Mycophenolate Mofetil for Infusion

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

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<th>EAG/Panel/Working Party</th>
<th>Medicinal Chemicals 1</th>
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<td>Deadline for Comment</td>
<td>31st December 2019</td>
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<td>Notes</td>
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<td>If limits are too restrictive, please provide batch/stability data to demonstrate that an increase is required.</td>
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Action and use

Inhibitor of nucleic acid synthesis; immunomodulator.

DEFINITION

Mycophenolate Mofetil for Infusion is a sterile material consisting of Mycophenolate Mofetil with or without excipients. It is supplied in a sealed container.

The contents of the sealed container comply with the requirements for Powders for Injections or Infusions stated under Parenteral Preparations and with the following requirements.

Content of mycophenolate mofetil, C_{17}H_{20}O_{6}

95.0 to 105.0% of the stated amount.

IDENTIFICATION

A. Dissolve a quantity of the powder for infusion with sufficient 0.1M hydrochloric acid to produce a solution containing 0.005% w/v of Mycophenolate Mofetil. The light absorption, Appendix II B, in the range 200 to 400 nm of this solution exhibits two maxima, at 250 and 304 nm and a minimum at 274 nm.

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

Acidity

Prepare the infusion as directed on the label.
pH, 2.7 to 4.1, Appendix V L.

**Clarity and colour of solution**

Prepare the infusion as directed on the label.

The solution is *clear*, Appendix IV A, and not more intensely coloured than *reference solution Y4*, Appendix IV B, Method II.

**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.*

Solution A 20 volumes of solution containing 1% v/v of *triethylamine* in *water*, adjusted to pH 3.0 with *orthophosphoric acid* or 1M potassium hydroxide, 35 volumes acetonitrile and 45 volumes of *water*.

1. Reconstitute the powder for infusion containing the equivalent of 2 g of mycophenolate mofetil in 56 mL of 5% w/v *glucose* in *water for injections*, dilute with sufficient *water* to produce 200 mL. Dilute 1 volumes of this solution to 25 volumes with solution A to produce a solution of 0.04% w/v of mycophenolate mofetil.
2. Dilute 1 volume of solution (1) to 100 volumes.
3. Dilute 1 volume of solution (2) to 10 volumes with solution A.
4. 0.04% w/v of *mycophenolate mofetil impurity standard BPCS* (mycophenolate mofetil with impurities A, B, C, F and G) in solution A.

**CHROMATOGRAPHIC CONDITIONS**

(a) Use a stainless steel column (25 cm × 4.6 mm) packed with *phenylsilyl silica gel for chromatography* (5 µm) (Inertsil Phenyl 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 a column temperature of 45°.
(e) Use an autosampler temperature of 5°.
(f) Use a detection wavelength of 249 nm.
(g) Inject 10 µL of each solution.
(h) Allow the chromatography to proceed for twice the retention time of mycophenolate mofetil.

**MOBILE PHASE**

217 volumes of solution containing 1% v/v of *triethylamine* in *water*, adjusted to pH 7.2 with *orthophosphoric acid* or 1M potassium hydroxide, 300 volumes acetonitrile and 483 volumes of *water*.

When the chromatograms are recorded under the prescribed conditions the retention times relative to mycophenolate mofetil (retention time about 27 minutes) are: impurity F, about 0.1; impurity G, about 0.3; impurity A, about 0.4; impurity H, about 0.45; impurity B, about 0.9 and impurity C, about 1.1.

**SYSTEM SUITABILITY**

The test is not valid unless, in the chromatogram obtained with solution (4), the *resolution* between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.
LIMITS

In the chromatogram obtained with solution (1), identify any peaks due to impurities A, B, F and G using the chromatogram obtained with solution (4). Multiply the area of any peak corresponding to impurity A by a correction factor of 0.6; multiply the area of any peak corresponding impurity B by a correction factor of 2.1 and multiply the area of any peaks corresponding impurity F and impurity G by a correction factor of 0.7.

In the chromatogram obtained with solution (1):

the area of any peak corresponding to impurity F is not greater than 1.5 times the area of the principal peak in the chromatogram obtained with solution (2) (1.5%);

the area of any peak corresponding to impurity B is not greater than twice the area of the principal peak in the chromatogram obtained with solution (3) (0.2%);

the area of any other secondary peak is not greater than the area of the principal peak in the chromatogram obtained with solution (3) (0.1%);

the sum of the areas of all secondary peaks, excluding impurity F, is not greater than half 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 (3) (0.05%).

ASSAY

Determine the weight of the contents of 10 containers as described in the test for uniformity of weight, Appendix XII C1, Powders for Parenteral Use.

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

Solution A 20 volumes of solution containing 1% v/v of triethylamine in water, adjusted to pH 3.0 with orthophosphoric acid or 1M potassium hydroxide, 35 volumes acetonitrile and 45 volumes of water.

(1) Prepare 10 injections following the manufacturer’s instructions and combine the resulting solutions. Dilute a quantity of the resulting solution with sufficient solution A to produce a solution containing the equivalent of 0.04% w/v of Mycophenolate Mofetil.

(2) 0.04% w/v of mycophenolate mofetil BPCRS in solution A.

(3) 0.04% w/v of mycophenolate mofetil impurity standard BPCRS (mycophenolate mofetil with impurities A, B, C, F and G) in solution A.

CHROMATOGRAPHIC CONDITIONS

The chromatographic conditions described under Related substances may be used.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (3), the resolution between the peaks due to mycophenolate mofetil and impurity C is at least 2.0.

DETERMINATION OF CONTENT
Calculate the content of mycophenolate mofetil, $\text{C}_{17}\text{H}_{20}\text{O}_6$, in the powder for infusion from the chromatograms obtained and using the declared content of $\text{C}_{17}\text{H}_{20}\text{O}_6$ in *mycophenolate mofetil BPCRS*.

**IMPURITIES**

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