

BRIEFING

**Mycophenolate Mofetil Capsules.** This monograph proposal was posted on the USP Pending Monographs Web page as a draft USP Pending Monograph on December 29, 2008, for public comments for more than 90 days. The MD-OOD Expert Committee has reviewed all the comments that were received and has approved the monograph as an Authorized USP Pending Monograph.

**Comment 1:** It was suggested that the test for *Infrared Absorption* (197M) or (197A) should be performed for *Identification*.

**Response 1:** The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentor is encouraged to submit comments for the USP Mycophenolate Mofetil Capsules monograph being published in PF 35(4).

**Comment 2:** It was requested that in the test for *Organic Impurities* the limit for mycophenolic acid should be increased from 0.5% to 1.0% and the limit for total impurities should be increased from 0.8% to 1.2%, to be consistent with the approved NDA.

**Response 2:** The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentor is encouraged to submit comments for USP Mycophenolate Mofetil Capsules monograph being published in PF 35(4).

**Comment 3:** It was suggested that the same mobile phase, sample solution, standard solution and diluent are used for both *Assay* and the test for *Organic Impurities*. It was also recommended a guard column for both the *Assay* and the test for *Organic Impurities*.

**Response 3:** The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentor is encouraged to submit comments for USP Mycophenolate Mofetil Capsules monograph being published in PF 35(4).

**Comment 4:** It was requested to change the limit for *Dissolution* from NLT 70% (Q) in 15 min to NTL 80% (Q) in 20 min.

**Response 4:** The comment was not incorporated because the comment is more relevant to the USP monograph rather than the USP pending monograph, as described in the *Pending Monographs Guideline* posted on the USP website. The commentor is encouraged to submit comments for USP Mycophenolate Mofetil Capsules monograph being published in PF 35(4).

The proposed chromatographic procedure in the *Assay* is based on analyses performed with a ZORBAX Rx-C8 brand of L7 column; the typical retention time for mycophenolate mofetil is about 5 min. The proposed chromatographic procedure in the test for *Organic Impurities* is based on analyses performed with a Zorbax SB-C8 brand of L7 column; the typical retention time reported for mycophenolate mofetil is about 21 min.

(MD-OOD: F. Mao. BPC: M. Marques.) RTS—C68499

## Mycophenolate Mofetil Capsules

v. 1 Authorized July 1, 2009

### DEFINITION

Mycophenolate Mofetil Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of mycophenolate mofetil ( $C_{23}H_{31}NO_7$ ).

### IDENTIFICATION

- A. ULTRAVIOLET ABSORPTION (197U)**  
**Sample solution:** 10 µg/mL in acetonitrile
- B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

### ASSAY

- PROCEDURE**  
**Solution A:** Mix 2 mL of triethylamine and 650 mL of water. Adjust with phosphoric acid to a pH of 5.3.  
**Mobile phase:** Acetonitrile and *Solution A* (3:2)  
**Diluent:** Acetonitrile and water (4:1)  
**Standard solution:** 0.4 mg/mL of USP Mycophenolate Mofetil RS in *Diluent*  
**Sample stock solution:** Mix the contents of NLT 20 Capsules. Transfer a weighed portion of the contents so obtained, equivalent to 200 mg of mycophenolate mofetil, into a 100-mL volumetric flask. Add 60 mL of *Diluent*. Sonicate for 30 min with intermittent shaking. Dilute with *Diluent* to volume, and mix.  
**Sample solution:** 0.4 mg/mL of mycophenolate mofetil from the *Sample stock solution* in *Diluent*. Pass a portion through a filter having a 0.45-µm or finer porosity.

#### Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

- Mode:** LC
- Detector:** UV 250 nm
- Column:** 4.6-mm × 25-cm column; 5-µm packing L7
- Column temperature:** 45 ± 5°
- Flow rate:** 1 mL/min
- Injection size:** 10 µL

#### System suitability

- Sample:** *Standard solution*
- Suitability requirements**  
**Tailing factor:** NMT 2.0  
**Relative standard deviation:** NMT 2.0%

#### Analysis

- Samples:** *Standard solution* and *Sample solution*  
Calculate the percentage of  $C_{23}H_{31}NO_7$  in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

- $r_U$  = peak response from the *Sample solution*
- $r_S$  = peak response from the *Standard solution*
- $C_S$  = concentration of mycophenolate mofetil in the *Standard solution* (mg/mL)
- $C_U$  = nominal concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)

**Acceptance criteria:** 90.0%–110.0%

### PERFORMANCE TESTS

- DISSOLUTION (711)**  
**Medium:** 0.1 N hydrochloric acid; 900 mL  
**Apparatus 2:** 40 rpm, with 8-mm × 23-mm sinkers  
**Time:** 15 min  
**Sample solution:** Pass a portion of the solution under test through a suitable 0.45-µm filter. Dilute 4.0 mL of the filtrate with *Medium* to 50 mL.  
**Standard solution:** 0.022 mg/mL of USP Mycophenolate Mofetil RS in *Medium*  
**Detector:** UV 250 nm  
**Blank:** *Medium*  
**Analysis**  
**Samples:** *Standard solution* and *Sample solution*  
Calculate the percentage of  $C_{23}H_{31}NO_7$  dissolved:

$$(A_U/A_S) \times (C_S \times V/L) \times 100$$

- $A_U$  = absorbance from the *Sample solution*
- $A_S$  = absorbance from the *Standard solution*
- $C_S$  = concentration of the *Standard solution* (mg/mL)
- $V$  = volume of *Medium*, 900 mL
- $L$  = label claim (mg/Capsule)

**Tolerances:** NLT 70% (Q) of the labeled amount of  $C_{23}H_{31}NO_7$  is dissolved.

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- **UNIFORMITY OF DOSAGE UNITS (905):** Meet the requirements

### IMPURITIES

#### Organic Impurities

##### • PROCEDURE

**Solution A:** Proceed as directed in the Assay.

**Mobile phase:** Acetonitrile and *Solution A* (7:13)

**Standard solution:** 0.02 mg/mL of USP Mycophenolate Mofetil RS in acetonitrile

**Sample solution:** Mix the contents of NLT 20 Capsules. Transfer a weighed portion of the contents so obtained, equivalent to 200 mg of mycophenolate mofetil, into a 100-mL volumetric flask. Add 60 mL of acetonitrile. Sonicate in ice-cold water for 30 min with intermittent shaking. Dilute with acetonitrile to volume, and mix. Pass a portion through a filter having a 0.45- $\mu$ m or finer porosity. [NOTE—Store the *Sample solution* at 5°.]

#### Chromatographic system

(See *Chromatography* (621), *System Suitability*.)

**Mode:** LC

**Detector:** UV 250 nm

**Column:** 4.6-mm  $\times$  25-cm column; 5- $\mu$ m packing L7

**Column temperature:** 45  $\pm$  5°

**Flow rate:** 1.5 mL/min

**Run time:** 3.3 times the retention time of the mycophenolate mofetil peak, *Sample solution*

**Injection size:** 10  $\mu$ L

#### System suitability

**Sample:** *Standard solution*

#### Suitability requirements

**Tailing factor:** NMT 2.0

**Relative standard deviation:** NMT 5.0%

#### Analysis

**Samples:** *Standard solution* and *Sample solution*

Calculate the percentage of each impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times 100$$

- $r_U$  = response of each individual impurity from the *Sample solution*
- $r_S$  = response of mycophenolate mofetil from the *Standard solution*
- $C_S$  = concentration of mycophenolate mofetil in the *Standard solution* (mg/mL)
- $C_U$  = concentration of mycophenolate mofetil in the *Sample solution* (mg/mL)
- F = relative response factor for each individual impurity (see *Impurity Table 1*)

#### Acceptance criteria

**Individual impurities:** See *Impurity Table 1*.

**Total impurities:** NMT 0.8%

[NOTE—Disregard any peaks less than 0.05%.]

**Impurity Table 1**

Name	Relative Retention Time (RRT)	Relative Response Factor	Acceptance Criteria, NMT (%)
Mycophenolic acid <sup>a</sup>	0.3	1.4	0.5
Mycophenolate mofetil	1.0	—	—
Any unspecified impurity	—	1.0	0.1

<sup>a</sup> (E)-6-(1,3-Dihydro-4-hydroxy-6-methoxy-7-methyl-3-oxo-5-isobenzofuranyl)-4-methyl-4-hexenoic acid.

#### ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS (11)**  
USP Mycophenolate Mofetil RS