Propofol Injection

General Notices

Details for the public consultation of this monograph are as follows:

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<thead>
<tr>
<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 1</th>
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<td>Deadline for Comment</td>
<td>30th September 2019</td>
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<td>Target Publication Date (subject to change)</td>
<td>BP 2021</td>
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Notes:

Revised monograph
If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.
Production: globule size controlled through production statement
Identification B: test deleted
Globule size: test deleted
Lysolecithin: method revised
Assay: weight per mL content determination added

Action and use

Intravenous general anaesthetic.

DEFINITION

Propofol Injection is a sterile emulsion of Propofol in a suitable basis.

The injection complies with the requirements stated under Parenteral Preparations and with the following requirements.

PRODUCTION

The formulation and production of Propofol injection are designed to control the globule size distribution of the injection. They ensure that, at any stage of the life cycle of the product, when tested by a suitable method which has been approved by the competent authority, compliance with the specified limit is achieved.

Where soya lecithins are present in the formulation, a suitable test is carried out to demonstrate that the content of soya lysolecithin is not more than 0.2% w/v.

Content of propofol, $C_{12}H_{18}O$
95.0 to 105.0% of the stated amount.

IDENTIFICATION

Extract a volume of the injection containing 0.1 g of Propofol with three 25-mL quantities of hexane and filter the combined extracts using a glass fibre filter (Whatman GF/C is suitable). Extract the filtrate with two 20-mL quantities of methanol (90%) and evaporate the combined extracts under reduced pressure. Dissolve the residue obtained in 2 mL of absolute ethanol and evaporate to dryness under reduced pressure. Dry the residue at 50° over phosphorus pentoxide for 1 hour. The infrared absorption spectrum of the residue, Appendix II A, is concordant with the reference spectrum of Propofol (RS 416).

TESTS

Acidity or alkalinity

pH, 6.0 to 8.5, Appendix V L.

Propofol quinone and propofol dimer

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of the well shaken injection with propan-2-ol to produce a solution containing 0.08% w/v of Propofol.
(2) 0.0008% w/v of propofol BPCRS, 0.00008% w/v of propofol impurity J BPCRS (propofol quinone) and 0.0002% w/v of propofol dimer BPCRS (impurity E) in propan-2-ol containing 6.8% v/v of water.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 4.6 mm) packed with octadecylsilyl silica gel for chromatography (5 µm) (Hypersil ODS is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2.0 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 254 nm.
(f) Inject 20 µL of each solution.
(g) For solution (1), allow the chromatography to proceed for at least three times the retention time of the principal peak.

MOBILE PHASE

40 volumes of tetrahydrofuran and 60 volumes of water.

When the chromatograms are recorded using the prescribed conditions, the relative retentions with reference to propofol (retention time about 7 minutes) are: impurity J, about 0.8 and impurity E about 2.5.

SYSTEM SUITABILITY

The test is not valid unless the resolution between the peaks due to propofol and impurity J is at least 2.5.

LIMITS

In the chromatogram obtained with solution (1):
the area of any peak corresponding to impurity E (propofol dimer) is not greater than the area of the peak due to
impurity E in the chromatogram obtained with solution (2) (0.25%);

the area of any peak corresponding to impurity J (propofol quinone) is not greater than the area of the peak due to
impurity J in the chromatogram obtained with solution (2) (0.1%).

Free fatty acid

Not greater than 7 millimoles per litre, when determined by the following method. To 5 mL of a well shaken injection
add 25 mL of a mixture of 40 volumes of propan-2-ol, 10 volumes of n-heptane and 1 volume of 0.5M sulfuric acid
and shake for 1 minute. Allow to stand for 10 minutes, add 15 mL of n-heptane and 15 mL of water. Mix by inverting
the container 10 times and allow to stand for 15 minutes. To 15 mL of the upper phase add 5 mL of aqueous nile
blue A solution and pass a stream of nitrogen, previously passed through 0.1M sodium hydroxide, through the
solution. Titrate with 0.02M sodium hydroxide VS, using a microburette. Calculate the content of free fatty acid from
a calibration curve prepared from quantities of 1, 2, 4, 6 and 8 mL of a 1.282% w/v solution of palmitic acid
in n-heptane, each diluted to 50 mL with n-heptane. Carry out the method described above, using 5 mL of each
solution and beginning at the words ‘add 25 mL of a mixture…’.

Lysolecithin

For injections containing egg lecithins

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

(1) Dilute a suitable volume of well shaken injection with ethanol to produce a solution containing 0.1% w/v of
Propofol. Centrifuge and filter the supernatant liquid through a 0.45-μm nylon filter.

(2) 0.01% w/v of lysophosphatidylcholine from egg yolk EPCRS (lysolecithin) in ethanol.

(3) 0.1% w/v each of lysophosphatidylcholine from egg yolk EPCRS (lysolecithin) and L-α-lecithin from egg yolk in
ethanol.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (10 cm × 2.1 mm) packed with silica gel for chromatography (5 μm) (Kromasil Sil
is suitable).

(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 0.2 mL per minute.

(d) Use a column temperature of 40°.

(e) Use a detection wavelength of 268 nm.

(f) Inject 40 μL of each solution.

MOBILE PHASE

16 volumes of water, 16.5 volumes of hexane and 67 volumes of propan-2-ol.

When the chromatograms are recorded under the prescribed conditions, the relative retention with reference to
lysolecithin (retention time about 9 minutes) is: L-α-lecithin, about 0.6.

SYSTEM SUITABILITY

The test is not valid unless the resolution between the peaks due to L-α-lecithin and lysolecithin is at least 2.0.

LIMITS
Not greater than 0.2% w/v, calculated using the following expression:

\[
\frac{A_1 \times C_2 \times f}{A_2}
\]

where:

- \(A_1\) = peak area of lysolecithin in solution (1)
- \(A_2\) = peak area of lysolecithin in solution (2)
- \(C_2\) = concentration of lysolecithin in solution (2)
- \(f\) = dilution factor used for solution (1)

**Bacterial endotoxins**

Carry out the test for Bacterial endotoxins, Appendix XIV C. Dilute the injection in water BET to give an emulsion containing 5 mg per mL (solution A). The endotoxin limit concentration of solution A is 1.65 IU endotoxin per mL.

**ASSAY**

Carry out the method for liquid chromatography, Appendix III D, using the following solutions.

1. Dilute a weighed volume of the well shaken injection with propan-2-ol to produce a solution containing 0.08% w/v of Propofol.
2. 0.08% w/v of propofol BPCRS in propan-2-ol containing 6.8% v/v of water.
3. 0.0008% w/v of propofol BPCRS and 0.00008% w/v of propofol impurity J BPCRS in propan-2-ol containing 6.8% v/v of water.

**CHROMATOGRAPHIC CONDITIONS**

The chromatographic procedure described under Propofol quinone and propofol dimer may be carried out but using a detection wavelength of 275 nm.

**SYSTEM SUITABILITY**

The test is not valid unless the resolution between the peaks due to propofol and propofol impurity J is at least 2.5.

**DETERMINATION OF CONTENT**

Determine the weight per mL of the Injection, Appendix V G, and calculate the content of \(C_{12}H_{18}O\) in the Injection using the declared content of \(C_{12}H_{18}O\) in propofol BPCRS.

**STORAGE**

Propofol Injection should be stored at a temperature not exceeding 25°. It should not be allowed to freeze.

**IMPURITIES**

The impurities limited by the requirements of this monograph include impurities E and J listed under Propofol and:

1. lysophosphatidylcholine