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

Fentanyl Injection

General Notices

Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Fentanyl Injection is a sterile solution of Fentanyl Citrate in Water for Injections.

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

Content of fentanyl, $C_{22}H_{28}N_2O$

95.0% to 105.0% of the stated amount.

IDENTIFICATION

A. The *light absorption*, Appendix II B, in the range 230 to 350 nm of the injection diluted, if necessary, to contain the equivalent of 0.005% w/v of fentanyl exhibits two maxima at 251 and 257 nm and a shoulder at 262 nm.
B. In the Assay, the principal peak in the chromatogram obtained with solution (1) has the same retention time as the principal peak in the chromatogram obtained with solution (2).

TESTS

Related substances

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

(1) The injection being examined, diluted with the mobile phase if necessary, to contain the equivalent of 0.005% w/v of fentanyl.
(2) Dilute 1 volume of solution (1) to 100 volumes with the mobile phase and dilute 5 volumes of the resulting solution to 20 volumes with the mobile phase.
(3) Dissolve 5 mg of *fentanyl citrate BPCRS* in 9 mL of *water*, add 1 mL of *hydrogen peroxide solution (30 per cent)* and heat at 95° for 1 to 2 hours. Allow to cool and dilute to 25 mL with the mobile phase (generation of impurity A).
(4) Dissolve 5 mg of *fentanyl citrate BPCRS* in 10 mL of 2M *hydrochloric acid*, heat on a waterbath under a reflux condenser for 4 hours and neutralise with 10 mL of 2M *sodium hydroxide*. Evaporate to dryness on a waterbath, cool, dissolve the residue in 10 mL of *methanol* and filter. Dilute 1 volume of the filtrate to 5 volumes with the mobile phase (generation of impurity D).

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (30 cm × 3.9 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Bondclone C18 10µ is suitable).
(b) Use isocratic elution and the mobile phase described below.

(c) Use a flow rate of 1.25 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 215 nm.
(f) Inject 100 µL of each solution. Inject *methanol* as a blank prior to the solutions.
(g) For solutions (1) and (2) allow the chromatography to proceed for twice the retention time of the principal peak.

MOBILE PHASE

0.3% w/v of *potassium dihydrogen orthophosphate* in a mixture of 4 volumes of *acetonitrile*, 40 volumes of *methanol* and 56 volumes of *water*, the solution adjusted to pH 3.2 with *orthophosphoric acid*.

When the chromatograms are recorded under the prescribed conditions, the relative time of fentanyl is about 6 minutes and the relative retention of fentanyl impurity A is about 1.6.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the retention time of fentanyl impurity D is about 0.8 relative to fentanyl.

LIMITS

Identify any peaks corresponding to impurities A and D in the chromatogram obtained with solution (1), using the chromatograms obtained with solutions (3) and (4) respectively.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to fentanyl impurity A is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the area of any peak corresponding to fentanyl impurity D is not greater than twice the area of the peak in the chromatogram obtained with solution (2) (0.5%);

the area of any other *secondary peak* is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.25%);

the sum of the areas of any *secondary peaks* apart from any peaks corresponding to fentanyl impurity A and fentanyl impurity D is not greater than three times the area of the principal peak in the chromatogram obtained with solution (2) (0.75%).

Disregard any peak obtained with the blank solution and any peak with an area less than 0.2 times the area of the principal peak in the chromatogram obtained with solution (2) (0.05%).

ASSAY

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions in the mobile phase.

(1) The injection diluted, if necessary, to contain the equivalent of 0.005% w/v of fentanyl.
(2) 0.008% w/v solution of *fentanyl citrate BPCRS*.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

DETERMINATION OF CONTENT

Calculate the content of $C_{22}H_{28}N_2O$ in the injection using the declared content of $C_{22}H_{28}N_2O$ in *fentanyl citrate BPCRS*.

STORAGE

Fentanyl Injection should be protected from light.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of fentanyl.

IMPURITIES

The impurities limited by the requirements of this monograph include impurity A and impurity D listed under Fentanyl Citrate.