

B. In the Assay, the principal peak in the chromatogram obtained with test solution (b) corresponds to the peak in the chromatogram obtained with reference solution (a).

## Tests

**pH** (2.4.24). 11.5 to 12.1.

**Weight per ml** (2.4.29). 1.025 g to 1.035 g.

**Ethanol and Propylene glycol content**. 9.0 per cent v/v to 11.0 per cent v/v of ethanol and 37.0 per cent v/v to 43.0 per cent v/v of propylene glycol.

Determined by gas chromatography (2.4.13).

*Internal standard solution*. A solution containing 2 per cent v/v of *methanol* and 4 per cent v/v of *ethylene glycol* in *water*.

*Test solution*. Dilute a suitable volume of the injection containing 50 mg of Phenytoin sodium into a 100-ml volumetric flask, add 50.0 ml of the internal standard solution and dilute to volume with *water*.

*Reference solution*. A solution containing 1 per cent v/v of *ethanol* and 4 per cent w/v of *propylene glycol* in *water*. Dilute 5.0 ml of the solution to 10.0 ml with the internal standard solution

Chromatographic system
– a fused silica capillary column 30 m x 0.53 mm, bonded to polyethylene glycol (film thickness 1 µm) (such as DB-wax),
– temperature:
column. 50º for 4 minutes, 50º to 230º @ 15º per minute and hold at 230º for 5 minutes,
– inlet port at 240° and detector at 250°,
– flame ionization detector,
– split ratio: 1:10,

– flow rate: 5 ml per minute, using helium as the carrier gas,
– injection volume: 0.2 µl.

| Name | Relative retention time |
|---|---|
| Methanol | 0.27 |
| Ethanol | 0.32 |
| Propylene glycol | 0.98 |
| Ethylene glycol | 1.0 |

Inject the reference solution. The test is not valid unless the resolution between the peak due to methanol and ethanol is not less than 5.0, between the peak due to propylene glycol and Ethylene glycol is not less than 5.0 and the relative standard deviation for replicate injections is not more than 2.0 per cent, for ethanol and propylene glycol peaks.

Inject the reference solution and the test solution. Calculate the percentage of ethanol and propylene glycol in the portion of the injection by using ratio of the area of the peak due to ethanol to the area of the peak due to methanol and the ratio of the area of the peak due to propylene glycol to the area of the peak due to ethylene glycol in the chromatogram obtained with the reference solution and the test solution.

**Related substances**. Determine by liquid chromatography (2.4.14).

*NOTE — Prepare the solutions immediately before use.*

*Test solution (a)*. Dilute a suitable volume of the injection containing 50 mg of Phenytoin Sodium with the mobile phase, and dilute to 50.0 ml with the mobile phase

*Test solution (b)*. Dilute 1.0 ml of test solution (a) to 10.0 ml with the mobile phase.

*Reference solution (a).* A 0.01 per cent w/v solution of *phenytoin sodium IPRS* in the mobile phase.

*Reference solution (b).* Dilute 2.0 ml of reference solution (a) to 100.0 ml with the mobile phase.

*Reference solution (c)*. A solution containing 0.1 per cent w/v of *phenytoin sodium IPRS*, 0.0002 per cent w/v of *diphenylglycoluril IPRS* and 0.003 per cent w/v of *phenytoin related compound B IPRS* in the mobile phase.

Chromatographic system
- a stainless steel column 25 cm × 4.6 mm, packed with end-capped octadecylsilane bonded to porous silica (5 µm) (such as YMC Pack ODS AQ 18),
- sample temperature: 5°,
- mobile phase: a mixture of 45 volumes of *0.05 M ammonium dihydrogen orthophosphate*, adjusted to pH 2.5 with *orthophosphoric acid*, 20 volumes of *methanol* and 35 volumes of *acetonitrile*,
- flow rate: 1.5 ml per minute,
- spectrophotometer set at 220 nm,
- injection volume: 20 µl.

| Name | Relative retention time | Correction factor |
|---|---|---|
| Phenytoin related compound A[1] | 0.5 | --- |
| Diphenylglycoluril[2] | 0.6 | 1.7 |
| Phenytoin related compound B[3] | 0.8 | 1.4 |
| Phenytoin (Retention time: about 4 minutes) | 1.0 | --- |
| Benzophenone[4] | 3.2 | --- |
| Benzil[5] | 3.8 | --- |

[1]2,2-diphenylglycine,
[2]3a,6a-diphenyltetrahydroimidazo[4,5-d]imidazole-2,5(1*H*,3*H*)-dione,
[3] 2,2-diphenyl-2-ureidoacetic acid,
[4]diphenylmethanone,
[5]diphenylethanedione.

Inject reference solution (b) and (c). The test is not valid unless the resolution between the peaks due to diphenylglycoluril and phenytoin related compound B is not less than 3.5 in the chromatogram obtained with reference solution (c) and the signal to noise ratio is not less than 40 in the chromatogram obtained with reference solution (b).

Inject reference solution (b) and test solution (a). Run the chromatogram 4 times the retention time of the principal peak for test solution (a). In the chromatogram obtained with test solution (a), the area of any peak corresponding to phenytoin related compound B is not more than 1.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.3 per cent), the area of any other secondary peak is not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (0.2 per cent) and the sum of the areas of all the secondary peaks is not more than 2.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.5 per cent). Ignore any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

**Other tests**. Comply with the tests stated under Parenteral Preparations (Injections).

**Assay**. Determine by liquid chromatography (2.4.14), as described under Related substances with the following modifications.

Inject reference solution (c). The test is not valid unless the resolution between the peaks due to diphenylglycoluril and phenytoin related compound B is not less than 3.5.

Inject reference solution (a) and test solution (b).

Calculate the content of $C_{15}H_{11}N_2NaO_2$ in the injection.

**Storage**. Store protected from light. Solutions in which a haziness or precipitate develops should not be used.