DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration
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Memorandum

Division of Clinical Trial Design and Analysis
HFM-576

Date: 11/4/97

From: M.Walton, DCTDA

Subject: Supervisory Overview of BLA 97-0200

To: File BLA 97-0200

Background

Abciximab (ReoPro©) is the Fab fragment of the chimeric monoclonal antibody c7E3 which binds to platelets and inhibits aggregation. Abciximab received initial marketing approval in 1994 for use as an adjunct during percutaneous transluminal coronary angioplasty (PTCA, now more broadly referred to as percutaneous coronary interventions, PCI) in patients believed to be at high risk for abrupt artery closure for the prevention of cardiac ischemic events.- This was based upon the EPIC trial, which showed improved outcome on the incidence of the three-part-composite event endpoint of death, myocardial infarction or urgent reintervention within thirty days of PTCA. However, this was associated with increased rates of clinically significant bleeding in the abciximab treated patients. Due to the increased rate of bleeding, an important phase 4 commitment made at the time of marketing approval was to study means of decreasing the bleeding associated with the use of abciximab.

Abciximab is recommended to be administered as a bolus shortly prior to initiating the PTCA, followed by a 12 hour infusion. Abciximab was studied only with a single specified concomitant regimen of aspirin and heparin, and all safety and efficacy information is in the setting of that concomitant regimen.

This BLA Supplement focuses upon a subsequent trial, EPILOG and an additional pharmacokinetic/pharmacodynamic study which examined patients to whom abciximab was readministered. Dr. Stolman has performed the clinical review of these data. This memorandum summarizes and comments upon the submission based upon Dr. Stolman's review, which should be referred to for full details.

EPILOG Study Design

The EPILOG study was a randomized, double-blind, placebo controlled phase 3-4 study conducted in 69 centers in the U.S. and Canada. The objectives of the study were to examine efficacy of abciximab in a broader group of patients than evaluated in the EPIC study in order to support expansion of the types of patients for whom abciximab is indicated and to evaluate if

modified patient management guidelines could result in lowered rates of bleeding as compared to that seen in the EPIC trial and included examining the safety and comparative efficacy of a lower dose heparin regimen. The study enrolled patients undergoing PCI (balloon angioplasty, STENT placement, and some types of atherectomy) for cardiac ischemia. EPILOG enrolled a broad group of patients with regards to risk for ischemic complications following PCI. Patients with acute coronary syndromes (those at the highest risk of abrupt closure who had been studied in EPIC: acute MI and unstable angina) were excluded, but patients were otherwise not excluded on the basis of assessed risk for ischemic events following PCI. There was substantial overlap between the two study populations in EPIC and EPILOG in that patients classified as high risk on the basis of angiographic lesion morphology were included in both studies. Consequently, the patients in the EPILOG study were, as a group, at lower risk than those in EPIC as a group. Patients enrolled in EPILOG were assessed as to high risk vs. low risk according to clinical characteristics and angiographic lesion morphology, and the randomization process was stratified by this risk assessment.

Patients enrolled in EPILOG were randomized to three treatment groups. The three study groups were a) placebo with standard dose heparin, b) abciximab plus standard dose heparin, and c) abciximab plus low dose heparin. Both abciximab groups used the same abciximab regimen of a 0.25 mg/kg bolus followed by a 0.125 μg/kg/min infusion (maximum of 10 μg/min) for twelve hours. The standard dose heparin groups had administered heparin to raise and maintain the ACT to > 300sec, the low dose heparin group had heparin administered to raise and maintain the ACT to > 200 sec. While the abciximab infusion was to be maintained for 12 hours, the heparin was encouraged to be discontinued at the conclusion of the PTCA (this early discontinuation occurred in 53% of the patients). A heparin dosing administrator at each site performed the heparin adjustments thereby maintaining the treatment group assignment blinding. Aspirin was given to all patients prior to the PTCA and daily thereafter. Other patient management procedures included arterial sheath removal following heparin discontinuation.

While planned for 4800 patients, the study was halted after 2792 patients were enrolled due to early demonstration of efficacy at an interim efficacy analysis. As directed by the protocol, due to the early termination of the study the endpoint used in the interim analysis as the primary endpoint of the study, the rate of occurrence of a composite endpoint of death or MI within 30 days following the PTCA. The important secondary endpoints included a) the rate of occurrence of a three part composite endpoint of death, MI or urgent revascularization intervention within 30 days and b) the rate of occurrence of a three part composite endpoint of death, MI or any repeat revascularization intervention within 6 months following enrollment.

EPILOG Study Results

The primary endpoint of death or MI within 30 days showed efficacy of both abciximab groups compared to the placebo group. The composite event rate was 3.8% in the abciximab + low dose heparin group, 4.2% in the abciximab + standard dose heparin group, while there were 9.1% of patients in the placebo + standard dose heparin group with an endpoint event ($p<0.001$, log rank test). The secondary endpoints (the three-part event composites at 30 days or 6 months) were also significantly reduced in incidence in both of the abciximab groups compared to placebo. However, the amount of reduction was notably less in the 6 month endpoint than in the 30 day endpoint. The incidence of the composite of death, MI or urgent intervention was 5.4% in the

abciximab + low dose heparin group, 5.2% in the abciximab + standard dose heparin group, vs. 11.7% in the placebo + standard dose heparin group. The endpoint of death, MI or any repeat intervention within 6 months occurred in 22.8% in the abciximab + low dose heparin group, 22.3% in the abciximab + standard dose heparin group, vs. 25.8% in the placebo + standard dose heparin group.

The mortality rates were largely similar in all three groups at both the 30 day and 6 month endpoint. The majority of the difference in event incidence between the treatment groups occurred in the MI component of the endpoints, at both the 30 day and 6 month time points. Urgent revascularization procedures also contributed to the treatment group related differences in rates of incidence of the composite endpoint.

The primary safety concerns associated with the use of abciximab were systemic bleeding (primarily at the femoral access site) and hemorrhagic stroke. Hemorrhagic stroke was not increased in the abciximab groups compared to the placebo group. Systemic bleeding was also not increased in the abciximab + low dose heparin group compared to the placebo + standard dose heparin group; however the abciximab + standard dose heparin group did have an increased rate of bleeding. Relatively few patients in the study required transfusions, and the incidence of transfusions was not increased in either abciximab group compared to the placebo group. No new safety concerns were raised by this study.

Risk Classification Subsets in the EPILOG Study

Study planning had projected that 60% of the patients enrolled would be classified at the time of randomization as lower risk for ischemic complications following PTCA. At the completion of the study, however, there were only 36% of patients classified at randomization as low-risk. Furthermore, a CRF page with a detailed description of the pre-PTCA lesion morphology was completed by investigators after completion of the procedure. When this description of morphology was utilized to perform risk assessment, many patients were re-classified as high risk so that only 19% of patients in the study were assessed as low risk by the CRF lesion descriptions.

Because expansion of the indication to include all patients undergoing PTCA (not just the currently indicated high risk patients) was a goal of the this study, exploratory analyses of the efficacy results within the risk classification subsets were conducted. Efficacy of abciximab was supported in the patient subset classified as high risk for the composite endpoint of death, MI or urgent revascularization at both 30 days and 6 months, and irrespective of whether the as-randomized or the per-CRF assessment was utilized to define the high risk subset. However, in the low risk subset of patients, efficacy of abciximab was supported only in the subset defined by the as-randomized assessment. The per-CRF assessment defined subset of low risk patients did not demonstrate a reduced incidence of endpoint events in the abciximab treated groups.

Which of the two risk assessments, the as-randomized or the per-CRF, was a more accurate or reliable assessment of the patient could not be determined from the EPILOG study data alone. As this was a crucial issue in the applicant's objective of expansion of the indicated patient population, an independent angiogram re-review was planned and carried out by the applicant. This re-review was prospectively planned, and had the concurrence of CBER. Eighteen

cardiologists from within the U.S. not previously involved with the EPILOG trial were brought to a central angiogram review center, where 360 patient angiograms selected from patients in the EPILOG study were each evaluated for lesion morphology by three of the cardiologists independently, resulting in 1080 angiogram evaluations.

The agreement between reviewers in overall risk assessment as well as individual morphology characteristics was evaluated. The amount of agreement as to risk classification for both the re-reviewer inter-rater comparison and the re-reviewer-study investigator comparison was summarized by the kappa statistic. The kappa values showed poor agreement between the re-reviewers themselves (kappa = 0.29), similarly poor agreement of re-reviewers with the study's per-CRF risk assessment (kappa = 0.22), and even less agreement of the re-reviewers with the study's as-randomized risk assessment (kappa = 0.09). The conclusion reached from this angiogram re-review process was that risk classification based upon lesion morphology was not a reproducible assessment. Therefore, since individual patients cannot be reliably classified as to risk level by the current commonly used method, a group classified as low risk cannot be reliably identified in whom abciximab efficacy can be evaluated. The risk assessment performed in the EPILOG study did produce low-risk subset groups with event rates less than seen in the high-risk subset groups. However, the generalizability of this subset analysis to patient populations in clinical practice is uncertain.

The Readministration Study

Centocor has conducted a small, single center, open label study examining the effects of readministration of abciximab to subjects. This study enrolled 41 subjects who were either patients with stable coronary artery disease or healthy volunteers. All subjects received a bolus of 0.25 mg/kg abciximab, followed by a 12 hour infusion of abciximab using either a weight adjusted (0.125 µg/kg/min) or a non-weight adjusted (10µg/min) regimen. Subjects were randomized between the weight-adjusted and non-weight adjusted infusion regimen groups. Aspirin was given prior to the infusion, but heparin was not utilized. Pharmacokinetic and pharmacodynamic parameters were assessed, as well as safety related evaluations and antibody response. At 14 weeks after the initial administration, 29 subjects who had not had a HAMA or HACA response at any of the intervening time points (1, 2, 4, 8, and 12 weeks) were readministered abciximab using the same regimen as for the initial administration (1 patient who had a low level HAMA at week 8 was reinjected).

There were 12% of the patients who developed a HACA response after the first injection within 12 weeks. Two more patients with positive HAMA within that period developed positive HACA within 6 months (for a total HACA response rate due solely to the first injection of 17%). Following the reinjection into 29 subjects, 24% became HACA positive within 12 weeks.

There were no anaphylactic reactions associated with the reinjection into HACA negative patients. There were two cases of thrombocytopenia seen in this study, one with the initial injection in a patient with a baseline positive HACA and one with the reinjection in a patient with a low level positive HAMA at the time of reinjection. Other patients with baseline positive HACA were not similarly affected.

Conclusions

The EPILOG study has demonstrated that when patients undergoing PTCA are viewed as a group (with patients at lower risk for abrupt closure included in the group) abciximab results in a lower incidence of ischemic events within 30 days. This supports and extends the data obtained in the EPIC study.

Centocor has also been successful in fulfilling their phase 4 commitment to evaluate means of lowering the bleeding risks associated with abciximab. The measures utilized in the EPILOG study resulted in lower bleeding rates, and the lower dosing heparin regimen with abciximab was associated with bleeding rates comparable to placebo with standard dose heparin, while still showing good efficacy.

An important objective of Centocor in conducting the EPILOG study was also to gain inclusion of patients assessed as at low risk for abrupt closure into the indication. However, uncertainty exists in how patients in the EPILOG study should be classified. Additionally, the reliability of risk assessment based on lesion morphology in the angiogram re-review study was low. The difficulties with this assessment thus prevent formation of a judgement regarding benefit in this subset that can be considered generalizable outside of the EPILOG trial. Low risk patients cannot be reliably distinguished from high risk patients.

However, with the lower dose heparin regimen and other patient management guidelines instituted by Centocor in EPILOG, the risks associated with abciximab treatment are not significantly greater than those associated with standard-dose heparin alone. Thus, if low risk patients are treated with abciximab under the new guidelines, they are exposed to little additional risk. Consequently, they will not have a significantly unfavorable risk-benefit profile even if they derive no benefit from the abciximab treatment. Therefore, in order to insure that high risk patients who do benefit from abciximab are not unknowingly excluded from abciximab treatment, treatment with abciximab can be safely expanded to all patients undergoing PTCA.

The small reinjection study conducted by Centocor has shown that in the absence of development of positive HACA (or HAMA) responses, reinjection with abciximab has a safety profile and a pharmacodynamic profile similar to that of an initial injection. However, the study suggested an increase in the incidence of HACA responses following reinjection. Additionally, neither the safety nor activity of abciximab has been evaluated in the setting of a positive HACA response. As a consequence of increasing abciximab usage in initial and second treatment courses, there will be an increasing prevalence of abciximab induced HACA titers. The uncertainties of safety and efficacy for these patients remains a concern.

Recommendations

I concur with Dr. Stolman in her major recommendations regarding this BLA Supplement.

The indication for abciximab should be broadened to include all patients undergoing PTCA.

However, there should be explicit acknowledgment in the package insert that the risk assessment method utilized in the EPILOG study did not prove to be reproducible, and thus no conclusions regarding the efficacy of abciximab in patients assessed as low risk may be reached with any generalizability outside of the EPILOG study.

Due to the use of a composite event endpoint in this trial as well as the other abciximab phase 3 trials, and that the most serious of the component events, mortality, does not appear to contribute to the efficacy of abciximab, it is important that the labeling and promotional materials provide some understanding of this differential in the components contributions to the observed efficacy.

The measures adopted by the investigators for the EPILOG study that appear to have successfully decreased the bleeding rates should be adopted as recommendations within the package insert for abciximab.

The limited information regarding reinjection should be incorporated into the package insert. However, as the important questions of the consequences of reinjection in the presence of a HACA response remains unanswered, Centocor should be asked to commit to further study to assess the risks that may occur in this setting, as well as the activity of abciximab under this condition.