Methadone Oral Solution (1 mg per mL)

**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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<tr>
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<tr>
<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 Oral Solution (1 mg per mL) contains 0.1% w/v of Methadone Hydrochloride in a suitable aqueous vehicle. It is supplied as a ready-to-use solution or it is prepared from Methadone Hydrochloride Oral Concentrate in accordance with the manufacturer's instructions.

*The oral solution complies with the requirements stated under Oral Liquids and with the following requirements.*

**Content of methadone hydrochloride, C\textsubscript{21}H\textsubscript{27}NO.HCl**

0.090 to 0.110 % w/v.

**IDENTIFICATION**

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

1. Add to 50 mL of the oral solution 30 mL of *water* and sufficient 1M *sulfuric acid* to make the solution acid to *litmus paper*. Extract with two 20-mL quantities of *petroleum spirit* (boiling range, 40° to 60°), discarding the extracts. Make the solution alkaline to *litmus paper* with 5M *sodium hydroxide*, add 4 g of *sodium chloride*, shake to dissolve, extract with two 25-mL quantities of *ether* and wash the combined extracts with five 20-mL quantities of *water*. Shake the ether extract with *anhydrous sodium sulfate*, filter, evaporate the filtrate to
dryness and dry the residue at a pressure of 2 kPa. Prepare a solution containing 0.5% w/v of the residue in ethanol (96%).

(2) 0.55% w/v of methadone hydrochloride BPCRS in ethanol (96%).

CHROMATOGRAPHIC CONDITIONS

(a) Use a TLC silica gel plate (Merck silica gel plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and spray with dilute potassium iodobismuthate solution.

MOBILE PHASE

1.5 volumes of concentrated ammonia R1 and 100 volumes of methanol.

CONFIRMATION

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

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

TESTS

Related substances

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

(1) For products containing ethylcellulose Extract a weighed quantity of the oral solution containing 5 mg of methadone hydrochloride with three 20-mL aliquots of dichloromethane and combine the organic layers. Filter through a phase separation filter, reduce the filtrate to a volume of 1 mL at a temperature not exceeding 30° under a stream of nitrogen and add sufficient dichloromethane to produce 5 mL.
(1) For products not containing ethylcellulose To a weighed quantity of the oral solution containing 10 mg of methadone hydrochloride add 10 mL of a 10% w/v solution of sodium carbamate. Extract with three 20-mL aliquots of dichloromethane and combine the organic layers. Filter through a phase separation filter, reduce the filtrate to a volume of 1 mL at a temperature not exceeding 30° under a stream of nitrogen and add sufficient dichloromethane to produce 10 mL.
(2) Dilute 1 volume of solution (1) to 100 volumes with dichloromethane, further dilute 1 volume of this solution to 5 volumes with dichloromethane.
(3) 0.005% w/v each of imipramine hydrochloride BPCRS and cyclobenzaprine hydrochloride BPCRS in dichloromethane.

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 1:5

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<th>Time (Minutes)</th>
<th>Temperature (°C)</th>
<th>Comment</th>
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<tr>
<td>0-4</td>
<td>150→250</td>
<td>linear gradient</td>
</tr>
<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 in the mobile phase.

(1) Dilute 1 volume of the oral solution to 10 volumes.
(2) 0.01% w/v of *methadone hydrochloride BPCRS*.
METHADONE ORAL SOLUTION (1 mg per mL)

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with octadecylsilyl silica gel for chromatography (10 µm) (Lichrosorb RP18 10µ 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 acetonitrile and 50 volumes of 0.02M potassium dihydrogen orthophosphate, the mixture adjusted to pH 5.5 with 2M orthophosphoric acid or 2M sodium hydroxide.

DETERMINATION OF CONTENT

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

METHADONE HYDROCHLORIDE ORAL CONCENTRATE

DEFINITION

Methadone Hydrochloride Oral Concentrate is a solution of Methadone Hydrochloride in a suitable aqueous vehicle.

The concentrate complies with the requirements stated under Oral Liquids and with the following requirements.

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

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) Add to 5 mL of the oral concentrate 30 mL of water and sufficient 1M sulfuric acid to make the solution acid to litmus paper. Extract with two 20-mL quantities of petroleum spirit (boiling range, 40° to 60°), discarding the extracts. Make the solution alkaline to litmus paper with 5M sodium hydroxide, add 4 g of sodium chloride, shake to dissolve, extract with two 25-mL quantities of ether and wash the combined extracts with five 20-mL quantities of water. Shake the ether extract with anhydrous sodium sulfate, filter, evaporate the filtrate to dryness and dry the residue at a pressure of 2 kPa. Prepare a solution containing 0.5% w/v of the residue in ethanol (96%).
(2) 0.55% w/v of methadone hydrochloride BPCRS in ethanol (96%).

CHROMATOGRAPHIC CONDITIONS
Methadone Oral Solution (1 mg per mL)

(a) Use a TLC silica gel plate (Merck silica gel plates are suitable).
(b) Use the mobile phase as described below.
(c) Apply 10 µL of each solution.
(d) Develop the plate to 15 cm.
(e) After removal of the plate, dry in air and spray with dilute potassium iodobismuthate solution.

MOBILE PHASE

1.5 volumes of concentrated ammonia R1 and 100 volumes of methanol.

CONFIRMATION

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

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

ASSAY

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

(1) Dilute the concentrate to produce a solution containing 0.01% w/v of Methadone Hydrochloride.
(2) 0.01% w/v of methadone hydrochloride BPCRS.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with octadecylsilyl silica gel for chromatography (10 µm) (Lichrosorb RP18 10µ 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 acetonitrile and 50 volumes of 0.02M potassium dihydrogen orthophosphate, the mixture adjusted to pH 5.5 with 2M orthophosphoric acid or 2M sodium hydroxide.

DETERMINATION OF CONTENT

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

LABELLING
At the specific request of the prescriber, the concentrate may be diluted to a concentration other than 0.1% w/v in accordance with the manufacturer’s instructions.