Furosemide Injections

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

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<th>EAG MC2</th>
<th>Medicinal Chemicals 2</th>
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| Deadline for Comment | 31st September 2019 |
| Target Publication Date (subject to change) | BP 2021 |
| Notes: | Monograph Revision  
|       | Subsidiary Title: To cover sale and use as an infusion  
|       | Related Substances: Use of new EPCRS for peak identification.  
|       | Adjustment to Impurity limits based on ICH guidelines.  
|       | Assay: Introduction of HPLC assay, replacing Assay by UV absorbance. |

Action and use

Loop diuretic.

**DEFINITION**

Furosemide Injection is a sterile solution of furosemide sodium, prepared by the interaction of Furosemide with Sodium Hydroxide, in Water for Injections.

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

**Content of furosemide, C_{12}H_{11}ClN_{2}O_{5}S**

95.0 to 105.0% of the stated amount.

**CHARACTERISTICS**

A colourless or almost colourless solution.

**IDENTIFICATION**
A. The light absorption, Appendix II B, in the range 215 to 320 nm of the final solution obtained in the Assay exhibits two maxima, at 228 nm and 271 nm.

B. In the test for Assay, the chromatogram obtained with solution (1) shows a peak with the same retention time as that of the principal peak in the chromatogram obtained with solution (2).

TESTS

Alkalinity

pH, 8.0 to 9.3, Appendix V L.

Related substances

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

(1) Dilute a quantity of the injection with sufficient mobile phase to produce a solution containing 0.1% w/v of Furosemide.

(2) Dilute 1 volume of solution (1) to 200 volumes with the mobile phase.

(3) 0.00025% w/v of each of furosemide BPCRS and furosemide impurity A EPCRS in the mobile phase.

(4) 0.1% w/v of furosemide for peak identification EPCRS in the mobile phase.

(5) Dilute 1 volume of solution (2) to 5 volumes with the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column 25 cm × 4.6 mm packed with octylsilyl silica gel for chromatography (5 µm) (Symmetry C8 is suitable).

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

(c) Use a flow rate of 1.0 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 238 nm.

(f) Inject 100 µL of each solution.

(g) Allow the chromatography to proceed for 3 times the retention time of furosemide.

MOBILE PHASE

30 volumes of propan-1-ol and 70 volumes of a solution of 0.2% w/v potassium dihydrogen phosphate and 0.25% w/v cetrimide in water adjusted to pH 7.0 using 6M ammonia.

When the chromatograms are recorded under the prescribed conditions, the retention times relative to furosemide (retention time about 9 minutes) are: impurity C, about 0.5; impurity A, about 0.8 and impurity D, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to impurity A and furosemide is at least 4.0.

LIMITS

Identify the peak due to impurity D using the relative retention time, multiply the area of this peak by a correction factor of 2.0.

In the chromatogram obtained with solution (1):
the area of any peak corresponding to 4-chloro-5-sulfamoylanthranilic acid (impurity C) is not greater than the area of the peak in the chromatogram obtained with solution (4) (1.0%);

the area of any peak corresponding to Impurity D is not greater than 1.5 times area of the principal peak in the chromatogram obtained with solution (5) (0.15%);

the area of any other secondary peak is not greater than 1.3 times the area of the principal peak in the chromatogram obtained with solution (5) (0.13%);

the sum of the areas of any secondary peaks excluding impurity C is not greater than the area of the peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than 0.5 times the area of the principal peak in the chromatogram obtained with solution (5) (0.05%).

**Bacterial endotoxins**

Carry out the test for bacterial endotoxins, Appendix XIV C. Dilute the injection with water BET, if necessary, to contain the equivalent of 10 mg of Furosemide per mL (solution A). The endotoxin limit concentration of this solution is 35 IU of endotoxin per mL.

**ASSAY**

Carry out the method for liquid chromatography, Appendix III D, using the following solutions. Prepare the solutions immediately before use and protect from light.

1. Dilute a quantity of the injection with sufficient amount of the mobile phase to produce a solution containing 0.01% w/v of Furosemide.
2. 0.01% w/v of furosemide BPCRS in mobile phase.
3. 0.00025% w/v each of furosemide BPCRS and furosemide impurity A EPCRS in mobile phase.

**CHROMATOGRAPHIC CONDITIONS**

When the chromatograms are recorded under the prescribed conditions, the retention time of furosemide is about 8 minutes.

**SYSTEM SUITABILITY**

The test is not valid unless the resolution between the peaks due to impurity A and furosemide is at least 4.0.

**DETERMINATION OF CONTENT**

Calculate the content of furosemide, C_{12}H_{11}ClN_{2}O_{5}S, in the injection from the chromatograms obtained and using the declared content of C_{12}H_{11}ClN_{2}O_{5}S in furosemide BPCRS.

**STORAGE**

Furosemide Injection should be protected from light.

**LABELLING**

The strength is stated in terms of the equivalent amount of Furosemide in a suitable dose-volume.
IMPURITIES

The impurities limited by the requirements of this monograph include those listed under Furosemide.