



PRIME EUROPEAN THERAPEUTICALS SpA - Sole Shareholder  
Registered Office: Viale Europa 5, 20122 Milano, Italy - Admin./Finance Office: Viale Europa 5, 20122 Milano, Italy  
Tel. +39 02 8246183 - Fax +39 02 8246183 - E-mail: info@euticals.it - Web: www.euticals.it

## CERTIFICATE OF ANALYSIS

Product: **SIROLIMUS**

MANUFACTURING SITE: EUTICALS SpA - Via Volturno 41/43 - 20089 Rozzano (MI)

Batch no.: **IE1400162A**

Code: **30124**

Manufacturing date: **February 2014**

Analysis date: **March 2014**

Re-test date: **February 2019**

| TEST                              | SPECIFICATIONS   | ANALYSIS VALUE   |
|-----------------------------------|--|------------------|
| <b>Characters:</b>                |  |                  |
| - Appearance                      | White to almost-white powder.  | complies         |
| - Solubility                      | Soluble in ether, acetone, methanol; slightly soluble in n-hexane; practically insoluble in water      | complies         |
| <b>Identification:</b>            |  |                  |
| - HPLC                            | the RT of the main peak of the product under analysis must be concordant with that of the standard     | complies         |
| - IR spectrum                     | comply with the standard material  | complies         |
| Loss on Drying (TGA):             | not more than 1.0 %  | not detectable   |
| Sulfated ash                      | not more than 0.1 %  | 0.0 %            |
| Specific optical rotation         | - 140 to -160° (on anhydrous and solvent free basis, 10 mg/mL in methanol)                             | - 149°           |
| Heavy metals                      | not more than 20 ppm   | less than 20 ppm |
| Water (K.F.)                      | not more than 0.5 %  | 0.2 %            |
| Sirolimus isomer (rtt 1.1)        | report the found value   | 2.5 %            |
| Assay (HPLC)                      | between 96.5 % and 102.0 %<br>(on anhydrous basis, expressed as sum of Sirolimus and Sirolimus isomer) | 100.4 %          |
| <b>Related substances (HPLC):</b> |  |                  |
| - 27-O-demethyl-rapamycin         | not more than 0.5 %  | 0.2 %            |
| - 16-O-demethyl-rapamycin         | not more than 0.5 %  | 0.1 %            |
| - Protylrapamycin                 | not more than 0.5 %  | 0.2 %            |
| - 27-demethoxyrapamycin           | not more than 0.2 %  | not detectable   |
| - 40-oxorapamycin                 | not more than 0.2 %  | 0.1 %            |
| - 11-ethyl- & 23-ethyl-rapam.     | not more than 0.5 %  | 0.2 %            |
| - Any other                       | not more than 0.2 % each   | 0.1 %            |
| - Total (specified+unspecified)   | not more than 1.5 %  | 0.8 %            |
| <b>Residual solvents:</b>         |  |                  |
| - Acetone                         | not more than 500 ppm  | 3 ppm            |
| - Ethyl ether                     | not more than 500 ppm  | not detectable   |
| TAMC                              | not more than 100 ufc/g  | < 10 ufc/g       |
| TYMC                              | not more than 10 ufc/g   | < 10 ufc/g       |

Milan - December 2, 2015

Q.C. Manager

DR. SSA MICHELA RAMPI

This is to certify that the batch was manufactured according to c-GMP

Qualified Person

DR. SSA MICHELA RAMPI

### Production Units - Lodi Area

Viale Milano, 56  
26900 Lodi (LO) ITALY  
Ph. +39 0371 49021  
Fax +39 0371 610019

Via delle Rimembranze, 1  
26952 Casalotto Lodigiano (LO) ITALY  
Ph. +39 0371 73971  
Fax +39 0371 71793

### Production Units - Milano Area

Via Volturno, 41/43  
20089 Rozzano (MI) ITALY  
Ph. +39 02 8222721  
Fax +39 02 8246183

Via Dante Rosa, 114/116  
20089 Rozzano (MI) ITALY  
Ph. +39 02 8228351  
Fax +39 02 8250573

### Production Units - Varese Area

Via Volturno, 20/22  
21100 Varese (VA) ITALY  
Ph. +39 0332 22991  
Fax +39 0332 212575

Viale Europa, 5  
21040 Origgio (VA) ITALY  
Ph. +39 02 965531  
Fax +39 02 96730456