Mycophenolate Mofetil Tablets

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>Target Publication Date (subject to change)</td>
<td>BP 2021</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 Tablets contain Mycophenolate Mofetil.

The tablets comply with the requirements stated under Tablets 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**

Shake a quantity of powdered tablets containing 100 mg of Mycophenolate Mofetil with 20 mL of acetone, filter and evaporate to dryness. The infrared absorption spectrum, Appendix II A, is concordant with the reference spectrum of mycophenolate mofetil (RS XXX).

**TESTS**

**Dissolution**

Comply with the requirements in the dissolution test for tablets and capsules, Appendix XII B1.

**TEST CONDITIONS**

(a) Use Apparatus 2, rotating the paddle at 50 revolutions per minute.

(b) Use 900 mL of 0.1m hydrochloric acid, at a temperature of 37°, as the medium.
PROCEDURE

(1) After 45 minutes withdraw a sample of the medium, and filter (a 0.45-µm nylon filter is suitable). Dilute the filtered sample with dissolution medium, if necessary to produce a solution containing 0.0056% w/v of Mycophenolate Mofetil. Immediately measure the absorbance of the solution, Appendix II B, at 304 nm using dissolution medium in the reference cell.

(2) Measure the absorbance of a 0.0056% w/v solution of mycophenolate mofetil BPCRS in the dissolution medium using dissolution medium in the reference cell.

DETERMINATION OF CONTENT

Calculate the total content of mycophenolate mofetil, C₁₇H₂₀O₆, in the medium using the declared content of C₁₇H₂₀O₆ in mycophenolate mofetil BPCRS.

LIMITS

The amount of mycophenolate mofetil released is not less than 80% (Q) of the stated amount.

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 Add 0.55 volumes of orthophosphoric acid to a 0.5679% w/v solution of ammonium dihydrogen orthophosphate in water, and adjust the pH to 3.0 using orthophosphoric acid or 1M potassium hydroxide. To the adjusted solution, add 700 volumes of acetonitrile.

(1) Shake a quantity of powdered tablets containing 1.5 g of Mycophenolate Mofetil with 60 mL of acetonitrile and then mix with the aid of ultrasound. Dilute to 250 mL with acetonitrile and centrifuge. Dilute the supernatant liquid with sufficient solution A to produce a solution containing 0.12% w/v of Mycophenolate Mofetil.

(2) Dilute 1 volume of solution (1) to 100 volumes with solution A.

(3) Dilute 1 volume of solution (2) to 10 volumes with solution A.

(4) 0.12% w/v of mycophenolate mofetil impurity standard BPCRS (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 octylsilyl silica gel for chromatography (5 µm) (Zorbax SB-C8 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°C.

(e) Use a detection wavelength of 249 nm.

(f) Inject 10 µL of each solution.

(g) Allow the chromatography to proceed for twice times the retention time of mycophenolate mofetil.

MOBILE PHASE

200 volumes of solution containing 0.05% v/v of orthophosphoric acid and 0.1% v/v of triethylamine in water, adjusted to pH 5.4 with orthophosphoric acid or 1M potassium hydroxide, 350 volumes of acetonitrile and 450 volumes of water.
When the chromatograms are recorded under the prescribed conditions, the relative retention times with reference to mycophenolate mofetil (retention time about 21 minutes) are: impurity F; about 0.3; impurity A; about 0.4; impurity H, about 0.45; impurity G; about 0.5; impurity B, about 0.9; impurity C; about 1.1; impurity D, about 1.2 and impurity E, about 1.5.

SYSTEM SUITABILITY

The test is not valid unless, in the chromatogram obtained with solution (4), the peak-to-valley ratio is at least 5.0, where \( H_p \) is the height above the baseline of the peak due to impurity C and \( H_v \) is the height above the baseline of the lowest point of the curve separating this peak from the peak due to mycophenolate mofetil.

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 the area of the principal peak in the chromatogram obtained with solution (2) (1.0%);
- 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

Weigh and powder 20 tablets. Carry out the method for liquid chromatography, Appendix III D, using the following solutions:

Solution A Add 0.55 volumes of orthophosphoric acid to a 0.5679% w/v solution of ammonium dihydrogen orthophosphate in water, and adjust the pH to 3.0 using orthophosphoric acid or 1M potassium hydroxide. To the adjusted solution, add 700 volumes of acetonitrile.

(1) Shake a quantity of powdered tablets containing 1.5 g of Mycophenolate Mofetil with 60 mL of acetonitrile and then mix with the aid of ultrasound. Dilute to 250 mL with acetonitrile and centrifuge. Dilute the supernatant liquid with sufficient solution A to produce a solution containing 0.036% w/v of Mycophenolate Mofetil.

(2) 0.036% w/v of mycophenolate mofetil BPCRS in solution A.

(3) 0.12% 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.

DETERMINATION OF CONTENT

Calculate the total content of mycophenolate mofetil, C₁₇H₂₀O₆, using the declared content of C₁₇H₂₀O₆ in mycophenolate mofetil BPCRS.

IMPURITIES

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