Furosemide Oral Solution

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

<table>
<thead>
<tr>
<th>EAG MC2</th>
<th>Medicinal Chemicals 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact Details</td>
<td><a href="mailto:helen.corns@mhra.gov.uk">helen.corns@mhra.gov.uk</a></td>
</tr>
<tr>
<td></td>
<td><a href="mailto:stephen.maddocks@mhra.gov.uk">stephen.maddocks@mhra.gov.uk</a></td>
</tr>
<tr>
<td>Deadline for Comment</td>
<td>31st September 2019</td>
</tr>
<tr>
<td>Target Publication Date (subject to change)</td>
<td>BP 2021</td>
</tr>
<tr>
<td>Notes:</td>
<td>New Monograph. Please review limits and tests specifically and let the BP know of any issues</td>
</tr>
</tbody>
</table>

Action and use

Loop diuretic

DEFINITION

Furosemide Oral Solution is a solution of Furosemide in a suitable flavoured vehicle.

The Oral Solution complies with the requirements stated under Oral Liquids 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.

IDENTIFICATION

A. Carry out the method for thin-layer chromatography, Appendix III A, using the following solutions.

(1) Dilute a quantity of the oral solution with methanol, if necessary to produce a solution containing 0.033% w/v of furosemide.

(2) 0.033% w/v of furosemide BPCRS in methanol.

CHROMATOGRAPHIC CONDITIONS

(a) Use as the coating silica gel F_{254} (Merck TLC Si 60 F_{254} plates are suitable).

(b) Use the mobile phase as described below.

(c) Apply 2 µL of each solution.

(d) Develop the plate to 5 cm.

(e) After removal of the plate, dry in air and examine immediately under ultraviolet light (254 nm).
5 volumes of acetic acid, 45 volumes of ethyl acetate and 50 volumes of toluene.

CONFIRMATION

The principal spot in the chromatogram obtained with solution (1) corresponds in position, and size to that in the chromatogram obtained with solution (2).

B. In the Assay, the retention time of the principal peak in the chromatogram obtained with solution (1) is similar to that of the peak in the chromatogram obtained with solution (2).

TESTS

ALKALINITY

pH, 7.0 to 9.0, 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 oral solution containing 20 mg of Furosemide to 50 mL with the mobile phase.
(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) 0.04% 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) (Luna 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 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 (2) (0.5%);

the area of any peaks corresponding to impurity A, B or D is not greater than half the area of the peak in the chromatogram obtained with solution (2) (0.25%);

the area of any other secondary peak is not greater than twice the area of the principal peak in the chromatogram obtained with solution (5) (0.2%);

the sum of the areas of any other secondary peaks 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 the area of the principal peak in the chromatogram obtained with solution (5) (0.1%).

**ASSAY**

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

1. To a weighed quantity of the oral solution containing 20 mg of furosemide, add 20 mL of 1M sodium hydroxide and dilute to 100 mL with the mobile phase. Further dilute 1 volume of this solution to 5 volumes.

2. 0.004% w/v of furosemide BPCRS.

**CHROMATOGRAPHIC CONDITIONS**

(a) Use a stainless steel column 10 cm × 4.6 mm packed with octadecylsilyl silica gel for chromatography (3.5 µm) (Symmetry C18 is suitable).

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

(c) Use a flow rate of 1.2 mL per minute.

(d) Use an ambient column temperature.

(e) Use a detection wavelength of 228 nm.

(f) Inject 20 µL of each solution.

**MOBILE PHASE**

30 volumes of acetonitrile and 70 volumes of a solution of 0.012% w/v of sodium dihydrogen orthophosphate, previously adjusted to pH 4.2 with orthophosphoric acid.

**SYSTEM SUITABILITY**

The test is not valid unless, in the chromatogram obtained with solution (2), the symmetry factor of the peak due to furosemide is between 0.8 and 2.0.

**DETERMINATION OF CONTENT**

Determine the weight per mL of the Oral Solution, Appendix V G, and calculate the content of C$_{12}$H$_{11}$ClN$_2$O$_5$S, in the oral solution using the declared content of C$_{12}$H$_{11}$ClN$_2$O$_5$S in furosemide BPCRS.

**STORAGE**

Furosemide Oral Solution should be protected from light.
IMPURITIES

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