# Rapamune

## Procedural steps taken and scientific information after the authorisation

| Application number | Scope | Opinion/ Notification[1] issued on | Commission Decision Issued[2] / amended on | Product Information affected[3] | Summary |
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| IB/0189 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 22/07/2022 | | SmPC and PL | Sections 4.4 and 4.5 of the SmPC have been updated to add the drug interaction with cannabidiol concerning the signal assessment leading to systematic calcineurin inhibitors and mTOR inhibitors serum levels increase and toxicity (EPITT no: 19614) in line with the PRAC recommendation adopted at March 2022 meeting. |

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

**Official address** Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
**Address for visits and deliveries** Refer to www.ema.europa.eu/how-to-find-us
**Send us a question** Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

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| IB/0188 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 18/05/2022 | n/a | | |
| II/0184 | Submission of the final report from non-interventional study B1741224, A Population Based Cohort Study to Monitor the Safety and Effectiveness of Sirolimus in Patients With Sporadic Lymphangioleiomyomatosis (S-LAM), designated as a Category 3 PASS.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 07/04/2022 | n/a | | N/a |
| IB/0187/G | This was an application for a group of variations.<br><br>B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation<br>B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation<br>B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation<br>B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation | 17/03/2022 | n/a | | |
| IB/0185/G | This was an application for a group of variations. | 04/03/2022 | n/a | | |

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| | B.II.c.2.d - Change in test procedure for an excipient - Other changes to a test procedure (including replacement or addition)<br>B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | | | | |
| IA/0183 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 09/12/2021 | n/a | | |
| IB/0182 | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 15/11/2021 | | SmPC, Annex II and PL | To update the shelf-life of Rapamune coated tablets 0.5 mg from '24 months' to '36 months' in section 6.3 of the Summary of Product Characteristics (SmPC).<br>To update the name and address of the site responsible for batch release for Rapamune 1 mg/mL oral solution in Annex II of the Product Information and to update the list of local representatives in the Patient Information Leaflet (PIL). |
| N/0181 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 01/10/2021 | | PL | |
| PSUSA/2710/202009 | Periodic Safety Update EU Single assessment - sirolimus | 20/05/2021 | 16/07/2021 | SmPC and PL | Please refer to Rapamune EMEA/H/C/PSUSA/00002710/202009 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation |
| IAIN/0180 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is | 09/06/2021 | n/a | | |

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| | not an integrated part of the primary packaging - Device with CE marking | | | | |
| IA/0179 | B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) | 09/03/2021 | n/a | | |
| IAIN/0178/G | This was an application for a group of variations.<br><br>A.7 - Administrative change - Deletion of manufacturing sites<br>B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing | 16/02/2021 | 16/07/2021 | Annex II and PL | |
| N/0176 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 27/11/2020 | 16/07/2021 | PL | |
| IB/0175 | C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation | 18/06/2020 | n/a | | |
| IB/0174 | B.I.z - Quality change - Active substance - Other variation | 20/02/2020 | n/a | | |
| IA/0173 | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure | 20/12/2019 | n/a | | |

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| IAIN/0172 | B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking | 11/07/2019 | n/a | | |
| IB/0171 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 17/06/2019 | 13/09/2019 | SmPC, Labelling and PL | |
| N/0169 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 11/01/2019 | 13/09/2019 | PL | |
| IA/0170 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient | 28/11/2018 | n/a | | |
| T/0168 | Transfer of Marketing Authorisation | 26/09/2018 | 16/10/2018 | SmPC, Labelling and PL | |
| IB/0167/G | This was an application for a group of variations.<br><br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<br>B.II.b.1.f - Replacement or addition of a | 27/09/2018 | 13/09/2019 | SmPC, Labelling and PL | |

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| | manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products<br>B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place<br>B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale | | | | |
| II/0164 | Extension of indication to include the treatment of patients with sporadic lymphangioleiomyomatosis with moderate lung disease or declining lung function. As a consequence section 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and the RMP (version 6.4) are updated in accordance. In addition the MAH took the opportunity to make very minor formatting changes in the Labelling.<br><br>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | 28/06/2018 | 02/08/2018 | SmPC, Labelling and PL | Please refer to Scientific Discussion: Rapamune-H-C-273-II-0164 |
| PSUSA/2710/ 201709 | Periodic Safety Update EU Single assessment - sirolimus | 12/04/2018 | n/a | | PRAC Recommendation - maintenance |

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| IA/0166 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient | 11/04/2018 | n/a | | |
| II/0163/G | This was an application for a group of variations.<br><br>Update of section 4.4 of the SmPC to update the current warning on angioedema to include a possible dose-dependent effect between sirolimus and angioedema based on post-marketing data. Update of section 4.8 of the SmPC to include 'neuroendocrine carcinoma of the skin' as new adverse drug reaction (ADR) with a frequency 'not known' and to replace the ADR 'skin cancer' by 'non-melanoma skin cancer' and 'malignant melanoma' with a 'common' and 'uncommon' frequency respectively, based on post-marketing data. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to combine the 0.5 mg, 1 mg and 2 mg tablets SmPC, to fully detail all components of the Rapamune printing ink in section 6.1 of the SmPC and in the Package Leaflet, to align the wording in section 4 of the Package Leaflet with section 4.8 of the SmPC regarding Clostridium difficile, to update the list of local representatives for the Czech Republic, Norway and Sweden in the Package Leaflet and to bring the product information in line with the latest QRD template version 10. | 16/02/2017 | 23/06/2017 | SmPC, Labelling and PL | Based on a literature and global safety database review, section 4.4 of the SmPC was updated to revise the current warning on angioedema to include that elevated sirolimus levels for example due to interaction with strong CYP3A4 inhibitors with or without concomitant angiotensin converting enzyme inhibitors may also potentiate angioedema and that in some cases the angioedema has resolved upon discontinuation or dose reduction of sirolimus. Following a signal of disproportionate reporting was identified for neuroendocrine carcinoma of the skin during routine MAH signal detection activities, section 4.8 of the SmPC was updated to add 'neuroendocrine carcinoma of the skin' as a new adverse drug reaction with a 'not known' frequency. In addition the adverse drug reaction 'skin cancer' was split into 'non-melanoma skin cancer' with a 'common 'frequency and 'malignant melanoma' with an 'uncommon' frequency. |

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| | C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data<br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | |
| II/0160 | Update of sections 4.4 and 5.1 of the SmPC in order to include data from the final Clinical Study Report of study B1741007 ("Planned Transition to Sirolimus-based Therapy Versus Continued Tacrolimus (TAC)-based Therapy in Renal Allograft Recipients"); in addition, the Marketing authorisation holder (MAH) took the opportunity to make minor editorial change in the SmPC.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 21/07/2016 | 23/06/2017 | SmPC | Based on information from an open-label randomised study, conversion from the calcineurin inhibitor tacrolimus to Rapamune in maintenance renal transplant patients was associated with an unfavourable safety profile without efficacy benefit and can therefore not be recommended.<br>In an open-label, randomised, comparative, multi-centre study where renal transplant patients were either converted from tacrolimus to sirolimus 3 to 5 months post-transplant or remained on tacrolimus, there was no significant difference in renal function at 2 years. There were more adverse events (99.2% vs. 91.1%, p=0.002*) and more discontinuations from the treatment due to adverse events (26.7% vs. 4.1%, p<0.001*) in the group converted to sirolimus compared to the tacrolimus group. The incidence of biopsy confirmed acute rejection was higher (p=0.020*) for patients in the sirolimus group (11, 8.4%) compared to the tacrolimus group (2, 1.6%) through 2 years; most rejections were mild in severity (8 of 9 [89%] T-cell BCAR, 2 of 4 [50%] antibody mediated BCAR) in the sirolimus group. Patients who had both antibody-mediated rejection and T-cell-mediated rejection on the same biopsy were counted once for each category. More patients converted to sirolimus developed new onset |

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| | | | | | diabetes mellitus defined as 30 days or longer of continuous or at least 25 days non-stop (without gap) use of any diabetic treatment after randomisation, a fasting glucose ≥126 mg/dL or a non-fasting glucose ≥200 mg/dL after randomisation (18.3% vs 5.6%, p=0.025, p-values not controlled for multiple testing). A lower incidence of squamous cell carcinoma of the skin was observed in the sirolimus group (0% vs. 4.9%). |
| IA/0162 | B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier | 24/06/2016 | n/a | | |
| II/0153 | Update of sections 4.4 and 5.1 of the SmPC in order to update the safety and efficacy information of the final clinical study report for Sirolimus study B1741001 (Wyeth 0468E5-4439), a randomized, placebo controlled, double blind comparative study in order to evaluate the effect of Ramipril on urinary protein excretion. Additionally the MAH took the opportunity to fully align the SmPC and Package leaflet with the EU Excipient guideline.<br><br>C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority | 24/09/2015 | 27/11/2015 | SmPC and PL | |
| N/0158 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 24/06/2015 | 27/11/2015 | PL | |
| IB/0159/G | This was an application for a group of variations. | 11/06/2015 | n/a | | |

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| | B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>B.II.d.1.g - Change in the specification parameters and/or limits of the finished product - Addition or replacement (excluding biological or immunological product) of a specification parameter wit its corresponding test method as a result of a safety or quality issue | | | | |
| II/0157 | Update of section 4.8 of the SmPC in order to update the frequency categories of ADRs based on all-causality clinical trial data. The Package Leaflet is updated accordingly.<br>In addition, the Marketing authorisation holder took the opportunity to bring the PI in line with the latest QRD template version 9 and to include minor editorial changes to the SmPC, Annex II, Labelling and Package Leaflet.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | 21/05/2015 | 27/11/2015 | SmPC, Annex II, Labelling and PL | |
| PSUSA/2710/ 201409 | Periodic Safety Update EU Single assessment - sirolimus | 07/05/2015 | n/a | | PRAC Recommendation - maintenance |
| II/0155 | Update of section 4.8 of the SmPC in order to update the safety information on frequency for diabetes mellitus from "Common" to "Very Common" and including the new Adverse Drug Reaction Posterior | 26/03/2015 | 27/11/2015 | SmPC, Annex II and PL | Diabetes mellitus is reassigned to a very common frequency after re-evaluation of pooled safety data. Posterior Reversible Encephalopathy Syndrome is included among the Adverse Drug reaction for Rapamune after |

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| | Reversible Encephalopathy Syndrome (PRES) under frequency "Not Known". The Package Leaflet is updated accordingly.<br>In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 9.0.<br><br>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data | | | | analysis of post marketing safety data. |
| IA/0156 | B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place | 25/02/2015 | n/a | | |
| IAIN/0152/G | This was an application for a group of variations.<br><br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site<br>B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing | 02/12/2014 | 27/11/2015 | Annex II and PL | |
| IA/0151 | A.7 - Administrative change - Deletion of manufacturing sites | 24/07/2014 | n/a | | |

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| IB/0150 | B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS | 10/01/2014 | n/a | | |
| IB/0148 | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 21/08/2013 | 11/11/2013 | SmPC | |
| N/0147 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 29/07/2013 | 11/11/2013 | PL | Inclusion of an additional local representative of the MAH for Croatia. |
| IAIN/0146/G | This was an application for a group of variations.<br><br>B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site<br>B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing | 26/03/2013 | 11/11/2013 | Annex II and PL | |
| IA/0145 | A.7 - Administrative change - Deletion of manufacturing sites | 08/03/2013 | n/a | | |
| IA/0144 | A.7 - Administrative change - Deletion of manufacturing sites | 13/02/2013 | n/a | | |
| IB/0143 | B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 17/12/2012 | n/a | | |
| II/0140 | Update of section 4.8 of the SmPC in order to add ovarian cysts and menstrual disorders (including amenorrhea and menorrhagia) as adverse reactions. | 13/12/2012 | 11/11/2013 | SmPC, Annex II and PL | The MAH has performed a review of all data from the completed and ongoing clinical studies, from their safety database and medical literature for any reports of ovarian |

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| | The Package Leaflet is updated accordingly. Furthermore the Annex II is being brought in line with the latest QRD template.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | cysts and menstrual disorders (including amenorrhea and menorrhagia) in sirolimus-treated patients. This review showed that subjects treated with sirolimus-based regimens had a higher incidence of ovarian cysts and menstrual disorders (including amenorrhea and menorrhagia) compared to non-sirolimus based regimens. The inclusion of ovarian cysts and menstrual disorders (including amenorrhea and menorrhagia) in section 4.8 of the SmPC will prompt prescribers to carefully monitor for these events in female patients and take appropriate measures based on the medical conditions of the individual subjects. |
| IG/0235/G | This was an application for a group of variations.<br><br>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation<br>C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV | 06/12/2012 | n/a | | C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF). |
| II/0139 | Update of section 4.5 of the SmPC to include examples of inhibitors of CYP3A4 which may decrease the metabolism of sirolimus and increase sirolimus blood levels. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre- | 15/11/2012 | 11/11/2013 | SmPC, Annex II, Labelling and PL | The MAH conducted a search of its clinical database, its safety database, and the medical literature for any reports of interactions or increase in adverse events in patients on concomitant sirolimus and boceprevir, telaprevir, indinavir or ritonavir. Although no clinical studies are available on the interaction between sirolimus and boceprevir, telaprevir, indinavir or ritonavir, the MAH concluded that based on the strong inhibitory effects of these drugs on CYP3A4, a significant interaction cannot be excluded and that prescribers should be informed of this potential interaction so that appropriate monitoring of the blood level |

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| | clinical, clinical or pharmacovigilance data | | | | of sirolimus can be initiated to avoid any potential adverse events. Therefore the existing SmPC warning on possible interactions with inhibitors of CYP3A4 was extended by adding examples of the above-mentioned protease inhibitors which may cause a significant drug interaction with sirolimus. This list of products is also expanded to include other known potent CYP3A4 inhibitors: antifungals (itroconazole, voriconazole) and antibiotics (telithromycin, clarithromycin). |
| IAIN/0141 | B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing | 09/11/2012 | 11/11/2013 | Annex II and PL | |
| IB/0138/G | This was an application for a group of variations.<br><br>B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place<br>B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions<br>B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation<br>B.II.b.5.z - Change to in-process tests or limits | 25/07/2012 | n/a | | |

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| | applied during the manufacture of the finished product - Other variation<br>B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation | | | | |
| IG/0169/G | This was an application for a group of variations.<br><br>C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD<br>C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system | 08/06/2012 | n/a | | |
| IB/0136/G | This was an application for a group of variations.<br><br>B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products<br>B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place<br>B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the | 24/05/2012 | n/a | | |

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| | manufacturing process of an immediate release solid oral dosage form or oral solutions<br>B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation<br>B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation<br>B.II.c.1.z - Change in the specification parameters and/or limits of an excipient - Other variation | | | | |
| IB/0135 | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 20/03/2012 | 10/10/2012 | SmPC | |
| IA/0134 | A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release) | 16/12/2011 | n/a | | |
| IB/0131 | B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation | 30/11/2011 | n/a | | |
| IA/0132 | A.7 - Administrative change - Deletion of manufacturing sites | 15/11/2011 | 06/02/2012 | PL | |
| IA/0130 | A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS | 05/10/2011 | n/a | | |
| T/0129 | Transfer of Marketing Authorisation | 27/06/2011 | 27/07/2011 | SmPC, | |

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| | | | | Labelling and PL | |
| WS/0117 | This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.<br><br>C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH | 14/04/2011 | 23/05/2011 | Annex II | |
| IA/0128 | A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release | 29/04/2011 | n/a | Annex II and PL | |
| IA/0127 | B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits | 06/04/2011 | n/a | | |
| IB/0126 | B.I.c.1.z - Change in immediate packaging of the AS - Other variation | 10/02/2011 | n/a | | |
| IA/0125 | B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test | 02/02/2011 | n/a | | |
| IA/0124 | B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 02/02/2011 | n/a | | |

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| II/0121 | Update of section 4.8 of the SmPC to add the adverse event "Clostridium difficile Enterocolitis". An editorial change has also been made to section 4.8 of the SmPC. The MAH has also taken the opportunity to correct the contact detail of the French local representative.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | 16/12/2010 | 21/01/2011 | SmPC and PL | The MAH's database was searched through to identify reports containing the Preferred Terms from the standardised MedDRA Query Pseudomembranous colitis. The search identified 90 reports: Clostridial infection (n=9), Clostridium colitis (n=2), Clostridium difficile colitis (n=35), Clostridium difficile sepsis (n=1), Gastroenteritis clostridial (n=8), and Pseudomembranous colitis (n=35). In 61 reports, the patients had recent antibiotic exposure. In 15 reports, it was unclear or unknown if these patients had received recent antibiotic therapy. The remaining 14 reports were selected for further review, as these patients were not receiving antibiotic therapy. In most of these reports, the association between Clostridium difficile enterocolitis and sirolimus could not be excluded. From this review, it was concluded that there was reasonable suspicion that the occurrence of Clostridium difficile enterocolitis may be causally related to the administration of sirolimus. As many of these identified reports were from independent studies, an estimated frequency of Clostridium difficile enterocolitis could not be determined. The MAH´s proposal to amend the table in section 4.8 of the Rapamune SmPC with Clostridium difficile enterocolitis as an adverse event with unknown frequency is therefore supported. |
| R/0120 | Renewal of the marketing authorisation. | 21/10/2010 | 06/01/2011 | SmPC, Annex II, Labelling and PL | Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit-risk balance, the CHMP is of the opinion that the quality, safety and efficacy of Rapamune continues to be adequately and sufficiently demonstrated and therefore considered that the benefit-risk profile of Rapamuen continues to be favourable. |

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| | | | | | The CHMP recommends the renewal of the Marketing Authorisation with unlimited validity. |
| IA/0123 | A.7 - Administrative change - Deletion of manufacturing sites | 16/12/2010 | n/a | | |
| IB/0122 | B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation | 03/11/2010 | n/a | | |
| IB/0115 | C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation | 20/08/2010 | n/a | SmPC, Annex II, Labelling and PL | |
| IB/0119 | B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) | 17/08/2010 | n/a | | |
| IB/0113 | B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) | 04/08/2010 | n/a | SmPC | |
| IA/0118 | A.7 - Administrative change - Deletion of manufacturing sites | 02/08/2010 | n/a | | |
| IA/0117 | B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test | 02/08/2010 | n/a | | |
| IA/0116/G | This was an application for a group of variations.<br><br>B.II.c.1.c - Change in the specification parameters | 02/08/2010 | n/a | | |

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| | and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | | | | |
| IB/0114/G | This was an application for a group of variations.<br><br>B.II.d.2.z - Change in test procedure for the finished product - Other variation<br>B.II.d.2.z - Change in test procedure for the finished product - Other variation | 29/07/2010 | n/a | | |
| IB/0112 | To implement minor changes to an analytical method for determination of Group II degradation productsof Rapamycin in Rapamune finished product, clarification of the range of temperature for the column from "35°C" to "35°C +/- 5°C" and for the sample chamber from "20°C" to "20°C +/- 2°C".<br><br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | 19/07/2010 | n/a | | |
| IB/0111 | To implement minor changes to an analytical method | 19/07/2010 | n/a | | |

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| | by HPLC for the finished product, tightening of the air flow rate from 0.6 - 2.0 mL/min to 0.8 - 1.0 mL/min and clarification of the range temperature for the column from "40°C" to "40 °C +/- 5°C".<br><br>B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) | | | | |
| X/0093 | Addition of a new strength<br><br>Annex I_2.(c) Change or addition of a new strength/potency | 22/04/2010 | 07/07/2010 | SmPC, Annex II, Labelling and PL | Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of sirolimus in the:<br>"prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant. It is recommended that Rapamune be used initially in combination with ciclosporin microemulsion and corticosteroids for 2 to 3 months. Rapamune may be continued as maintenance therapy with corticosteroids only if ciclosporin can be progressively discontinued (refer to sections 4.2 and 5.1)."<br>was favourable and therefore recommended the granting of the extension of the marketing authorisation. |
| II/0098 | Update of section 4.4 of the SmPC to delete the qualifier "rare" in the description of the concurrent administration of sirolimus and ACE-inhibitors in patients with angioedema and to reflect that rhabdomyolysis has been observed in patients receiving sirolimus with an HMG-CoA reductase inhibitor with or without ciclosporine administration. The PL has been updated accordingly.<br>Minor editorial changes have been made to section | 20/05/2010 | 01/07/2010 | SmPC and PL | The MAH identified 53 cases of patients who experienced angioedema, with In 26 (49%) of these reports having the co-administration of an ACE-inhibitor documented or suspected. Based on these number of cases of angioedema reported with sirolimus in combination with an ACE inhibitor, the proposal to delete the qualifier "In rare cases" from the corresponding sentence in the Rapamune SmPC is endorsed by the CHMP.<br>The MAH's database was searched prior to the IBD and |

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| | 10 of the SmPC and the PL.<br><br>C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | | | | through 14 September 2009 for all reports on MedDRA preferred term Rhabdomyolysis/Myopathy. 37 cases were identified. In 22 of the 37 cases, patients were receiving ciclosporine (CsA) concomitantly or very limited information was provided. From the remaining 15 reports, 11 patients had rhabdomyolysis and 7 of these patients were receiving a fibrate or HMG-CoA reductase inhibitor and/or fibrate without CsA administration. It is therefore concluded that rhabdomyolysis has been observed in patients receiving sirolimus with an HMG-CoA reductase inhibitor and/or fibrate, with or without CsA administration and that the recommendation to monitor patients on sirolimus with or without CsA for elevated lipid levels is considered to be in accordance with common clinical practice. |
| IA/0109/G | This was an application for a group of variations.<br><br>- To delete Wyeth Pharmaceuticals, Havant (Hampshire P09 2HG UK) as a testing site for Rapamune oral solution.<br>- To update the hold tank pressure.<br>- To add a control sample parameter for an excipient used in Rapamune.<br>- To add a sensivity solution for Rapamune sample solution analysis by HPLC.<br>- To update the test from infra-red to visual for the syringe used for Rapamune finished product.<br>- To change in the name of the supplier from Lawson Mardon Wheaton to Gerresheimer Glass Inc.<br><br>A.7 - Administrative change - Deletion of manufacturing sites | 24/06/2010 | n/a | | |

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| | B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions<br>B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure<br>B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure<br>B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)<br>B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier | | | | |
| IB/0104 | To change in the description of the bulk storage secondary packaging.<br><br>B.I.c.1.a - Change in immediate packaging of the AS - Qualitative and/or quantitative composition | 20/04/2010 | n/a | | |
| IB/0103 | To change in the production test process for Sirolimus active substance.<br><br>B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure | 20/04/2010 | n/a | | |
| IB/0102 | B.I.b.2.a - Change in test procedure for AS or | 20/04/2010 | n/a | | |

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| | starting material/reagent/intermediate - Minor changes to an approved test procedure | | | | |
| IB/0101/G | This was an application for a group of variations.<br><br>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate<br>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate<br>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate<br>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate<br>B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate | 20/04/2010 | n/a | | |

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| IA/0108 | To delete an specification parameter from an intermediate of the active substance<br><br>B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 31/03/2010 | n/a | | |
| IA/0107 | To delete an obsolete test procedure performed on an intermediate of the active substance.<br><br>B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised | 31/03/2010 | n/a | | |
| IA/0106/G | This was an application for a group of variations.<br><br>To delete a non-significant specification parameter for residual solvent limits in 3 excipients<br><br>B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)<br>B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | 31/03/2010 | n/a | | |

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| | B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) | | | | |
| IA/0105 | To delete an In Process Control for appaerance at the curing stage.<br><br>B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test | 31/03/2010 | n/a | | |
| IA/0100 | To include a minor change in the manufacturing process of the active substance<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 31/03/2010 | n/a | | |
| IA/0099 | To include a minor change in the manufacturing process of the active substance<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS | 31/03/2010 | n/a | | |
| IA/0097 | To introduce a minor change in the manufacturing process of the acitve substance<br><br>B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process | 22/02/2010 | n/a | | |

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| | of the AS | | | | |
| II/0094 | Update of section 4.2 of the SPC to with information on the assay methods used for the determination of sirolimus concentration.<br><br>Update of Summary of Product Characteristics | 17/12/2009 | 28/01/2010 | SmPC | Adjustments to the targeted therapeutic dose range of sirolimus must only be made with a detailed knowledge of the specific assay used to measure the drug concentration in the patient. Currently, sirolimus whole-blood concentrations are measured using either the reference assay high performance liquid chromatography (HPLC), or an immunoassay. Switching between different immunoassays, or between an immunoassay and HPLC, in a single patient can lead to clinically significant differences in results, and, therefore, incorrect dose adjustments. This, in turn, may have potential adverse consequences, such as allograft rejection if drug exposure is too low or toxic side effects if exposure is too high. Prescribers are therefore encouraged to regularly contact their laboratory and ascertain whether the assay used recently has been changed, and whether there have been any changes to the laboratory's reference range. On the basis of these findings, section 4.2 of the SPC has been revised. The MAH agreed with the CHMP on a Direct Healthcare Professional and a communication plan informing healthcare professionals of these findings. |
| IA/0096 | IA_09_Deletion of manufacturing site | 23/12/2009 | n/a | PL | |
| II/0090 | Update of section 4.8 of the SPC to include the adverse events "ascites" and "diabetes mellitus" and information regarding reports of fluid accumulation in different tissues in patients receiving Rapamune. Section 5.1 of the SPC has also been updated with information on hepatic veno-occlusive disease. The | 19/11/2009 | 21/12/2009 | SmPC and PL | Data from the literature, clinical studies and post-marketing experience cannot exclude a causal association between sirolimus treatment and ascites. Ascites has been added as a common adverse event to section 4.8 of the SPC for Rapamune.<br>Due to the number of fluid accumulation reports that were |

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| | Package leaflet is updated accordingly.<br>This variation application is submitted further to the request of the CHMP following assessment of PSUR 13 for Rapamune, covering the period 15 September 2007 - 14 September 2008.<br>The MAH has also taken the opportunity to update the list of local representatives in the PL for Spain, Portugal, Germany, Austria and Greece.<br><br>Update of Summary of Product Characteristics and Package Leaflet | | | | considered to be related to SRL and also its possible mechanism, the occurrence of fluid accumulation with SRL cannot be ruled out. Information regarding reports of fluid accumulation in different tissues in patients receiving sirolimus has been added to section 4.8 of the SPC.<br>Data from the literature and clinical studies suggest that sirolimus may be associated with an increased incidence of new onset diabetes. Diabetes mellitus has therefore been added to section 4.8 of the SPC.<br>Based on the review of the literature, an association between sirolimus and hepatic veno-occlusive disease in bone marrow transplant patients cannot be ruled out. Section 5.1 of the SPC was therefore updated with information regarding the increased incidence of hepatic VOD in patients treated with Rapamune. |
| IB/0095 | IB_34_b_01_Change in colour/flavour - Increase or addition: colouring system | 17/12/2009 | n/a | | |
| IA/0092 | IA_09_Deletion of manufacturing site | 18/08/2009 | n/a | | |
| IB/0091 | IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) | 13/08/2009 | n/a | | |
| II/0079 | To replace the storage site of the Master Cell Bank.<br><br>Quality changes | 23/07/2009 | 29/07/2009 | | |
| IA/0089 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 20/07/2009 | n/a | | |

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| IA/0088 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 20/07/2009 | n/a | | |
| IB/0087 | IB_10_Minor change in the manufacturing process of the active substance | 22/06/2009 | n/a | | |
| IA/0086 | IA_13_a_Change in test proc. for active substance - minor change | 18/06/2009 | n/a | | |
| IA/0085 | IA_13_a_Change in test proc. for active substance - minor change | 18/06/2009 | n/a | | |
| IA/0084 | IA_13_a_Change in test proc. for active substance - minor change | 18/06/2009 | n/a | | |
| IA/0082 | IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure | 16/06/2009 | n/a | | |
| IA/0081 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 16/06/2009 | n/a | | |
| II/0078 | To remove the three in-process tests that are currently performed prior to the end of bulk Rapamune oral solution manufacture.<br><br>Quality changes | 25/06/2009 | 04/06/2009 | | |
| II/0075 | To update the sites of testing and specification of a solvent used in the preparation of Sirolimus active substance. | 29/05/2009 | 04/06/2009 | | |

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| | Quality changes | | | | |
| IA/0080 | IA_13_a_Change in test proc. for active substance - minor change | 29/05/2009 | n/a | | |
| IB/0077 | IB_17_a_Change in re-test period of the active substance | 30/04/2009 | n/a | | |
| II/0074 | Update of Summary of Product Characteristics, Labelling and Package Leaflet | 19/03/2009 | 29/04/2009 | SmPC, Annex II, Labelling and PL | |
| IA/0076 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 08/04/2009 | n/a | | |
| IA/0073 | IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure | 17/12/2008 | n/a | | |
| II/0070 | Update of Summary of Product Characteristics and Package Leaflet<br>Update of sections 4.4 and 4.8 of the SPC and section 4 of the PL to implement the warning on BK virus associated nephropathy and JC virus associated progressive multifocal leukoencephalopathy (PML) requested by the CHMP in July 2008.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 25/09/2008 | 30/10/2008 | SmPC and PL | Cases of BK virus associated nephropathy (BKVN) and cases of JC virus associated progressive multifocal leukoencephalopathy (PML) have been reported in patients treated with immunosuppressants, including Rapamune. These infections are often related to a high total immunosuppressive burden and may lead to serious or fatal conditions. Thus physicians should consider BKVN and PML in the differential diagnosis in immunosuppressed patients with deteriorating renal function or neurological symptoms. |
| II/0068 | Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet<br>Update of section 4.8 of the SPC to include the | 25/09/2008 | 30/10/2008 | SmPC, Annex II, Labelling | Based on a review of reports from the MAH's safety database, from clinical trials and from the literature, there is a reasonable suspicion of a causal relationship between |

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| | adverse events 'focal segmental glomerulosclerosis', 'alveolar proteinosis', 'headache', 'pain', 'hypertension', 'constipation', 'nausea', 'increased creatinine' as well as a revised frequency for 'pyrexia', based on a review of data from published literature, the MAH's pharmacovigilance database and clinical trials, as relevant. Section 4 of the Package Leaflet (PL) was updated accordingly.<br>The MAH also took the opportunity of this variation to make linguistic corrections to the SPC, Annex II, Labelling and PL, as relevant, for Bulgaria, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Italy, Latvia, Lithuania, Malta, Norway, Poland, Portugal, Romania, Slovak Republic, Spain and Sweden.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | | | and PL | treatment with immunosuppressive regimens containing Rapamune and the occurrence of 'focal segmental glomerulosclerosis', 'alveolar proteinosis', 'headache', 'pain', 'hypertension', 'constipation', 'nausea', and 'increased creatinine'. Thus, these adverse reactions have been included in the SPC and PL. In addition, the frequency of pyrexia has been increased from 'common' to 'very common' (greater than or equal to 1 in 10 patients). |
| II/0067 | Update of Summary of Product Characteristics and Package Leaflet<br><br>Update of sections 4. 2, 4.8, 5.1 and 5.2 of the SPC to include data from completed clinical trials in paediatric patients, as requested by the CHMP in April 2006. The MAH also took the opportunity to update the contact details of a local representative in the PL.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 25/09/2008 | 30/10/2008 | SmPC and PL | In a controlled clinical trial with paediatric renal transplant patients considered at high immunologic risk (i.e. with a history of acute rejection or with chronic allograft nephropathy), the use of sirolimus in combination with a calcineurin inhibitor and corticosteroids failed to show superiority to the control group (standard calcineurin inhibitor-based regimen) in terms of the first occurrence of acute rejection, graft loss or death, and was associated with an increased risk of deterioration of renal function, serum lipid abnormalities, and urinary tract infections. In another study in which corticosteroids were eliminated from a full dose immunosuppressive regimen with sirolimus and |

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| | | | | | a calcineurin inhibitor with basiliximab induction in paediatric primary renal transplant patients, corticosteroid withdrawal was associated with improved linear growth after one year; however, the frequency of post transplant lymphoproliferative disorders was unacceptably high. A combined pharmacokinetic analysis of these two trials showed that younger children had a higher weight normalised oral-dose clearance which suggest that those patients might require higher bodyweight-adjusted doses than adolescents and adults to achieve similar target concentrations. It should be noted that the treatment regimens used in these studies (continuous use of a calcineurin inhibitor in combination with sirolimus) is not approved for Rapamune. Although these studies do not support a paediatric indication or specific dose recommendations in children, the CHMP agreed that relevant information should be included in the SPC. |
| IA/0071 | IA_13_a_Change in test proc. for active substance - minor change | 03/09/2008 | n/a | | |
| IA/0072 | IA_09_Deletion of manufacturing site | 01/09/2008 | n/a | | |
| IA/0069 | IA_47_b_Deletion of a strength | 17/07/2008 | n/a | SmPC, Labelling and PL | |
| II/0062 | Update of Summary of Product Characteristics and Package Leaflet | 19/03/2008 | 21/04/2008 | SmPC and PL | |
| IA/0066 | IA_39_Change/addition of imprints, bossing or other markings | 03/04/2008 | n/a | SmPC and PL | |

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| IB/0064 | IB_13_b_Change in test proc. for active substance - other changes (replacement/addition) | 28/01/2008 | n/a | | |
| IA/0065 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site | 24/01/2008 | n/a | | |
| II/0060 | Quality changes | 13/12/2007 | 20/12/2007 | | |
| IA/0063 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 04/12/2007 | n/a | | |
| II/0058 | Update of Summary of Product Characteristics, Labelling and Package Leaflet<br><br>To update section 4.4 of the SPC with information on impaired wound healing and on pleural effusion, section 4.6 with information on male fertility and section 4.8 with the adverse events 'tuberculosis', 'pleural effusion' and 'incisional hernia' and information on male fertility. These changes are based on a review of relevant data from published literature, the MAH's pharmacovigilance database and clinical trials.<br>In addition, section 4.2 of the SPC for Rapamune tablets has been updated with a statement indicating that tablets should be administered intact.<br>The PL has been updated accordingly.<br>The MAH also took the opportunity of this variation to make minor changes to the SPC and labelling for Rapamune oral solution as well as to the PL of all | 18/10/2007 | 20/11/2007 | SmPC, Annex II, Labelling and PL | A review of data from the literature, clinical trials and the company's pharmacovigilance database revealed that treatment with Rapamune could be associated with reversible impairments of male fertility (changes in sperm parameters). Impairments of wound healing have also been observed in patients treated with Rapamune with a greater risk in those with a body mass index greater than 30 kg/m2. In addition, pleural effusion (fluid around the lungs) and tuberculosis were commonly reported (in more than 1 in 100 but less than 1 in 10 patients). This information has been added or further detailed as appropriate in the SPC and PL. Furthermore, in the absence of adequate bioavailability data, it has been highlighted that Rapamune tablets should not be chewed, split or crushed before swallowing. |

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| | pharmaceutical forms in line with the EMEA/QRD template (version 7.2). Furthermore, minor linguistic corrections have been made to the SPC, Annex II, Labelling and PL for Bulgaria, Estonia, Latvia, Lithuania, Romania and Slovenia.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | | | | |
| IA/0061 | IA_39_Change/addition of imprints, bossing or other markings | 15/10/2007 | n/a | SmPC and PL | |
| IB/0059 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site<br>IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 20/09/2007 | n/a | | |
| II/0053 | Update of section 4.4 of the SPC to include information on the adverse reaction "exfoliative dermatitis" and of section 4.8 to add the adverse reactions "exfoliative dermatitis", "hypophosphataemia" and "hyperglycaemia". These changes follow the update of the Company Reference Safety Information and are based on a review of reports from published literature, pharmacovigilance database and clinical trials. Section 4 of the PL has been updated accordingly.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 19/07/2007 | 27/08/2007 | SmPC and PL | A review of cases of exfoliative dermatitis (a skin condition whereby the skin can peel off), hypophosphataemia (low blood phosphorus) and hyperglycaemia (elevated blood sugar) was performed by the MAH on data from the literature, from clinical trials and from the company's pharmacovigilance database. This review revealed that hypophosphataemia and hyperglycaemia are adverse reactions very commonly observed in immunosuppressive regimens containing Rapamune (in more than 1 in 10 patients). Rapamune can also be associated with exfoliative dermatitis in rare cases (in less than 1 in 1000 patients). This information was included in the SPC and the PL. |

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| IB/0056 | IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site<br>IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release<br>IB_07_b_03_Replacement/add. of manufacturing site: Primary packaging site - liquid ph. forms | 23/08/2007 | n/a | | |
| IA/0057 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 31/07/2007 | n/a | | |
| II/0051 | To update sections 4.4 and 4.8 of the SPC with information on pericardial effusions based on a cumulative review performed at the CHMP request following assessment of PSUR 8 (covering the period from 15 September 2005 to 14 September 2006). Section 4 of the Package Leaflet (PL) has been updated accordingly. The MAH also took the opportunity to make minor linguistic corrections to the Danish, Finnish, German, Dutch, Spanish and Swedish versions of the SPC, Annex II and Package Leaflet, as relevant.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 21/06/2007 | 25/07/2007 | SmPC, Annex II and PL | A cumulative review of cases of pericardial disorders was performed by the MAH based on data from the literature, from clinical trials in cardiac and renal transplant patients and from the MAH's pharmacovigilance database. Most of all, the results of the studies showed that cardiac transplant patients treated with sirolimus have an increased risk of pericardial effusion (collection of fluid in the pericardial space), but no significant difference in the rates of pericardial events was observed in the renal transplant trials (currently approved indication). Although the suspicion that sirolimus may be associated with pericardial effusion is stronger in cardiac transplantation, it can not be ruled out for other solid organ transplant recipients. Based on these findings, a warning regarding reports of fluid accumulation was included in section 4.4 of the SPC and "pericardial effusion" was included in section 4.8 of the SPC and in section 4 of the PL as an uncommon adverse reaction. |
| II/0052 | Quality changes | 19/07/2007 | 24/07/2007 | | |

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| IA/0055 | IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms | 06/07/2007 | n/a | | |
| IA/0054 | IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing | 28/06/2007 | n/a | Annex II and PL | |
| IA/0050 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 11/04/2007 | n/a | | |
| II/0048 | Update of sections 4.4 and 5.1 of the Rapamune SPC, following CHMP request on 21 September 2006, to include information concerning the results from a terminated study and the discontinued arm of another study, both of which used a sirolimus-based, calcineurin inhibitor-free regimen at the initiation of treatment in de novo renal transplant patients.<br><br>Update of Summary of Product Characteristics | 22/02/2007 | 29/03/2007 | SmPC | This variation has been submitted to update the SPC with information on two clinical trials conducted with Rapamune that have been prematurely stopped by the MAH due to safety concerns. Both clinical trials evaluated the safety and efficacy of Rapamune in a calcineurin inhibitor-free regimen at the initiation of treatment in de novo renal transplant patients, i.e. in indications and combinations not currently approved for Rapamune. A higher rate of acute rejection and a higher rate of deaths were observed in these patients, without a supporting benefit in renal function. |
| II/0047 | Update of sections 4.4, 4.8 and 5.1 of the SPC with data from an ongoing clinical study evaluating the conversion from calcineurin inhibitors to sirolimus, and from the 60-month clinical study report of the pivotal study. The Package Leaflet was updated accordingly.<br>In addition, the MAH completed the list of local representatives in the Package Leaflet to include the two new EU Member States (Bulgaria and Romania) and updated the product information according to the latest EMEA QRD template. | 22/02/2007 | 29/03/2007 | SmPC, Labelling and PL | The MAH has presented for this variation new safety data from the 24-month analyses of an ongoing clinical study designed to evaluate the conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant patients. These new results indicate that sirolimus was associated with the development or the progression of proteinuria. Nephrotic syndrome was also reported. On the other hand, sirolimus was associated with less frequency of malignancy development, compared with continued therapy with calcineurin inhibitors. The results also support that the target population for conversion to sirolimus therapy are |

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| | Update of Summary of Product Characteristics, Labelling and Package Leaflet | | | | patients with a glomerular filtration rate superior to 40.0 ml/min and a normal urinary protein excretion at the time of conversion. These findings warrant an update of sections 4.4, 4.8 and 5.1 of the SPC. Furthermore, section 5.1 of the SPC has been completed with additional data from another clinical study performed at the time of the initial registration of Rapamune, and which compared continuous therapy with ciclosporin and sirolimus versus induction with ciclosporin and sirolimus followed by ciclosporin elimination. In this study, up to 36 months, graft and patient survival were similar for both groups. However, after the third year of study, it was identified that the combination treatment (sirolimus and ciclosporin) was less beneficial to patients than the other arm of the study and patients were discontinued from the combination. |
| II/0044 | Update sections 4.2 and 5.2 of the SPC for Rapamune to include further advice on how to make dose adjustments in patients during the maintenance phase after discontinuation of ciclosporin and revise the information concerning assay methodologies for therapeutic drug monitoring.<br><br>Update of Summary of Product Characteristics | 27/07/2006 | 07/09/2006 | SmPC | The advice given in the SPC on how to make dose adjustments in patients during maintenance after discontinuation of ciclosporin has been updated.General update concerning the developments in assay methodologies for therapeutic monitoring since the approval of Rapamune in 2001 was also made. |
| II/0043 | Update of sections 4.4 and 4.8 of the SPC for Rapamune to include the safety concept of delayed recovery of renal function in patients with delayed graft function (DGF).<br><br>The contact of the local representative in Iceland is being updated in section 6 of the Package Leaflet. | 27/07/2006 | 07/09/2006 | SmPC and PL | The results from an interim analysis of a submitted clinical study did not demonstrate any significant differences between treatment groups considering delayed graft function (DGF) frequency or duration. This study, however, included only patients at low risk for DGF so the data did not permit conclusions to be drawn on kidney graft recipients at high risk of DGF. Data from literature, both in |

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| | Update of Summary of Product Characteristics and Package Leaflet | | | | vitro and clinical data, strongly support the hypothesis that sirolimus can inhibit renal tubular cell proliferation, thereby delaying healing of acute tubular necrosis and prolonging the period of delayed graft function. Sections 4.4 and 4.8 of the SPC include information that sirolimus can delay recovery from acute tubular necrosis in the clinical transplant situation. As no influence was seen on long term transplant function, this information does not alter the overall benefit risk balance for Rapamune. |
| IA/0046 | IA_13_a_Change in test proc. for active substance - minor change | 08/08/2006 | n/a | | |
| II/0041 | Update of section 4.4 of the SPC with the addition of a statement that in rare cases the concomitant administration of sirolimus and angiotensin converting enzyme (ACE) inhibitors has resulted in angioneurotic oedema-type reactions. At the same time, the MAH has taken the opportunity to correct a minor typographical error in section 4.5 about the increase of sirolimus Cmax when given concomitantly with ketoconazole.<br><br>Update of Summary of Product Characteristics | 28/06/2006 | 28/07/2006 | SmPC | SPC sections 4.4 and 4.8 already report hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, and hypersensitivity vasculitis, with the administration of sirolimus. Following a literature review it was concluded that there is reasonable evidence that, in rare cases, the concomitant administration of sirolimus and ACE inhibitors has resulted in angioneurotic oedema-type reactions. This information has now been included in section 4.4 of the SPC. |
| II/0040 | Revision of section 4.8 of the SPC according to the MedDRA terminology, the SPC guideline and in line with relevant post-marketing experience as requested by the CHMP further to the renewal assessment in January 2006. The PL has been amended as appropriate | 28/06/2006 | 28/07/2006 | SmPC and PL | Fulfilling a commitment made as part of the renewal of the MA for Rapamune, the MAH has reviewed sections 4.8 of the SPC. Section 4.8 is now updated in line with the MedDRA terminology and frequency as well as the latest SPC guideline. Based on the available post-marketing data, no new adverse drug reaction or any new safety information was identified. The PL was updated accordingly, |

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| | Update of Summary of Product Characteristics and Package Leaflet | | | | as relevant. |
| IB/0045 | IB_42_a_01_Change in shelf-life of finished product - as packaged for sale | 10/07/2006 | n/a | SmPC | |
| II/0038 | Change in formulation | 27/04/2006 | 31/05/2006 | SmPC and PL | |
| IA/0042 | IA_05_Change in the name and/or address of a manufacturer of the finished product | 26/04/2006 | n/a | Annex II and PL | |
| R/0037 | Renewal of the marketing authorisation. | 23/02/2006 | 06/04/2006 | SmPC, Annex II, Labelling and PL | The information and data that have become available since the time of the initial marketing authorisation approval are consistent with the known profile of Rapamune (sirolimus) in the prophylaxis of renal transplant rejection in adults at low to moderate immunologic risk. This includes the long-term efficacy and safety data from the pivotal clinical study 310 that continues to support the approved indication, mode of use, and product information in the SPC.<br><br>Based upon the data that have become available since the marketing authorisation approval, Rapamune has been shown to maintain a positive benefit-risk balance, in spite of the serious safety profile of the medicinal product. In the context of this renewal application, the MAH has adequately addressed the benefit-risk balance, taking into account the updated, consolidated data and all relevant new information. Based on the re-evaluation of the benefit risk balance, the product can be safely renewed for another 5-year period at which time the MAH will submit another renewal application. |

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| IA/0039 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 10/03/2006 | n/a | | |
| II/0036 | Update of section 4.8 of the SPC to include skin cancer following the MAH's review of the malignancy data in the final 60 month Clinical Study Report for the pivotal registration study.<br><br>Section 4 of the PL has been updated accordingly. Also, update of section 4 of the PL to add a warning about angiooedema as already included in section 4.8 of the SPC.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 26/01/2006 | 28/02/2006 | SmPC and PL | Data presented support the hypothesis that sirolimus differs from calcineurin inhibitors in cancer promotive action and therefore section 4.4 of the Rapamune SPC is now mentioning the difference in cancer incidence between treatment arms in the 5 year data from the pivotal study in line with other data already presented in the SPC.<br><br>Based on this data, sections 4.8 of the SPC and 4 of the PL have been updated to include a warning about the incidences of skin cancer in connection with the use of the immunosuppressive Rapamune to draw patients and health care professionals' attention to the need for extra precautions to minimise exposure to UV light. |
| II/0035 | Update of sections 4.4 and 4.8 of the SPC and consequential changes to point 4 of the PL for the oral solution and tablets following the CHMP assessment of the sixth Periodic Safety Report covering the period from 15 March 2004 to 14 March 2005. The update adds angioedema, hypersensitivity vasculitis and the potential enhancement of calcineurin-inhibitor-induced haemolytic uraemic syndrome, thrombotic microangio-pathy and thrombotic thrombocytopaenic purpura to the indicated sections of the SPC and PL of sirolismus.<br><br>Update of Summary of Product Characteristics and Package Leaflet | 17/11/2005 | 10/01/2006 | SmPC and PL | The addition of angioedema, hypersensitivity vasculitis and haemolytic uraemic syndrome, thrombotic microangiopathy and thrombotic thrombocytopaenic purpura to the SPC has been recommended by the CHMP on 28 July 2005 post review of the 6th PSUR. There is reason to believe that there is a causal relationship between the treatment with Rapamune and angioedema in at least six cases referred to above. Hypersensitivity vasculitis has been attributed to Rapamune administration in at least three documented cases according to the MAH's Global Safety Surveillance and Epidemiology database. Data from the literature and results from pivotal studies suggest that sirolimus may increase the risk of calcineurin inhibitors-induced haemolytic uraemic syndrome /thrombotic |

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| | | | | | microangiopathy/thrombotic Thrombocytopaenic purpura. |
| II/0033 | To introduce lymphoedema in section 4.8 of the SPC and point 4 of the PL for the oral solution and tablets, further to the CHMP assessment of PSUR 6 covering the period between 15 March 2004 and 14 March 2005. Furthermore, information is updated in section 6.2 of the SPC for the oral solution.<br><br>In addition, the Marketing Authorisation Holder updated the SPC, labelling and PL for the 5mg Tablet to bring the Product Information of this presentation in line with the changes introduced for the other strengths and presentations of Rapamune in recent variation EMEA/H/C/273/II/29.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 15/09/2005 | 07/11/2005 | SmPC, Labelling and PL | In the MAH's assessment of three reports described in the literature, there was a similar pattern of the oedema worsening and become non-pitting, and there was no evidence of infection and no family history of lymphoedema. Further, there was a temporal relationship between the administration of Rapamune and the development of lymphoedema, with a positive dechallenge in all three patients. There is a reasonable suspicion that the occurrence of lymphoedema may be causally related to the administration of Rapamune in these literature reports. During the last PSUR period 7 cases of lymphoedema was reported. The patient exposure to Rapamune during the same period was 517339 patient-months. The proposal to include lymphoedema as a rare event is endorsed. |
| IB/0034 | IB_25_a_02_Change to comply with Ph. - compliance with EU Ph. - excipient | 31/08/2005 | n/a | | |
| II/0030 | Change(s) to the manufacturing process for the active substance.<br><br>Quality changes | 23/06/2005 | 30/06/2005 | | In the MAH's assessment of three reports described in the literature, there was a similar pattern of the oedema worsening and become non-pitting, and there was no evidence of infection and no family history of lymphoedema. Further, there was a temporal relationship between the administration of Rapamune and the development of lymphoedema, with a positive dechallenge in all three patients. There is a reasonable suspicion that the occurrence of lymphoedema may be causally related to the administration of Rapamune in these literature reports. |

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| | | | | | During the last PSUR period 7 cases of lymphoedema was reported. The patient exposure to Rapamune during the same period was 517339 patient-months. The proposal to include lymphoedema as a rare reaction is endorsed. |
| IA/0032 | IA_09_Deletion of manufacturing site | 23/05/2005 | n/a | | |
| II/0029 | To update the SPC, Labelling and PL with changes that are consequential to those made to the Product Information for Rapamune 5 mg tablets during the scientific evaluation and QRD review. The SPC amendments especially concern the addition of a recommendation to monitor/control trough concentrations following a switch between tablet strengths and these affect the coated tablet SPC sections 4.2 and 5.2<br><br>In addition, a cross-reference to section 5.1 is added to the SPC, section 4.4 of oral solution and coated tablet formulations.<br><br>A minor change is proposed to section 6 of the PL concerning the name of the local French representative, the contact details of the local Norwegian and Finnish representatives, and a further minor change is made to one of the sub-heading of section 2 of the PL for 1mg and 2mg coated tablets.<br><br>Update of Summary of Product Characteristics, Labelling and Package Leaflet | 17/03/2005 | 28/04/2005 | SmPC, Labelling and PL | In bioequivalence study 187-UK (10 mg dose of sirolimus as ten 1-mg tablets, five 2-mg tablets, or two 5-mg triangular tablets) and also in study 179-UK (5 mg sirolimus as five 1 mg tablets or as one 5 mg tablet), the parameter C24h showed bio-inequivalence based on the pairwise comparison of 5 mg and 1 mg. An estimation of the impact of this difference at steady state was made, and indicated that sirolimus steady-state trough values would be expected to be 24% higher after switching from a multiple-dose regimen of 1-mg tablets (10-mg/day) to a multiple-dose regimen of 5-mg tablets (10-mg/day). A 24% difference in trough levels when switching between formulations can be considered to lie within the normal variability and therefore the same target trough ranges might be used for the different strengths, despite the potential difference in C24 hours.<br><br>Since switching of tablet strengths would most likely occur during initial therapy when the Rapamune dose is individualized to obtain whole blood trough levels of 4 to 12 ng/ml and when ciclosporin A (CsA) is discontinued and the Rapamune dose adjusted to obtain whole blood trough levels of 12 to 20 ng/ml, any effect of switching between tablet strengths would be entirely mitigated by the use of therapeutic drug level monitoring. Hence, it was proposed |

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| IA/0031 | IA_39_Change/addition of imprints, bossing or other markings | 11/04/2005 | n/a | | |
| X/0021 | Addition of a new strength.<br><br>Annex I_2.(c) Change or addition of a new strength/potency | 21/10/2004 | 20/01/2005 | SmPC, Annex II, Labelling and PL | Please refer to the Scientific Discussion. Rapamune H-273-X-21. |
| IB/0028 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 10/11/2004 | n/a | | |
| IA/0027 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 20/09/2004 | n/a | | |
| IA/0026 | IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site | 20/09/2004 | n/a | | |
| II/0024 | Update of Summary of Product Characteristics, Labelling and Package Leaflet | 23/06/2004 | 02/09/2004 | SmPC, Labelling and PL | |
| N/0025 | Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification) | 20/05/2004 | n/a | PL | |
| IA/0023 | IA_38_a_Change in test procedure of finished | 07/04/2004 | n/a | | |

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| | product - minor change to approved test procedure | | | | |
| IA/0022 | IA_38_a_Change in test procedure of finished product - minor change to approved test procedure | 07/04/2004 | n/a | | |
| IB/0020 | IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release | 30/01/2004 | n/a | | |
| II/0019 | Update of Summary of Product Characteristics and Package Leaflet | 20/11/2003 | 29/01/2004 | SmPC and PL | |
| II/0017 | Change(s) to the manufacturing process for the active substance | 17/12/2003 | 07/01/2004 | | |
| I/0013 | 17_Change in specification of the medicinal product | 03/10/2003 | 10/10/2003 | | |
| I/0018 | 01_Change in the name of a manufacturer of the medicinal product | 01/10/2003 | 09/10/2003 | | |
| II/0014 | Update of Summary of Product Characteristics and Package Leaflet | 22/05/2003 | 01/09/2003 | SmPC and PL | |
| I/0016 | 20_Extension of shelf-life as foreseen at time of authorisation | 04/07/2003 | 05/08/2003 | SmPC | |
| I/0015 | 23_Change in storage conditions | 14/05/2003 | 30/06/2003 | SmPC, Labelling and PL | |
| II/0011 | Update of Summary of Product Characteristics and Package Leaflet | 19/09/2002 | 28/01/2003 | SmPC and PL | |

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| X/0005 | X-3-iv_Change or addition of a new pharmaceutical form | 19/09/2002 | 10/01/2003 | SmPC, Annex II, Labelling and PL | |
| I/0010 | 20_Extension of shelf-life as foreseen at time of authorisation | 23/08/2002 | 08/10/2002 | SmPC | |
| I/0012 | 01_Change in the name of a manufacturer of the medicinal product | 13/09/2002 | 20/09/2002 | | |
| I/0009 | 12_Minor change of manufacturing process of the active substance | 23/08/2002 | 16/09/2002 | | |
| I/0008 | 12_Minor change of manufacturing process of the active substance | 23/08/2002 | 16/09/2002 | | |
| I/0007 | 12_Minor change of manufacturing process of the active substance | 23/08/2002 | 16/09/2002 | | |
| I/0006 | 12a_Change in specification of starting material/intermediate used in manuf. of the active substance | 23/08/2002 | 16/09/2002 | | |
| X/0001 | X-3-iv_Change or addition of a new pharmaceutical form | 15/11/2001 | 12/04/2002 | SmPC, Annex II, Labelling and PL | |
| II/0004 | Update of Summary of Product Characteristics and Package Leaflet | 15/11/2001 | 12/04/2002 | SmPC and PL | |
| I/0003 | 01_Change following modification(s) of the manufacturing authorisation(s) | 20/07/2001 | 16/10/2001 | Annex II and PL | |

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| I/0002 | 30_Change in pack size for a medicinal product | 01/06/2001 | 03/08/2001 | SmPC, Labelling and PL | |