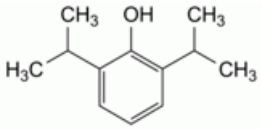
Edition: BP 2025 (Ph. Eur. 11.6 update)

# Propofol

General Notices

*(Ph. Eur. monograph 1558)*



$C_{12}H_{18}O$ 178.3 *2078-54-8*

**Action and use**

Intravenous general anaesthetic.

**Preparation**

Propofol Injection

Ph Eur

## DEFINITION

2,6-Bis(1-methylethyl)phenol.

**Content**

98.0 per cent to 102.0 per cent.

This monograph applies to propofol prepared using distillation for purification.

## CHARACTERS

**Appearance**

Colourless or very light yellow, clear liquid.

**Solubility**

Very slightly soluble in water, miscible with hexane and with methanol.

## IDENTIFICATION

Infrared absorption spectrophotometry (2.2.24).

*Comparison* propofol CRS.

## TESTS

**Refractive index** (2.2.6)

1.5125 to 1.5145.

**Related substances**

Liquid chromatography (2.2.29).

*Test solution (a)* Dissolve 1.00 g of the substance to be examined in hexane R and dilute to 10.0 mL with the same solvent.

*Test solution (b)* Dissolve 0.240 g of the substance to be examined in hexane R and dilute to 100.0 mL with the same solvent.

*Reference solution (a)* Dissolve 5 µL of the substance to be examined and 15 µL of propofol impurity J CRS in hexane R and dilute to 50.0 mL with the same solvent.

*Reference solution (b)* Dilute 0.1 mL of propofol for peak identification CRS (containing impurities E and G) to 1.0 mL with hexane R.

*Reference solution (c)* Dilute 1.0 mL of test solution (a) to 100.0 mL with hexane R. Dilute 1.0 mL of this solution to 10.0 mL with hexane R.

*Reference solution (d)* Dissolve 0.240 g of propofol CRS in hexane R and dilute to 100.0 mL with the same solvent.

*Column*:

— *size*: *l* = 0.20 m, *Ø* = 4.6 mm;

— *stationary phase*: silica gel for chromatography R (5 µm).

*Mobile phase* anhydrous ethanol R, acetonitrile R, hexane R (1.0:7.5:990 *V/V/V*).

*Flow rate* 2.0 mL/min.

*Detection* Spectrophotometer at 275 nm.

*Injection* 10 µL of test solution (a) and reference solutions (a), (b) and (c).

*Run time* 7 times the retention time of propofol.

*Identification of impurities* Use the chromatogram obtained with reference solution (b) to identify the peaks due to impurities G and E.

*Relative retention* With reference to propofol (retention time = about 3 min): impurity G = about 0.5; impurity I = about 0.6; impurity B = about 0.7; impurity N = about 2.3; impurity D = about 2.5; impurity P = about 2.9; impurity A = about 3.0; impurity C = about 3.4; impurity E = about 4.0; impurity F = about 5.8; impurity H = about 6.4.

*System suitability* Reference solution (a):

— resolution: minimum 4.0 between the peaks due to impurity J and propofol.

*Limits*:

— *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity E = 0.25; impurity G = 5.0;

— *impurity G*: not more than twice the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.2 per cent);

— *impurity E*: not more than 0.1 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.01 per cent);

— *unspecified impurities*: for each impurity, not more than 0.5 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.05 per cent);

— *total*: not more than 3 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.3 per cent);

— *disregard limit*: 0.3 times the area of the peak due to propofol in the chromatogram obtained with reference solution (c) (0.03 per cent), except for impurity E.

**Impurities J, K, L and O**

Gas chromatography (*2.2.28*).

*Test solution* Dissolve 40.0 mg of the substance to be examined in *methylene chloride R* and dilute to 10.0 mL with the same solvent.

*Reference solution (a)* Dilute 1.0 mL of the test solution to 100.0 mL with *methylene chloride R*. Dilute 1.0 mL of this solution to 10.0 mL with *methylene chloride R*.

*Reference solution (b)* Dissolve 5 µL of *propofol impurity J CRS* (corresponding to 5 mg) in *methylene chloride R* and dilute to 100 mL with the same solvent. Dilute 1.0 mL of this solution to 25 mL with *methylene chloride R*.

*Reference solution (c)* Dissolve 4 mg of *propofol CRS* in reference solution (b) and dilute to 1 mL with the same solution.

*Column*:

— *material*: fused silica;

— *size*: *l* = 30 m, Ø = 0.32 mm;

— *stationary phase*: *phenyl(50)methyl(50)polysiloxane R* (film thickness 0.5 µm).

*Carrier gas* *helium for chromatography R*.

*Flow rate* 1.7 mL/min.

*Split ratio* 1:5.

*Temperature*:

| | Time (min) | Temperature (°C) |
|---|---|---|
| Column | 0 - 3 | 80 |
| | 3 - 25 | 80 → 210 |
| | 25 - 40 | 210 |
| Injection port | | 100 |
| Detector | | 270 |

*Detection* Flame ionisation.

*Injection* 1 µL of the test solution and reference solutions (a) and (c).

*Relative retention* With reference to propofol (retention time = about 17 min): impurity K = about 0.76; impurity L = about 0.81; impurity J = about 1.01; impurity O = about 1.03.

*System suitability* Reference solution (c):

— *peak-to-valley ratio*: minimum 3.0, where $H_p$ = height above the baseline of the peak due to impurity J, and $H_v$ = height above the baseline of the lowest point of the curve separating this peak from the peak due to propofol.

*Limits*:

— *impurities J, K, L, O*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

## ASSAY

Liquid chromatography (2.2.29) as described in the test for related substances with the following modification.

*Injection* Test solution (b) and reference solution (d).

Calculate the percentage content of $C_{12}H_{18}O$ using the declared content of *propofol CRS*.

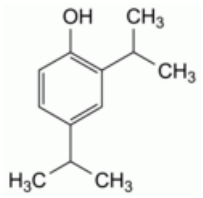
## STORAGE

Protected from light under an inert gas.

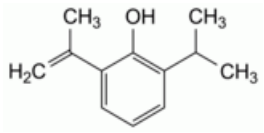
## IMPURITIES

*Specified impurities* *E, G, J, K, L, O.*

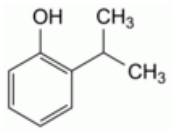
*Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical use (2034). It is therefore not necessary to identify these impurities for demonstration of compliance. See also 5.10. Control of impurities in substances for pharmaceutical use)* *A, B, C, D, F, H, I, N, P.*



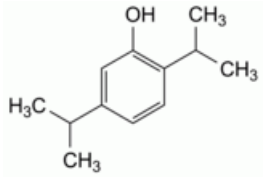

A. 2,4-bis(1-methylethyl)phenol,



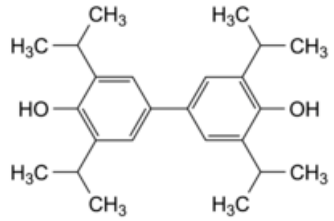

B. 2-(1-methylethenyl)-6-(1-methylethyl)phenol,



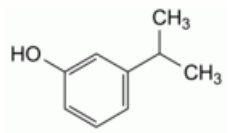

C. 2-(1-methylethyl)phenol,



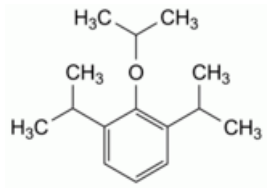

D. 2,5-bis(1-methylethyl)phenol,



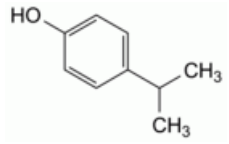
E. 3,3′,5,5′-tetrakis(1-methylethyl)biphenyl-4,4′-diol,



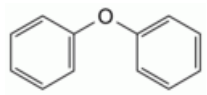
F. 3-(1-methylethyl)phenol,



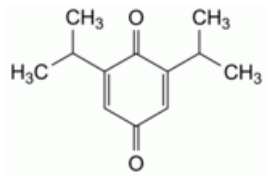
G. 2-(1-methylethoxy)-1,3-bis(1-methylethyl)benzene,



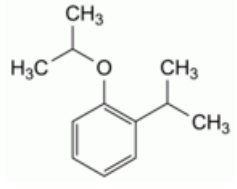
H. 4-(1-methylethyl)phenol,



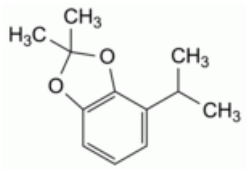
I. oxydibenzene,



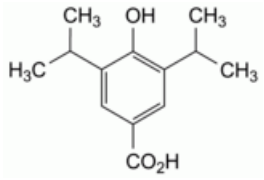
J. 2,6-bis(1-methylethyl)benzene-1,4-dione,



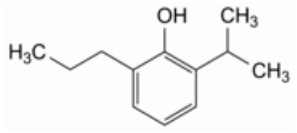
K. 1-(1-methylethoxy)-2-(1-methylethyl)benzene,



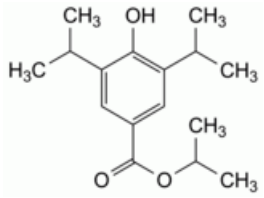
L. 2,2-dimethyl-4-(1-methylethyl)-1,3-benzodioxole,



N. 4-hydroxy-3,5-bis(1-methylethyl)benzoic acid,



O. 2-(1-methylethyl)-6-propylphenol,



P. 1-methylethyl 4-hydroxy-3,5-bis(1-methylethyl)benzoate.

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Ph Eur