New Drug Application 21-628, Certican (Everolimus), for the Proposed Indication of Prophylaxis of Rejection in Heart Transplantation

Report From the Cardiovascular and Renal Drugs Advisory Committee, US Food and Drug Administration, November 16, 2005, Rockville, Md

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The Cardiovascular and Renal Drugs Advisory Committee (Committee) of the Food and Drug Administration (FDA), Center for Drug Evaluation and Research, met on November 16, 2005, to discuss the new drug application (NDA) 21-628 by Novartis Pharmaceuticals Corporation for Certican (everolimus), for the proposed indication of prophylaxis of rejection in heart transplantation. The Committee reviewed 1 primary trial in heart failure and additional background information, as well as 2 studies of everolimus in renal transplantation. The meeting consisted of presentations by the sponsor and the FDA regarding an overview of heart transplantation; a summary of the efficacy and safety of everolimus, including the intravascular ultrasound (IVUS) results and renal toxicity; and an overall assessment of risk and benefit.

Heart Transplantation Background

The primary causes of heart failure in patients undergoing transplantation are coronary artery disease and noncoronary cardiomyopathy. After transplant, there is an initially high mortality rate due to acute postsurgical complications. Survivors have a subsequent average mortality of 3.4% per year. Risk factors for mortality at 5 years include need for repeat transplant, cerebrovascular disease, and the development of coronary artery vasculopathy. IVUS identification of rapidly progressive vasculopathy is an independent predictor of adverse outcomes and mortality in heart transplant recipients. Morbidity rates are also high in heart transplantation patients, with more than 30% developing renal dysfunction within 1 year, 1.5% requiring dialysis, and 0.3% requiring renal transplantation. After 3 years, more than 16% will develop chronic renal failure, of whom 15-29% will require maintenance dialysis or renal transplantation. The development of chronic renal failure is an independent predictor of mortality.

There are 2 FDA-approved drugs to prevent cardiac rejection. The first is the calcineurin inhibitor cyclosporin A (CsA), and the other is mycophenolate mofetil (MMF), which is used as adjunctive therapy with CsA. In 2004, however, the calcineurin inhibitor tacrolimus was commonly used off label (in 50% of patients), whereas CsA was used in 47% of patients. The use of rapamycin has been increasing (14% in 2004), and the use of azathioprine has been decreasing (<10% in 2004). Side effects of CsA include nephrotoxicity (which is related to exposure), hypertension, diabetes mellitus, and hyperlipidemia. The major toxicity of azathioprine relates primarily to suppression of the bone marrow.

Evidence Supporting the Use of Everolimus in Heart Transplantation

Everolimus is a macrolide antibiotic and immunosuppressant derived from rapamycin. Everolimus binds to FK binding protein, and this complex inhibits the mammalian target of rapamycin but does not inhibit calcineurin. This action decreases cytokine-driven cell proliferation but does not inhibit the production of interleukin with T-cell activation. Everolimus may also protect against transplant vasculopathy by slowing intimal proliferation. Side effects include hyperlipidemia, thrombocytoxia, and impaired wound healing.

Everolimus has been evaluated in 1 heart transplantation study that was presented by the sponsor and reviewed extensively by the FDA. This was a prospective, double-blind trial of 634 patients undergoing primary heart transplantation. Patients were randomized to everolimus 1.5 or 3.0 mg/d or azathioprine 1.0 to 3.0 mg/kg per day as an active comparator. All patients received a background of CsA, prednisone, and lipid-lowering therapy. The CsA dose was adjusted to maintain specific target trough levels that progressively decreased at specific intervals after transplantation. The primary end point at 12 months was death, graft loss, or a second transplantation; rejection associated with hemodynamic compromise; loss to follow-up; and histological grade 3A rejection from endomyocardial biopsy (multifocal inflammatory infiltrates and some damage to myocytes). IVUS assessment of the mean change in maximal intimal thickness in a single coronary artery was a secondary end point. At 12 months, the primary end point was reached in 53% of patients taking azathioprine, 42% of patients taking everolimus 1.5 mg/d, and 32% of those taking everolimus 3.0 mg/d; results with both doses of everolimus were significantly better than with azathioprine. However, the benefit of everolimus was driven by differences in grade 3A rejection, because the other components of...
the primary end point were similar between groups. Concerns were raised that a greater number of patients in the everolimus 3.0 mg/d arm missed the cardiac biopsy at 6, 12, and 24 months than in the everolimus 1.5 mg/d and azathioprine arms. This imbalance could have biased the biopsy results in favor of the everolimus 3.0 mg/d arm.

IVUS analysis showed reduction in vasculopathy with less change in maximal intimal thickness in the 2 everolimus groups compared with those taking azathioprine. However, there were several limitations noted with the IVUS data. The 12-month IVUS examination was ascertained in only one third of patients, and the criteria for selection of these patients was not defined prospectively. Thus, patients who were studied were not chosen randomly. More importantly, patients who had 12-month follow-up IVUS data had to be able to tolerate the procedure. Renal dysfunction was a common reason not to evaluate patients, which meant that the sickest patients, with potentially the most severe vasculopathy, were excluded from analysis.

**Toxicities of Everolimus**

There were significant toxicities associated with the everolimus regimen. At month 12, there was a significant reduction in estimated creatinine clearance in both everolimus groups compared with azathioprine. This reduction in renal function with everolimus use was not different between the groups and was sustained out to 24 months of follow-up. It was this decrease in creatinine clearance that resulted in the unblinding of the study at month 12, with an amendment that allowed investigators to switch everolimus patients with renal impairment to open-label therapeutic drug monitoring (TDM) to adjust the CsA and everolimus regimens. The TDM targeted lower CsA levels while maintaining everolimus above a target minimum concentration. A total of 170 patients entered this open-label TDM, but 6 months after this amendment, creatinine levels in these TDM patients remained essentially unchanged. Thus, it was unclear whether the decline in renal function observed in the 2 everolimus arms was reversible.

**Committee Discussions With the Sponsor and the FDA**

The Committee recognized that the study of everolimus in heart transplant patients was positive on its primary end point, but that end point was driven by biopsy evidence of acute rejection, which in itself may be a surrogate marker. Everolimus may also improve transplant-associated vasculopathy. However, several Committee members found significant methodological problems with the IVUS data that limited interpretation. This included a high percentage of missing data from the study population, potential bias in selection of patients for IVUS testing, and the limitation that IVUS data were a secondary end point. Given the overall results, the Committee believed that the everolimus regimen may offer a potential long-term advantage of preventing more clinically relevant rejection (graft loss, a second transplantation, or rejection associated with hemodynamic compromise) and vasculopathy, but these results were not proven. The Committee was concerned that everolimus, in either dose, was associated with significantly worse renal function that appeared to be irreversible. The concept of TDM, particularly for the CsA component, was supported by the Committee. However, the sponsor did not present evidence that a more rapid taper of CsA would prevent the renal complications.

**Questions to the Committee**

Novartis provided the Committee with information from 1 pivotal trial that used 2 fixed doses of everolimus with a full-dose regimen of cyclosporine. Both the FDA and Novartis had previously agreed that this exact fixed-dose regimen should not be used prospectively for the prophylaxis of organ rejection in cardiac transplantation because of short-term and long-term loss of renal function. The Advisory Committee unanimously agreed with this conclusion.

During the presentations, Novartis proposed an alternative, TDM-based regimen for the use of everolimus in combination with cyclosporine. However, in the absence of a prospective study of this regimen, a majority of the Committee believed there was insufficient evidence to support the use of the TDM regimen.

The Committee discussed the use of everolimus in subgroups and found no uniquely responsive clinical group. However, the Committee did identify subgroup restrictions for everolimus therapy, specifically those patients with severe end-stage kidney disease at baseline. There was insufficient information in women and blacks to know whether changes should be made in dosing for those groups.

Given that a majority of the Committee voted against approval, the FDA asked what additional information would be necessary for approval. Specific reference was made to the ongoing European study and the planned US cardiac transplantation study. The Committee believed that the proposed studies would provide critical information for approval, particularly in addressing the safety concerns. Delaying the approval of everolimus was appropriate because there is approved drug therapy (mycophenolate) for heart transplantation.

**Disclosures**

The authors have no conflicts to disclose. Dr Hiatt is the current chair of the Cardiovascular and Renal Drugs Advisory Committee. Dr Nissen is the former chair of the Committee and served as a consultant to the Committee for the everolimus meeting. This report reflects the deliberations of the Committee and subsequent minutes of the meeting that were reviewed and edited by Dr Hiatt.

**References**


**Key Words:** drugs ■ immune system ■ heart failure ■ transplantation
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