Methadone Concentrate for Oral Solution

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

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<tr>
<th>EAG MC3</th>
<th>Medicinal Chemicals 3</th>
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<td>Deadline for Comment</td>
<td>30th June 2020</td>
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<td>BP 2022</td>
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<td>Notes:</td>
<td>New monograph</td>
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Action and use

Opioid receptor agonist; analgesic.

DEFINITION

Methadone Concentrate for Oral Solution contains Methadone Hydrochloride in a suitable aqueous vehicle. It is a concentrate that is prepared in accordance with the manufacturer's instructions prior to administration.

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

Content of methadone hydrochloride, $\text{C}_{21}\text{H}_{27}\text{NO}_3\text{HCl}$

95.0 to 105.0 % w/v.

IDENTIFICATION

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

(1) To a quantity of the oral concentrate containing 50 mg of Methadone Hydrochloride, add 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 concentrate 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 concentrate 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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<tbody>
<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 a quantity of the oral concentrate with sufficient of the mobile phase to produce a 0.01% w/v solution 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 oral solution 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.