London, 21 October 2004
Product name: Rapamune
Procedure No. EMEA/H/273/X/21

SCIENTIFIC DISCUSSION

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1. Introduction

A Community Marketing Authorisation for Rapamune 1mg/ml oral solution was granted by the European Commission on 13 March 2001 for prophylaxis of organ rejection in adult patients at low to moderate immunological risk receiving a renal transplant.
On 12 April 2002, the Marketing Authorisation for Rapamune 1 mg coated tablets was granted. In the pivotal studies supporting the approved indication, the average daily dose (to be taken as a single dose in the morning) was about 8 mg. The applicant committed to develop higher tablet strengths in order to reduce the pill burden. The 2 mg tablet strength was approved subsequently on 10 January 2003.

Pursuant to Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II, point 2, indent (iii), Wyeth Europa applied with the present application to add a new strength i.e. 5 mg coated tablets in order to further improve dosing convenience and patient compliance.

The application does not include a change neither in indication nor in dosage recommendations. Specific efficacy and safety studies for the 5 mg tablet were not considered necessary, since the sirolimus dose is individualised over a wide range of doses based on target concentrations.
To confirm the relative bioavailability of the approved 1 mg, 2 mg tablets and of the proposed 5 mg tablet, one bioequivalence study (187-UK) was conducted in healthy volunteers. In addition, one supportive bioavailability study (179-UK) was included in the application together with 2 previously submitted studies (165-US and 186-UK).

The drug substance and excipients used in the manufacture of this new tablet strength are similar to those used in the manufacture of the currently approved strengths.

2. Quality aspects

Introduction

Rapamune 5 mg coated tablets are tan and biconvex.

The inert tablet core is composed of lactose monohydrate, macrogol 8000, magnesium stearate, and talc. The tablet coating is composed of several layers of coatings consisting of a nanodispersion (containing the active substance and a stabiliser), macrogol 20000, glycerol monooleate, pharmaceutical glaze, calcium sulphate anhydrous, microcrystalline cellulose, sucrose, titanium dioxide, brown iron oxide (E172), yellow iron oxide (E172), α-alpha tocopherol, povidone, carnauba wax and red printing ink.
This tablet strength differs qualitatively from the ones currently authorised in that it contains *dl*-α-alpha tocopherol as an antioxidant in the nanodispersion. The tablet colour is tan rather than white or yellow/beige tablet for the 1 and the 2 mg strengths respectively. In addition, the sugar seal layer used in the 2 mg tablet is not included.
Rapamune is supplied in PVC/aclar/aluminium blister.

Drug Substance

Sirolimus is a macrocyclic lactone produced by fermentation of *Streptomyces Hygroscopicus*, for which a new strain (LL4510) enhancing to have higher yield and a more robust process (so called process II) has been recently approved (see type II variation EMEA/H/C/273/II/17). Sirolimus batches made by process II have been shown to be comparable to those made by process I.

A full description of the manufacture and control of the active substance has been provided. The synthesis, impurity control and characteristics controlled in the specifications are identical to the active substance already authorised for the oral solution and for the 1 and 2 mg coated tablets. Batch analysis data provided comply with the specifications.

A retest period of 2 years is currently authorized for sirolimus bulk substance. The active substance exists in a form of a nanocrystal colloid dispersion (see drug product) and a storage time of 14 weeks at refrigerated conditions has already been accepted for it.

Drug Product

- Pharmaceutical Development

This new strength has been developed to improve dosing convenience and patient compliance.

As for the currently authorised strengths and in order to improve the stability and bioavailability of the drug substance, sirolimus is incorporated in a NanoCrystal Colloidal Dispersion (nanodispersion) in which the drug particle size is reduced to nanometre dimensions in the presence of a stabiliser. The nanodispersion is added to a sugar coating suspension (active coat), used to coat inert tablet cores previously overcoated with shellac and inert filler coats. The last coat is the colour coat.

Sirolimus is susceptible to oxidative degradation in the presence of atmospheric oxygen and of iron oxide based colorants acting as Lewis-acids. For the 2 mg strength, this issue was resolved by applying a sucrose seal coat between the active coat and the colour coat containing the iron oxides. In the present formulation, *α*-alpha tocopherol has been selected as a true antioxidant to be added to the active coat based on satisfactory stability profile and global acceptance.

As for the 1 and 2 mg strengths, a 2 % overage of active substance is used in the formulation. It has been adequately justified due to losses during manufacture.

All the excipients are common pharmaceutical ingredients, the majority of which are compendial grade except 5 excipients, which are tested according to satisfactory in-house specifications.

Regarding the TSE risk, compliance with the current requirements has been satisfactorily demonstrated.

The PVC/aluminium blister is adequately controlled.

- Manufacture of the Product

The manufacturing process of the 5 mg strength is almost identical to the already described process for Rapamune 1 and 2 mg coated tablets apart from the addition of dl-α-alpha tocopherol to the active coat and the removal of the thin sugar seal introduced between the colour and the active coat for the 2 mg strength only. Satisfactory validation data have been provided.

- Product Specification

The specifications for Rapamune 5 mg tablets are the same as those currently approved for Rapamune 1 mg and 2 mg tablets, with the exception of appearance (tablet colour and printing) and dissolution (NLT 80% dissolved in 60 minutes).

The current dissolution method has been improved, resulting in a more rugged test and faster dissolution. As a result, a single point measurement is proposed.

Batch analysis data have been provided for 3 batches. All data comply with the specifications and indicate consistent and reproducible manufacture.

- Stability of the Product

3-month data have been provided for 3-production scale batches manufactured at the intended production site under long term (25ºC/60%RH - package intended for marketing), intermediate (30ºC/70%RH - package intended for marketing) and accelerated conditions (40ºC/75%RH - package intended for marketing). In addition, 1-year supportive data have been provided under long term and intermediate conditions. Photostability studies have shown that the drug product is non-light sensitive.

The data provided support the proposed shelf life and storage conditions as defined in the SPC.

- Bioequivalence

Process II (see drug substance) was used for the manufacture of the 1, 2 and 5 mg tablets administered to healthy subjects in the main bioequivalence study 0468H1-187-UK, while sirolimus used in study 179-UK was produced via process I.

The 3 tablets showed bioequivalence under fasting conditions and single dose conditions with respect to extent of absorption (AUC) and peak concentration (C_{max}) (see clinical aspects).

Discussion on chemical, pharmaceutical and biological aspects

The active substance manufacture and control is the same as that reviewed for the already authorised strengths. The development of the formulation and manufacturing process for the finished product is essentially the same as well. The information presented indicates that the product is manufactured and controlled in a reproducible way, and should perform consistently in clinical practice, from batch to batch. Stability tests under ICH conditions indicate that the products are stable for the proposed shelf life.

Non-clinical aspects

This application does not concern any change in dosage or indication for Rapamune. The 5 mg tablet differs qualitatively from the previously approved 1 and 2 mg tablets by addition of dl-α-tocopherol (Vitamin E USP) 0.051 mg per tablet as antioxidant to improve stability, and a change in pigmentation from brown iron oxide 70 to brown iron oxide 75. These changes are not likely to alter the toxicological profile. Therefore additional non-clinical studies are not considered necessary to support the new strength.

3. Clinical aspects

Introduction

Relative bioavailability of the approved 1 mg and 2 mg tablets and the proposed 5 mg tablet was explored in one bioequivalence study (187-UK), conducted in healthy volunteers. In addition, one supportive bioavailability study (179-UK; performed with sirolimus produced via a previous manufacturing process) was included in the application. Two previously submitted bioavailability studies (165-US and 186-UK, submitted with the applications for the 1 mg and 2 mg tablets, respectively) were also discussed. Specific efficacy and safety studies for the 5 mg tablet were not deemed necessary.

Pharmacokinetics

Methods

Study 187-UK was a single-dose, open-label, randomised, three-period crossover study in healthy subjects. The subjects received a 10 mg dose of sirolimus during each period as ten 1-mg tablets, five 2-mg tablets, or two 5-mg triangular tablets. The doses were administered after an overnight fast of at least 10 hours and the intake of any food or beverage was prohibited during the first 4 hours after dose administration. Study periods were separated by a washout interval of at least 3 weeks between doses of sirolimus. Blood samples for sirolimus were collected before and at 0.33, 0.67, 1, 2, 3, 5, 8, 12, 24, 48, 72, 96, 120, and 144 hours after dose administration.

Study 179-UK was a single dose two-period, crossover study in healthy subjects. In each period, the subjects received 5 mg sirolimus as five 1 mg tablets or as one 5 mg tablet. Blood sampling was performed during 144 hr postdose. There was a three-week washout period between periods.

Population studied

Twenty-four healthy subjects were enrolled in study 187-UK and 22 completed all treatment periods and were included in the pharmacokinetic analysis. Of the 22, 20 were male and 21 were Caucasians. Ages ranged from 20 to 45 years (mean 31.5 years) and weights from 62.5 to 99.7 kg (mean 79.6 kg).

In study 179-UK, 24 healthy, male subjects were enrolled and completed the study.

Pharmacokinetic data analysis and statistical analysis

The concentration versus time data for sirolimus for each subject was analysed using non-compartmental methods.

Descriptive statistics were obtained for drug concentrations and pharmacokinetic parameters. Statistical comparisons between treatments were performed using analysis of variance (ANOVA). Pre-specified criteria for concluding bioequivalence were 90% confidence intervals (CI) within the 80% to 125% range, or 80% to 120% for the logarithmically untransformed parameter T_{max}.

Trial formulations

The originally marketed formulations for sirolimus oral solution and the 1 and 2 mg tablets were manufactured using sirolimus batches made by Process I API. A new process was developed using a new strain of *Streptomyces hygroscopicus* for the fermentation process, together with a slightly modified purification step. Sirolimus batches made by Process II have been shown to be comparable to those made by Process I during process validation. Process II was used for the manufacture of the tablets that were administered in the main bioequivalence study, 187-UK, while sirolimus used in study 179-UK was produced via Process I.

Test formulations in the bioequivalence study 187-UK were:
sirolimus 1 mg triangular tablet, batch 2002B0078
sirolimus 2 mg triangular tablet, batch 2002B0080
sirolimus 5 mg triangular tablet, batch 2002B0130

These are the same formulations as the currently marketed 1 and 2 mg tablets and the 5 mg tablet intended for market, respectively. The three strengths have the same size and shape, but differ in colour. The active substance is encapsulated in the coating of the tablet.
Results of Bioequivalence Studies 0468H1-187-UK and 0468H1-179-UK

Concentration-time profiles for sirolimus in the main bioequivalence study, 187-UK, are shown in Figure 1. Pharmacokinetic parameters and the statistical analysis are summaries in Table 1.

It was concluded that the 1, 2 and 5 mg tablets were bioequivalent with respect to C_{max}, AUC_t and AUC, since the 90% log-transformed confidence intervals for these parameters fell within the 80% to 125% acceptance range. Bioequivalence could not be demonstrated for T_{max} based on all pairwise comparisons. Overall, the results indicate slower absorption the larger the tablet, leading to a lower C_{max} (although within limits for bioequivalence) and longer T_{max}. The parameter C_{24h} 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). The mean extrapolated area of $AUC_{0\text{-}inf}$ for all treatments was 17.0%. However, for 3, 3 and 5 subjects after treatment with the 1 mg, 2 mg and 5 mg tablet, respectively, the extrapolated area exceeded the generally accepted 20%. In these 8 cases, the extrapolated area ranged between 20.4 – 29.3% (mean 23.5%).

Figure 1. Whole-blood sirolimus concentrations after administration of 10 mg sirolimus as 1 mg, 2 mg and 5 mg tablets, respectively.

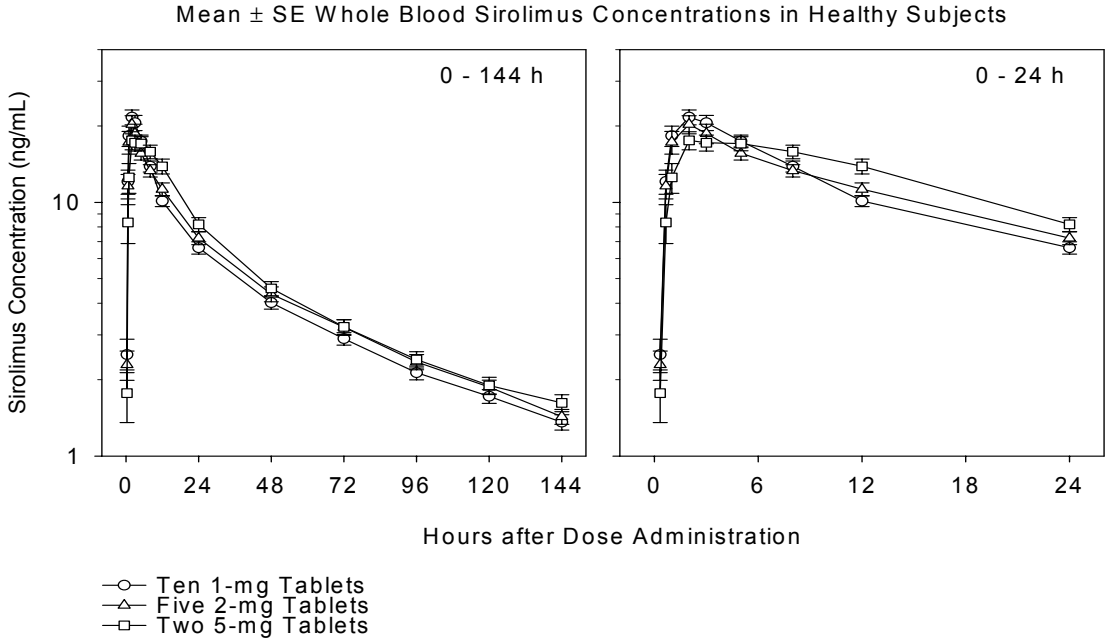

Table 1. Sirolimus pharmacokinetic parameters and bioequivalence testing of pairwise comparisons (n=22) in study 187-UK

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	C_{24h} (ng/mL)	$t_{1/2}$ (h)	AUC_t (ng∗h/mL)	AUC (ng*h/mL)
Ten 1-mg tablets	Mean ± SD	23.6 ± 6.6	2.55 ± 1.77	6.62 ± 1.73	66.6 ± 12.1	629 ± 144	765 ± 191
Five 2-mg tablets	Mean ± SD	22.4 ± 7.4	2.82 ± 2.65	7.23 ± 1.96	63.5 ± 9.1	661 ± 175	792 ± 212
Two 5-mg tablets	Mean ± SD	20.8 ± 6.0	4.14 ± 2.82	8.19 ± 2.40	65.7 ± 11.6	711 ± 185	866 ± 241
GLS Mean Ratios and 90% CIs for Pairwise Comparisons							
2 mg to 1 mg							
GLS Mean Ratio		93	113	110	96	105	104
90% Log-Transformed CI		84-102	84-146	103-118	88-104	98-112	98-110
5 mg to 1 mg[b]							
GLS Mean Ratio		88	163	124	99	113	113
90% Log-Transformed CI		80-96	112-239	114-134	91-107	106-120	106-120
5 mg to 2 mg[b]							
GLS Mean Ratio		95	144	113	103	107	109
90% Log-Transformed CI		85-105	108-201	104-122	96-111	101-114	103-115

Abbreviations: CI = confidence interval; GLS = geometric least squares; SD = standard deviation.

Pharmacokinetic and statistical results from study 179-UK, performed with 1 mg and 5 mg tablets from the previous manufacturing process, are shown in table 2.

Table 2. Sirolimus pharmacokinetic parameters and bioequivalence testing of pairwise comparisons (n=24) in study 179-UK

Treatment	Statistic	C_{max} (ng/mL)	t_{max} (h)	AUC_t (ng*h/mL)	AUC_{0-inf} (ng*h/ml)	$C_{24\ hours}$ (ng/ml)	$t_{1/2}$ (h)
Five 1 - mg tablets	Mean ± SD	10.5 ± 4.8	2.6 ± 1.6	247 ± 83.8	306 ± 102	2.5 ± 0.96	71,5 ± 8,8
One 5 - mg tablet	Mean ± SD	8.6 ± 4.8	4.0 ± 2.6	255 ± 81.8	312 ± 99.4	2.8 ± 0.82	67,4 ± 10,4
		GLS Mean Ratios and 90% CIs					
one 5 mg to five 1 mg tablets GLS Mean Ratio		80	142	103	102	116 [a]	
90% Log - Transformed CI		72 - 89	114 - 178	97 - 110	97 - 108	104-130	

[a] the study was slightly underpowered to detect a difference in $C_{24\ hours}$

In this study, bioequivalence was demonstrated for extent of absorption but not for rate of absorption, with the 5 mg tablet showing a slower absorption rate (longer T_{max} and lower C_{max}).

The mean extrapolated area of AUC_{0-inf} for all treatments in this study was 18.8%. In 19 (of 48) cases, the extrapolated area exceeded the generally accepted 20%. In these cases, the extrapolated area ranged between 20.1 to 27.2% (mean 22.3%).

The MAH discussed a previous interstudy analysis of potential factors contributing to differences in rate of absorption for different formulations (including oral solution). It has been suggested that T_{max} be related to three factors: the type of formulation, the unit dose strength and the number of dose units. It was also suggested that a difference in rate of absorption is not important for the efficacy and safety of sirolimus.

Discussion

1. The slower absorption from the higher tablet strengths did not lead to bio-inequivalence for total exposure (AUC) or C_{max}, in study 187-UK. Also in study 179-UK, AUC was similar for the 1 and 5 mg tablets while bioequivalence could not be concluded for C_{max}. In both studies, the tendency was that C_{max} was lower with the higher strengths, in accordance with the slower absorption rate. A difference in T_{max} is not considered clinically relevant at steady state for a continuous treatment. A difference in C_{max} has previously been deemed as not clinically important based on comparisons of bioavailability as well as clinical efficacy/safety of the 1 mg tablet and the oral solution. (TDM is recommended after a switch between tablet and solution since they differ slightly also in extent of absorption).

The observed difference in $C_{24\ hours}$ between the 1 and 5 mg tablets might indicate a different relationship between trough levels and exposure for the two tablet strengths. The target sirolimus trough levels are within 4 to 12 ng/ml for patients also receiving cyclosporine and 12 to 20 ng/ml when cyclosporine has been discontinued. The inter- and intra-subject variability in sirolimus trough levels has previously been reported to be approximately 45% and 38%, respectively. 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 $C_{24\ hours}$.

The extrapolated areas of $AUC_{0\text{-}inf}$ in both studies indicate that the sampling period was slightly too short for adequate determination of $AUC_{0\text{-}inf}$ in some cases. However, the mean deviation from 20% was only minor, and the extrapolated area was acceptable for most of the AUC determinations. Therefore, the observed deviations are not considered likely to affect the overall assessment of bioequivalence. Moreover, all patients had detectable levels at the last timepoint (144 hr) in all treatment periods and bioequivalence was also shown for $AUC_{0\text{-}144hr}$ (AUC_t).

2. Bioequivalence studies were not conducted at steady state. Pursuant to a request of CHMP (LoQ) to discuss the significance of absence of steady state kinetics, the MAH responded that multiple-dose administration of 2-mg daily doses of the tablet and solution formulations in renal transplant patients were found to be therapeutically equivalent.

The MAH commented that sirolimus is a drug with a relatively long half-life (62 hours in stable renal transplant patients) which is dosed daily and which accumulates to a very significant extent. Given this, single dose studies are generally conducted because at steady state, differences in PK behaviour would be more difficult to detect given that most sirolimus detected will be accumulated drug substance. For example, if conducting PK comparability studies at steady state, it would be more difficult to detect moderate differences in the rate of absorption of sirolimus. Therefore, it can be predicted that differences that are detectable in single-dose studies may be undetectable and not clinically relevant at steady state.

Also, the statistically-significantly increased C_{24hr} concentrations suggests that the target trough range should be adjusted upward in patients switching from 1-mg tablets to 5-mg tablets. However, such a recommendation would be mitigated by several factors:

- The increase applies most strictly to 10 mg doses of the 1-mg and 5-mg tablets. In practice, patients may potentially switch from a combination 1- and 2-mg tablets to various combinations of 1-, 2-, and 5-mg tablets;
- A mean increase of 24% in sirolimus troughs is well within the intrasubject variability of whole blood sirolimus trough measurements and;

There is a broad overlap in the current sirolimus target trough concentrations (4 to 12 ng/mL) and a potentially adjusted target range (approximately 5 to 15 ng/mL) due to the 24% increase in C_{24hr}.

3. No food interaction study was submitted. Since the absorption of sirolimus is affected by concomitant food intake (slower absorption and increased AUC) a difference in food effect might lead to altered exposure in a patient consistently taking Rapamune with food and switching from the lower strengths to the 5 mg tablet to achieve the same dose. It is however recognised that the food effect might be considered relatively small, and that switching between tablet strengths will not be made regularly. Hence, it was noted that in case a clinically relevant difference in food effect cannot be excluded, a food interaction study and/or appropriate recommendations in the SPC might be necessary.

This issue was further addressed by the MAH, which asserted that from data already available on the 1 mg tablet and the oral solution, it is projected that the effect of food on the extent of absorption (AUC) of sirolimus delivered by the 5 mg tablet will be moderate. For the oral solution, AUC was increased 35% by food, and for the 1 mg tablet, AUC was increased by 23%. The effect of food on the rate of absorption of sirolimus (T_{max}) from the 5 mg tablet may be moderately different from the 1 and 2 mg tablets given that the rate of absorption differs somewhat from the 1 and 2 mg tablets. However, based on a previous efficacy study, which compared the efficacy of the oral solution and the 1 mg tablet (dosage forms with very different rates of absorption), it appears that even potentially large differences in the rate of absorption do not affect clinical activity.

Further, the 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 cyclosporine is discontinued and the Rapamune dose adjusted to obtain whole blood trough levels of 12 to 20 ng/ml. Given this, any effect of switching between tablet strengths would be entirely mitigated by the use of therapeutic drug level monitoring**.**

Additionally, the MAH proposed to include a recommendation in section 4.2 of the SPC to monitor plasma C_{min} levels after a switch between tablet strengths. This is deemed acceptable, and resolves any concerns regarding potential lack of bioequivalence between strengths under other conditions than those tested in the bioequivalence study. However, the CHMP requested that the information should also be given in section 5.2 of the SPC, in line with the recommendation for a switch between oral solution and tablet. The new recommendation should be included also in the 1 mg and 2 mg tablet SPCs in a future variation.

4. In light of a previously observed difference in effect of concomitant administration of CsA between an experimental 10 mg tablet and the oral solution (and the oral solution showing more rapid absorption than the tablet), the MAH was also requested to discuss whether the difference in absorption rate between the three tablet strengths might lead to different impact of CsA on sirolimus AUC when switching between strengths.

It was clarified that the CsA drug interaction study (0468H1-168-US) using tablets was conducted with 10x1-mg tablets and not a 1x10-mg tablet. Also, since any potential effect of switching tablet strengths on the CsA-sirolimus interaction would be limited generally to the initial 3 months after transplantation, the effect would be mitigated by therapeutic drug level monitoring.

A direct comparison of the 1-mg and 5-mg tablet formulations in a sirolimus-CsA drug interaction study has not been made. However, it is anticipated that the increased t_{max} for the 5-mg tablet would not be a factor in the CsA-sirolimus interaction. Since the t_{max} for CsA (approximately 1.5 hours) is less than the t_{max} for sirolimus tablets (2.5 to 4.1 hours), it appears that a typically large dose of CsA (300 mg) could saturate the intestinal CYP3A/P-gp sites prior to sirolimus absorption regardless of tablet strength and obviate significant effects of Rapamune tablet strengths on the interaction.

From the 0468H1-187-UK report, it may be shown that the median (min, max) t_{max} values for the 1-, 2-, and 5-mg tablets were 2 (1, 8) hours, 2 (1, 12) hours, and 3 (1, 12) hours, respectively. Based on the median, the t_{max} distributions among the 3 tablet strengths were very similar, while the observed mean t_{max} value for the 5-mg tablet may have been skewed by several high values. In contrast, the effect of CsA on the sirolimus AUC during 10x 1-mg Rapamune tablet administration (148% increase for simultaneous administration, and 33% increase for staggered administration; study 0468H1-168-US;) far outweighs the effect of the 5-mg tablet on sirolimus AUC (13% increase). Thus, the increased t_{max} for the 5-mg tablet would not be a factor in the CsA-sirolimus interaction.

The CHMP is in agreement with the argumentation provided by the MAH. Moreover, any remaining concerns would be resolved with the new recommendation to monitor plasma levels of sirolimus at a switch between tablet strengths.

Pharmacodynamics

Not applicable

Clinical efficacy

Not applicable

Clinical safety

Not applicable

4. Overall conclusions, benefit/risk assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

N/A

Clinical pharmacology

The 5 mg tablet strength has been shown to be bioequivalent to the previously approved 1 mg and 2 mg tablets under fasting, single-dose conditions as concerns extent of absorption (AUC) and, in the main bioequivalence study, also peak concentrations. The rate of absorption was lower for the higher strengths, and there was a tendency towards lower C_{max}. A difference in rate of absorption at a switch between tablet strengths is not deemed to be clinically important, based on e.g. previously submitted data for the 1 mg tablet vs. the oral solution. Bioequivalence between the 5 mg and 1 mg tablet could not be concluded for $C_{24\ hours}$ in the single-dose study 187-UK, and the difference was estimated to lead to on average 24% higher $C_{24\ hours}$ for the 5 mg tablet at steady state. A difference in C_{trough} levels at the same AUC could potentially indicate a different relationship between trough levels and exposure for the two tablet strengths. However, the observed difference is within the variability of sirolimus concentrations and should not necessitate specification of a different target trough level range for the 5 mg tablet.

It is recognised that the food effect might be considered relatively small, and that switching between tablet strengths will not be made regularly. However, since, in the absence of a food interaction study, a clinically relevant difference in food effect cannot be excluded, the MAH has agreed to include a recommendation to check sirolimus plasma trough levels after a switch between tablet strengths. The new recommendation should be included also in the 1 mg and 2 mg tablet SPCs in a future variation.

A previous between-study comparison suggested that the effect of concomitant CsA was different for the oral solution (about 80% increase in sirolimus AUC at the recommended staggered dosing) and the tablet (about 30% increase in sirolimus AUC at staggered dosing). The difference might be due to the slower absorption of the tablet compared with the solution. It has not been studied whether the difference in absorption rate between tablet strengths might lead to different effects of CsA on sirolimus AUC. This issue is, however, resolved with the recommendation to monitor sirolimus plasma levels after switch between tablet strengths.

Benefit/risk assessment

The quality of the new strength is sufficient. Bioequivalence has been demonstrated between the 1 mg, 2 mg and 5 mg tablets as concerns extent of absorption of sirolimus administered in the fasted state, while the rate of absorption was lower for the higher strengths. The difference in rate of absorption is not considered clinically important. However, concomitant food intake has been shown to decrease the absorption rate and increase AUC of sirolimus administered as oral solution or 1 mg tablet. From the presently submitted data, it cannot be excluded that e.g. a food-induced, reduced rate of absorption from the already "slower" 5 mg tablet will have a larger effect on AUC than with the 1 mg tablet, leading to an altered exposure in a patient consistently taking Rapamune with food and switching from

lower to higher strengths to achieve the same dose. Moreover, the extent of the effect of Cyclosporin A on the bioavailability of sirolimus might be dependent on absorption rate. Thus, although the tablet strengths can be considered exchangeable when administered in the fasting state and without cyclosporin A or other CYP3A4 inhibitors, a recommendation has been introduced in the SPC to monitor sirolimus trough concentrations two weeks after a switch between tablet strengths. The same text should be included in the 1 and 2 mg tablet SPCs via a variation procedure.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered that the benefit/risk ratio of Rapamune 5 mg coated tablets in the following indication "Rapamune is indicated for the 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 cyclosporin microemulsion and corticosteroids for 2 to 3 months. Rapamune may be continued as maintenance therapy with corticosteroids only if cyclosporin microemulsion can be progressively discontinued (see Sections 4.2 and 5.1)." was favourable and therefore recommended the granting of the marketing authorisation for this new strength.