Methadone Injection

General Notices

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

<table>
<thead>
<tr>
<th>EAG MC3</th>
<th>Medicinal Chemicals 3</th>
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<tbody>
<tr>
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<td>Deadline for Comment</td>
<td>30th June 2020</td>
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<tr>
<td>Target Publication Date (subject to change)</td>
<td>BP 2022</td>
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<td>Notes:</td>
<td>Revised monograph</td>
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Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Methadone Injection is a sterile solution of Methadone Hydrochloride in Water for Injections.

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

Content of methadone hydrochloride, C_{21}H_{27}NO,HCl

92.5 to 107.5% of the stated amount.

IDENTIFICATION

Make a volume containing 0.1 g of Methadone Hydrochloride alkaline with 5M sodium hydroxide, stir with a glass rod until the precipitate solidifies, filter, wash with water and dry over phosphorus pentoxide at room temperature at a pressure of 2 kPa. The infrared absorption spectrum, Appendix II A, of the residue is concordant with the reference spectrum of methadone (RS 218).

TESTS
**Related substances**

Carry out the method for gas chromatography, Appendix III B, using the following solutions.

(1) Dilute a quantity of the injection containing 10 mg of methadone hydrochloride to 10 mL with methanol.
(2) Dilute 1 volume of solution (1) to 100 volumes with methanol, further dilute 1 volume of this solution to 5 volumes with methanol.
(3) 0.005% w/v each of *imipramine hydrochloride BPCRS* and *cyclobenzaprine hydrochloride BPCRS* in methanol.

**CHROMATOGRAPHIC CONDITIONS**

(a) Use a (5%-phenyl)-methylpolysiloxane nonpolar column (50 m x 0.32 mm) (1.05 µm) (Agilent HP-5 is suitable).
(b) Use helium as the carrier gas.
(c) Use a flow rate of 1.2 mL per minute.
(d) Use an inlet temperature of 200°, detector temperature of 250° and the column oven temperature described below.
(e) Use a flame ionisation detector.
(f) Inject 2 µL of each solution.
(g) Use a split ratio of 1:10

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<tr>
<th>Time (Minutes)</th>
<th>Temperature (°C)</th>
<th>Comment</th>
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<tbody>
<tr>
<td>0-4</td>
<td>150→250</td>
<td>linear gradient</td>
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<tr>
<td>4-35</td>
<td>250</td>
<td>isothermal</td>
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When the chromatograms are recorded under the prescribed conditions, the relative retentions with reference to methadone hydrochloride (retention time, about 23 minutes) are: imipramine, about 1.2 and cyclobenzaprine, about 1.25.

**SYSTEM SUITABILITY**

The test is not valid unless:

in the chromatogram obtained with solution (3), the **resolution** between the peaks due to imipramine and cyclobenzaprine is at least 3.0.

in the chromatogram obtained with solution (2), the **signal-to-noise ratio** of the principal peak is at least 20.

**LIMITS**

In the chromatogram obtained with solution (1):

the area of any **secondary peak** is not greater than the area of the principal peak in the chromatogram obtained with solution (2) (0.2%).
the sum of the areas of all secondary peaks is not greater than 2.5 times the area of the principal peak in the chromatogram obtained with solution (2) (0.5%).

Disregard any peak with an area less than half the area of the principal peak in the chromatogram obtained with solution (2) (0.1%).

**ASSAY**

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

(1) Dilute a quantity of the injection containing 10 mg of methadone hydrochloride to 100 mL with methanol.
(2) 0.01% w/v of methadone hydrochloride BPCRS in the mobile phase.
(3) 0.01% w/v each of methadone hydrochloride BPCRS and imipramine BPCRS in the mobile phase.

**CHROMATOGRAPHIC CONDITIONS**

(a) Use a stainless steel column 25 cm × 4.6mm packed with octadecylsilyl silica gel for chromatography (10 µm) (Phenomenex Bondclone C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 1.5 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 220 nm.
(f) Inject 20 µL of each solution.

**MOBILE PHASE**

50 volumes of a 0.02 M solution of potassium dihydrogen orthophosphate and 50 volumes of acetonitrile, adjust the pH of the final solution pH 5.5 with 2M sodium hydroxide

**SYSTEM SUITABILITY**

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between imipramine and methadone hydrochloride is at least 1.5.

**DETERMINATION OF CONTENT**

Calculate the content of methadone hydrochloride, C_{21}H_{27}NO,HCl, in the tablets from the chromatograms obtained and using the declared content of C_{21}H_{27}NO,HCl, in methadone hydrochloride BPCRS.

**IMPURITIES**

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