CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20718/S2

MEDICAL REVIEW(S)

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS (HFD-110)
MEDICAL REVIEW OF NDA SUPPLEMENT 002
FOR INTEGRILIN

NDA: 20-718
DRUG NAME: Eptifibitide
TRADE NAME: Integrilin
FORMULATION: For intravenous injection
SPONSOR: Cor Therapeutics
TYPE OF DOCUMENT: Supplement for Labeling Change

MEDICAL REVIEWER: Douglas C. Throckmorton, M.D.
DATE OF SUBMISSION: 5.7.99
DATE RECEIVED BY FDA: 5.10.99
DATE ASSIGNED: 5.10.99
DATE REVIEW COMPLETED: 6.24.99

BACKGROUND AND RATIONALE:

Background

Integrilin (eptifibatide), an inhibitor of platelet aggregation, is approved for use in acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction (UAP/NQWMI), and in patients undergoing percutaneous coronary intervention (PCI). This approval was based on the results from two-phase III trials: IMPACT-II and PURSUIT.

Based on follow-up data not submitted in the NDA, the sponsor proposed several labeling changes, which are discussed in my last memo Of these, the only outstanding issue is the inclusion of 'six-month follow-up data' from the PURSUIT trial in the label. This current memo reviews the most recent submission related to this data, as well as the statistical review by Dr. Hung. For details of the PURSUIT trial the reader is referred to my previous memo.

/S/
Douglas C. Throckmorton, M.D.

DOCUMENTS USED FOR REVIEW

1) NDA 20-718 (Integrilin) Supplements submitted 11.19.98 and 5.7.99.
2) Medical Review of PURSUIT by Dr. Hammond, submitted 2.17.98.
3) Published results from the RESTORE, PRISM-PLUS, PRISM, EPIC, EPILOG, PURSUIT, and CAPTURE trials.
4) NDA 20-912 (Aggrastat) Letter from Merck Research Laboratories regarding the 6-month F/U data from the PRISM-PLUS and RESTORE trials, dated 3.19.99.
5) NDA 20-718 (Integrilin) Samples of clinical data collected as part of the 6-month follow-up for the PURSUIT trial, dated 3.17.99.

SIX-MONTH FOLLOW-UP DATA FROM PURSUIT

In the initial submission, dated 9.98, the sponsor proposed that the following language be inserted in the approved label, reflecting post-hoc analysis of the PURSUIT data.

Table S1 Proposed language for the label, submitted 9.98.

CLINICAL STUDIES: PURSUIT
'A secondary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (as reported by the investigators) within 6 months of randomization. As shown in the Kaplan-Meier curve (not reproduced in this review), investigators reported a reduction in death or MI from 13.6% with placebo to 12.1% with eptifibatide (p=0.021) within 6 months of randomization.'

SIX-MONTH FOLLOW-UP DATA FROM PURSUIT

As part of my previous review, I noted that not all patients had 6-month follow-up data. Some individuals were lost to follow-up, died, or had their last contact prior to 180 days. The first table below is the summary of the follow-up submitted by the sponsor as part of their initial labeling proposal (9.98).

Table S2 6-Month Follow-up in the PURSUIT trial.

	Placebo	Eptifibatide 180/2.0
Total Randomized	4739	4722
Verified Deaths	291 (6.1%)	301 (6.4%)
Timing of Last Follow-Up[a]		
Lost to Follow-Up[b]	26 (0.5%)	30 (0.6%)
<120 Days	3 (0.1%)	4 (0.1%)
120 to <150 Days	21 (0.4%)	29 (0.6%)
150 to <180 Days	746 (15.7%)	758 (16.1%)
≥180 Days	3652 (77.1%)	3600 (76.2%)

a. For patients known not to have died. Data from submission dated 9.98.
b. Status unknown beyond 30 day visit.

Following review of these data, this reviewer recommended against allowing the inclusion of the 6-month data in the approved label, primarily because the follow-up available for the PURSUIT trial is significantly less complete than that available for the other trials of IIb/IIIa inhibitors. The other deficiencies noted for the PURSUIT data (discussed in my earlier memo)... "are similar to those seen with other trials that have been previously included in labeling. Given the inclusion of the PRISM-PLUS trial in approved labeling, precedent would suggest that the PURSUIT data should also be included in the Aggrastat label, but only for the 150 day data where there is follow-up for >98% of the subjects. The sponsor should be required to submit the 150 day follow-up, to be analyzed for inclusion in the approved Integrilin label, and should not be allowed to include the incomplete 180 day follow-up data in the label." (from my memo dated 3.31.99).

This opinion was concurred with by the secondary reviewer, Dr. Ganley, and transmitted to the sponsor. As part of their response, the sponsor submitted a new set of proposed language to be included in the label. At the FDA's request, they also submitted SAS sets detailing the extent of follow-up for all of the treatment groups, along with the treatment codes, allowing the FDA statistician, Dr. James Hung, to evaluate the pattern of follow-up in the PURSUIT trial. His analysis appears as a separate consultation. A portion of his analysis is included in the current document below.

The sponsor has now submitted a new proposal for language reflecting the long-term follow-up of patients in the PURSUIT trial, which appears below.

Table S3 Proposed language for the label, submitted 5.7.99.

CLINICAL STUDIES: PURSUIT

A secondary endpoint of PURSUIT was the occurrence of death from any cause or new myocardial infarction (as reported by the investigators) within 6 months or randomization. Based on data available for 96.9% of patients (n=10,611), who were followed for 165 days or longer, endpoint events were reduced from 13.6 percent with placebo to 12.1% with eptifibatide 180/2.0 (p=0.021 log rank) at the six-month timepoint.

The sponsor also submitted a SAS dataset, which allowed Dr. Hung to examine the distribution of follow-up duration by treatment group. As can be seen from the table below, a large number of patients were lost to follow-up after 165-179 days of follow-up. In contrast, relatively few patients were lost during the intervals from 120-164 days. Data for the 180/1.3 arm (which was discontinued early) are not shown in this table, but are to be found in Dr. Hung's review. It can also be seen that individuals lost to follow-up are fairly well balanced between the two treatment groups (although Dr. Hung concluded that there were slightly more early losses of follow-up in the eptifibatide group).

SIX-MONTH FOLLOW-UP DATA FROM PURSUIT

Table S4 Distribution of follow-up duration by treatment group in the PURSUIT trial[a].

	Placebo	Eptifibatide 180/2.0
Lost to Follow-Up[b]	26 (0.5%)	30 (0.6%)
<120 Days	3 (0.1%)	4 (0.1%)
120 to 149 Days	21 (0.4%)	29 (0.6%)
150 to 154 Days	29 (0.61%)	24 (0.51%)
155 to 159 Days	29 (0.61%)	35 (0.74%)
160 to 164 Days	41 (0.8%)	34 (0.72%)
165 to 169 Days	154 (3.25%)	152 (3.22%)
170 to 174 Days	202 (4.26%)	218 (4.62%)
175 to 179 Days	291 (6.14%)	295 (6.25%)
≥180 Days	3943 (83.2%)	3901 (82.6%)

a. For patients known not to have died. Data from Dr. J. Hung's analysis of SAS sets submitted by the sponsor.
b. Status unknown beyond 30 day visit.

Dr. Hung also compared the incidence of Death/MI at the six-month follow-up data for the two treatment groups, and confirmed the sponsor's results. If the patients that are lost to follow-up are treated as events, however, the statistical significance of the difference is reduced. This was due to the slightly more early losses of follow-up in the eptifibatide group.

Table S5 Incidence of Death/MI in all randomized patients at six months (analysis treats all losses of follow-up before day 166 as non-events).

Eptifibatide 180/2.0 N=4722	Placebo N=4739	Logrank p Value	Absolute Reduction	Relative Reduction	Hazard Ratio (95% C.I.)
570 (12.1%)	643 (13.6%)	0.021	1.5%	11.0%	0.88 (0.78, 0.98)

Table S6 Incidence of Death/MI in all randomized patients at six months (analysis treats all losses of follow-up before day 166 as events).

Eptifibatide 180/2.0 N=4722	Placebo N=4739	Logrank p Value	Absolute Reduction	Relative Reduction	Hazard Ratio (95% C.I.)
732 (15.5%)	792 (16.7%)	0.076	1.2%	7.2%	0.91 (0.83, 1.01)

MEDICAL REVIEWER'S COMMENTS FOR SIX-MONTH FOLLOW-UP DATA FROM THE PURSUIT TRIAL

The current submission, along with the analysis by Dr. Hung, demonstrates the following points about the long-term follow-up for the PURSUIT trial:

1. The difference between the rate of Death/MI seen at the end of 30 days persists through (roughly) six months.

2. The patients were not lost to follow-up randomly between days 120 and 179, with a large fraction of those lost to follow-up represented in three groups between 160 and 179 days.

The latter observation suggests that the loss to follow-up was non-random, and that a decision was made not to seek follow-up for some patients with sufficiently long follow-up. This may have been the Duke clinical center, which felt that 'a follow-up interval of 120 days would be adequate to characterize the long-term result.' (from submission dated 9.98).

The decision to include the proposed language in labeling, then, depends on three factors: 1) Adequacy of the data collection, 2) Results of the data analysis, and 3) Comparison of the proposed label changes with other approved labels for IIb/IIIa inhibitor.

MEDICAL REVIEWER'S COMMENTS FOR SIX-MONTH FOLLOW-UP DATA FROM THE PURSUIT TRIAL (cont)

Adequacy of data collection

As discussed in my earlier memo, the collection of the data was similar to that used to support statements about 6-month follow-up data in the Aggrastat and Reopro labels. The following table summarizes the salient features of the current and proposed language describing 6-month data in the current and proposed labels for abciximab, tirofiban and eptifibatide. Note that the percentage of follow-up is still less in the PURSUIT trial than for the other long-term results included in product labels.

Table C1 Comparison of the proposed Integrilin label with other approved IIb/IIIa drug labels

Drug/ Trial	6-Month Information in Label[e]	Blinded?	Centrally-Adjudicated?	% Follow-Up	Pre-specified Endpoint?
Abciximab					
EPIC	MI/Death/Revascularization in writing	Y	Y	99%	N
EPILOGUE	MI/Death/Revascularization in writing	Y	Y	>95%[b]	N
CAPTURE	MI/Death/Urgent Intervention in writing	Y	Y	99%	N
Tirofiban					
PRISM-PLUS	MI/Death/Refractory Ischemia in K-M Curve	Y	N	98.8%	Y
CAPTURE	MI/Death/Revascularization in K-M Curve	Y	Y	99%	Y
Integrilin PURSUIT (proposed)	Death/MI in writing and K-M curve	[g]	N	96.9%	No

b. Per Primary Medical Reveiwer in CBER, Dr. Stolman.

c. CRFs were reviewed centrally and events excluded if sufficient data existed. This occurred in <2% of the events submitted by investigators per the sponsor.

d. The following was a pre-specified composite endpoint at 6 months: Death/MI/recurrence of ischemic symptoms, repeat attempts at coronary intervention and readmission for ischemic symptoms.

e. Results are all included in the Clinical Trials Section.

g. The sponsor does not specify maintaining the blind with regard to treatment in any document reviewed. However, the six-month CRFs identify the patients only by number/treatment site, with no treatment group identified. This suggests the maintenance of the blinding.

Results of the data analysis

The data analysis by Dr. Hung confirms that the treatment effect of eptifibatide persists through the 6-month follow-up period. If patients who were lost to follow-up were treated as events (conservative analysis), however, the statistical power of the treatment effect was diminished.

Comparison of the proposed label changes with other approved labels for IIb/IIIa inhibitor.

As discussed in my earlier memo, the proposed label changes are similar to what has been approved for other IIb/IIIa inhibitors. This is not the same thing as saying the methods of data collection were without criticism. The reliance on investigators to determine events, the post-hoc nature of the analysis, and the proposed inclusion of a non-pre-specified endpoint into label gives this reviewer some pause. However, these criticisms have not precluded inclusion of similar long-term data into other approved labels.

MEDICAL REVIEWER'S COMMENTS FOR SIX-MONTH FOLLOW-UP DATA FROM THE PURSUIT TRIAL (cont)

Reviewer's Conclusions (My previous conclusions regarding the six-month follow-up data are repeated where appropriate).

1. The collection of six-month data in the PURSUIT trial was less than perfect, especially with regard to the reliance on investigators for evaluating clinical events and the extent of the 180-day follow-up. In comparison with other trials that are included in currently approved labels, the data collection are less stringent than for some (EPIC, CAPTURE, RESTORE), but apparently equal to the PRISM-PLUS trial. In the PRISM-PLUS trial, similar to PURSUIT, the only data collected were the occurrence of death or clinical cardiac events, as judged by the investigators. In one respect, however, PURSUIT was more 'rigorous' than PRISM-PLUS: PURSUIT investigators also collected other clinical details (e.g., ECGs, hospital summaries).

2. The follow-up available for the PURSUIT trial is less complete than that available for the other trials, although there is no evidence that the difference would alter the conclusions regarding the treatment effect of eptifibatide at 6 months. The PURSUIT trial results summarized above suggest a durable, if declining, effect of eptifibatide on the combined endpoint of death/MI through 6 months. It is notable that the nominal incidence of mortality is higher in the eptifibatide group at the end of six months, relative to placebo. A similar trend was seen for some (RESTORE, CAPTURE), but not all (EPIC, EPILOGUE, PRISM-PLUS) of the other trials with IIb/IIIa antagonists.

3. That the six-month data from PURSUIT was not a pre-specified endpoint is similar to the data included in the Reopro label from the EPIC and EPILOGUE trials. While this should not be used to prevent the data from being included in the label, the sponsor should not be able to claim that the Death/MI endpoint is a 'secondary endpoint' (as currently proposed).

4. The decision to include the six-month data from PURSUIT in the approved label, then, revolves around the importance of the full 180-day follow-up. The other deficiencies noted for the PURSUIT data are similar to those seen with other trials that have been previously included in labeling. Given the inclusion of the PRISM-PLUS trial in approved labeling, precedent would suggest that the PURSUIT data should also be included in the eptifibatide label, emphasizing the lower degree of follow-up available (as proposed by the sponsor).

OVERALL RECOMMENDATION OF MEDICAL OFFICER:

1. The six-month follow-up data for PURSUIT should be included in the label, including information about the lower percentage of follow-up (96.9%).

2. The approved language should not refer to the incidence of Death/MI in PURSUIT as a 'secondary endpoint.'

cc: ORIG: NDA 20-718
HFD-110 Division File
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DIVISION OF CARDIO-RENAL DRUG PRODUCTS (HFD-110)
MEDICAL REVIEW OF NDA SUPPLEMENT 002
FOR INTEGRILIN

NDA: 20-718
DRUG NAME: Eptifibitide
TRADE NAME: Integrilin
FORMULATION: For intravenous injection
SPONSOR: Cor Therapeutics
TYPE OF DOCUMENT: Supplement for Labeling Change

MEDICAL REVIEWER: Douglas C. Throckmorton. M.D.
DATE OF SUBMISSION: 9.9.98
DATE RECEIVED BY FDA: 9.10.98
DATE ASSIGNED: 9.10.98
DATE REVIEW COMPLETED: 3.31.99

BACKGROUND AND RATIONALE:

Background

Integrilin (eptifibatide), an inhibitor of platelet aggregation, is approved for use in acute coronary syndrome (unstable angina or non-Q-wave myocardial infarction (UAP/NQWMI), and in patients undergoing percutaneous coronary intervention (PCI). This approval was based on the results from two-phase III trials: IMPACT-II and PURSUIT.

Based on follow-up data not submitted in the NDA, the sponsor is requesting several labeling changes.

1. Addition of language to the label describing the incidence of death/MI through 6 months from the PURSUIT trial.

2. Changes in the label to include a reduced heparin dose when used with eptifibatide. This request is derived from two sources. First, while a lower ACT was used in the EPILOG trial with abciximab (≥200 seconds), the clinically significant effect of abciximab to reduce the incidence of death/MI/ urgent revascularization remained. Second, the sponsor has submitted analyses from the eptifibatide NDA database supporting the safety of a lower target ACT in patients receiving eptifibatide.

3. Changes in the label to describe the results of eptifibatide use with and without procedures from the PURSUIT trial.

4. Changes in label regarding the dose of eptifibatide to be used in renal insufficiency.

5. Addition of language to the label summarizing the occurrence of intracranial hemorrhage and stroke in the PURSUIT trial after six months.

These data submitted in support of these proposed labeling changes will be examined in turn, followed by an overall summary and conclusions. For the proposed inclusion of 6 month data, comparisons will be drawn with the approved labels for Aggrastat and Reopro, along with the clinical data used to support these labels.

/S/

Douglas C. Throckmorton, M.D.

(1) INCLUSION OF SIX-MONTH FOLLOW-UP DATA IN LABELING

Summary of Data from PURSUIT Trial

Documents used for Review: 1) NDA 20-718 (Integrilin) Supplement submitted 11.19.98.

2) Medical Review of PURSUIT by Dr. Hammond, submitted 2.17.98.

3) Published results from the RESTORE, PRISM-PLUS, PRISM, EPIC, EPILOG, PURSUIT, and CAPTURE trials.

4) NDA 20-912 (Aggrastat) Letter from Merck Research Laboratories regarding the 6 month F/U data from the PRISM-PLUS and RESTORE trials, dated 3.19.99.

5) NDA 20-718 (Integrilin) Samples of clinical data collected as part of the 6 month follow-up for the PURSUIT trial, dated 3.17.99.

The sponsor proposes to include a Kaplan-Meier plot showing the incidence of death/MI within 6 months of randomization, with the language reproduced below to be placed in labeling. Bold letters reflect proposed language.

CLINICAL STUDIES: PURSUIT

'A secondary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (as reported by the investigators) within 6 months of randomization. As shown in the Kaplan-Meier curve (not reproduced in this review), **investigators reported a reduction in death or MI from 13.6% with placebo to 12.1% with eptifibatide (p=0.021) within 6 months of randomization.'**

To support this change, the sponsor has submitted the results from the 6-month follow-up of the PURSUIT trial, which is reviewed below.

PURSUIT Trial Design

Protocol Number: 94-016

Title of Study: Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy

Study Design: This multi-center, randomized, blinded, placebo-controlled study examined the effect of eptifibatide in patients with UAP/NQWMI. Eptifibatide was administered as a bolus (180μg/kg IV) followed by an infusion (1.3 or 2.0 g/kg/min) for up to 72 hours. During the trial, the low dose (180/1.3) was discontinued on recommendation of the Data Safety Monitoring Board. The major results, then, were reported for the placebo group compared with the eptifibatide 180/2.0 group.

The primary endpoint of the trial was the combined incidence of death and/or MI in patients presenting with UAP/NQWMI at 30 days. For this endpoint, the incidence of MI through 30 days was adjudicated by an external, blinded, Clinical Events Committee (CEC), using pre-specified definitions. Data on the incidence of MI through 30 day, as assessed by the investigators, was also collected. For the six-month follow-up results, only investigator-reported events were collected. The sponsor states that an effort was made to verify any diagnoses by obtaining source documents. Per the sponsor, 'if no source documentation was provided, no changes were made (in the clinical event attribution).' If documentation was received, and 'the documentation showed clearly that an MI had not occurred, then the database was corrected accordingly.' Less than 2% of the events reported by the investigators at the 6 month time point were excluded for this reason, again per the sponsor (6-10 total patients dropped from the database).

Objectives (Endpoints)

The objectives of this study were to determine the efficacy of eptifibatide in reducing the incidence of death and/or MI in patients presenting with UAP/NQWMI and to determine the safety of eptifibatide in this indication.

Primary Endpoint

1. The incidence of death and/or MI during the first 30 days after randomization.

Secondary Endpoints

1. Incidence of death and/or MI at 30 days in subsets of the population (gender, ethnicity, and age)
2. Incidence of death and/or MI at other time points (96 hrs, 7 days and 30 days).
3. Incidence of death and/or MI in patients undergoing coronary angioplasty.
4. Rehospitalization for cardiac symptoms within 30 days.
5. A comparison of severity of myocardial (re)infarction using CK-MB values.
6. Death, MI, recurrence of ischemic symptoms, repeat attempts at coronary revascularization and readmission for ischemic symptoms at 6 months after enrollment.

PURSUIT Trial Design (cont)

Number of Patients

A total of 10,948 patients were randomized: 1487 to the discontinued 180/1.3 arm, 4722 to the 180/2.0 arm, and 4739 to placebo. The current report reflects the results from the 9461 randomized to either 180/2.0 or placebo.

Inclusion Criteria

All subjects must have the following:

1. Angina at rest within previous 24 hours.
2. ECG findings consistent with UAP/NQWMI, but not acute Q-wave MI.

or

3. CK-MG >upper limits of normal on screen.

Exclusion Criteria (Following must not be present)

1. Evidence of acute MI
2. Recent history of major surgery, hemorrhagic stroke, bleeding or increased risk of bleeding, or use of and investigational product.
3. Severe hypertension or renal failure.
4. Pregnancy.
5. Planned or current use of drug prohibited by protocol (e.g., other IIb/IIIa inhibitor).

Dosage/Administration

The dose of eptifibatide used by all patients covered in this submission was 180μg/kg IV bolus followed by 2.0 μg/kg/min IV infusion for 72 hours (up to 96 hours if the patient underwent PTCA).

In addition to these doses, all subjects received concomitant heparin. A protocol for administration has been prepared by the sponsor, with a target ACT of 300-350 seconds. Patients also received ASA, unless contraindicated.

Duration of Study

The initial study had a duration of 30 days (a follow-up visit).

Efficacy and Safety Parameters

The 6 month data submitted here was collected through telephone contacts with the patient or the patient's family regarding the occurrence of any important clinical event: death, non-fatal MI, recurrent cardiac ischemia, rehospitalization for cardiac symptoms, stroke, and invasive diagnostic and therapeutic cardiac procedures. These phone contacts were to be augmented where possible by collection of hospital records. The investigator recording the 6 month data was not blinded to treatment group.

Statistical Issues

Three data sets were defined for analysis in the protocol.

1. 'All Randomized' Data Set: all randomized patients, whether treated or not, according to randomized treatment assignment, plus three patients who were treated without randomization.

2. 'Treated-as Randomized' Data Set: all randomized patients who received any dose of study drug, according to randomized treatment assignment, plus three patients who were treated without randomization.

3. 'As Treated' Data Set: all patients who received any amount of study drug, according to the treatment actually received.

One patient was re-enrolled 3 months after the initial enrollment. Data from the first and second enrollment were included in the data sets, and the enrollments were considered as different patients for the purposes of analysis.

The table below summarizes the three analysis sets used.

Because not all patients had follow-up at 6 months, the sponsor chose to perform a log-rank test using Kaplan-Meier of time to event.

PURSUIT Trial Results

Demographics

As discussed above, analyses were performed using three sets of patients, defined in the Statistical Section above. The derivation of each of the groups is summarized below. No data concerning the 'As Treated' population was submitted in the current supplement.

Table D1: Demographics of the PURSUIT trial.

Treatment Group	Placebo	Eptifibatide 180/2.0	Total
Assigned Randomization	4738	4720	9458
Tx Without Randomization	1	2	3
"All Randomized" Data Set	4739	4722	9461
Randomized, Not Treated	42	42	84
"Treated As Randomized" Data Set	4697	4680	9377
Received Tx Other Than Randomized[a]	1	1	2
"As Treated" Data Set	4696	4679	9375

a. Shows the summation of patients who received one study drug after being randomized to another group. There were a total of 18 such individuals in the overall dataset.

Not all patients had 6 month follow-up data. Some individuals were lost to follow-up, died, or had their last contact prior to 180 days. Overall, >98% of both treatment groups had a final contact >120 days after enrollment or were known to have died, and (per the sponsor) only 0.6% of the patients lacked information beyond the 30 day mark. As noted above, data collection beyond 30 days was not blinded to treatment group.

While the protocol specified a 6 month follow-up contact, the Duke Clinical Center felt that 'a follow-up interval of 120 days would be adequate to characterize the long-term result.' (addendum, p. 17). As a result, not all patients have 180 day data, as shown below.

Table D2: 6 Month Follow-up in the PURSUIT trial.

	Placebo	Eptifibatide 180/2.0
Total Randomized	4739	4722
Verified Deaths	291 (6.1%)	301 (6.4%)
Timing of Last Follow-Up[a]		
Lost to Follow-Up[b]	26 (0.5%)	30 (0.6%)
<120 Days	3 (0.1%)	4 (0.1%)
120 to <150 Days	21 (0.4%)	29 (0.6%)
150 to <180 Days	746 (15.7%)	758 (16.1%)
≥180 Days	3652 (77.1%)	3600 (76.2%)

a. For patients known not to have died.
b. Status unknown beyond 30 day visit

PURSUIT Trial Results: 6 Month F/U

The sponsor compared the results through 30 days with those at the end of 6 months. For the results, investigator-adjudicated MIs were used to calculate the incidence of Death/MI at the end of 6 months. The 'All-Randomized' data set was used in this calculation, and there was a nominally significant effect of eptifibatide to lower the incidence of Death/MI relative to placebo.

Table R1 Incidence of Death/MI in the 'All-Randomized' population from the PURSUIT trial[e].

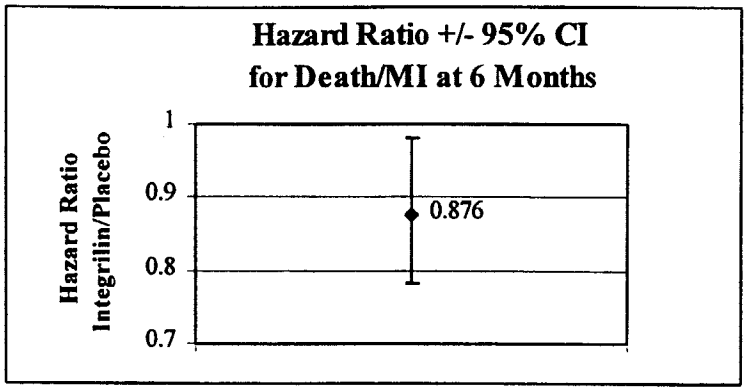
Time	Placebo N=4739	Eptifibatide N=4722	p Value	Absolute % Reduction[a]	Relative % Reduction[b]
96 Hours	241 (5.1%)	158 (3.4%)	<0.001[c]	1.7	33.3
7 Days	325 (6.9%)	228 (4.8%)	<0.001[c]	2.1	30.4
30 Days	476 (10.0%)	380 (8.0%)	0.001[c]	1.9	19.0
6 Months	643 (13.6%)	570 (12.1%)	0.021[d]	1.5	11.0

a. Reduction in incidence with eptifibatide relative to placebo in absolute percentage terms. MIs are centrally-adjudicated.
b. Reduction in incidence with eptifibatide relative to placebo expressed as a percent of the placebo incidence.
c. Pearson's chi-square test.
d. Log-rank test based on Kaplan-Meier estimates.
e. From NDA 20-718 addendum, text table 3.

PURSUIT Trial Results: 6 Month F/U (cont)

Note that the log-rank test was used for the p Value at 6 months. Per the sponsor, this was to allow for the testing the differences in distribution over time. Given the low number of censored events (<5% per the sponsor at 6 months), the power of log-rank to accommodate censoring was not critical. Testing the event incidence at 6 months using a corrected Chi-square test the two-sided p Value would be 0.029, rather than 0.021.

The figure below shows the hazard ratio for the incidence of death/MI at six months for the 'All-Randomized' population, along with the 95% confidence intervals.



For comparison, the incidence of Death/MI in the 'Treated as Randomized' population for the investigator-identified MIs and death are shown below. In this population there was also a nominally significant effect of eptifibatide to lower the incidence of Death/MI relative to placebo.

Table R2 Incidence of Death/MI in the 'Treated as Randomized' population from the PURSUIT trial[e].

Time	Placebo N=4697	Eptifibatide 180/2.0 N=4680	p Value	Absolute % Reduction[a]	Relative % Reduction[b]
96 Hours	236 (5.0%)	156 (3.3%)	<0.001[c]	1.7%	34%
7 Days	320 (6.8%)	226 (4.8%)	<0.001[c]	2.0%	29.4%
30 Days	471 (10.0%)	378 (8.1%)	0.001[c]	1.9%	19.0%
6 Months	636 (13.6%)	567 (12.2%)	0.028[d]	1.4%	10.4%

a. Reduction in incidence with eptifibatide relative to placebo in absolute percentage terms. MIs are investigator-adjudicated.

b. Reduction in incidence with eptifibatide relative to placebo expressed as a percent of the placebo incidence.

c. Pearson's chi-square test per the sponsor.

d. Log-rank test based on Kaplan-Meier estimates per the sponsor.

e. From NDA 20-718 addendum, text table 3, and from primary review of PURSUIT by Dr. Hammond.

PURSUIT Trial Results: 6 Month F/U (cont)

The majority of the effect of eptifibatide was seen on the reduction in the incidence of MIs, as seen in the tables below, summarizing the individual contributions of the two clinical events. Note that at six months there is a nominally higher incidence of death for eptifibatide relative to placebo.

Table R3 Incidence of Death in the 'All-Randomized' population from the PURSUIT trial[a].

Time	Placebo N=4739	Eptifibatide 180/2.0 N=4722	% Change in Incidence[c]
96 Hours	58 (1.2%)	42 (0.9%)	-25
7 Days	95 (2.0%)	70 (1.5%)	-25
30 Days	177 (3.7%)	165 (3.5%)	-5.4
6 Months	291 (6.2%)	301 (6.4%)[b]	+3.2

a. From NDA 20-718 addendum, table 4.
b. Kaplan-Meier estimate of incidence using available information from each patient.
c. Calculated as the difference between placebo and eptifibatide divided by the placebo rate (X100).

Table R4 Incidence of MIs in the 'All-Randomized' population from the PURSUIT trial[a].

Time	Placebo N=4739	Eptifibatide 180/2.0 N=4722	% Change in Incidence[c]
96 Hours	209 (4.4%)	132 (2.8%)	-36.3
7 Days	270 (5.7%)	190 (4.0%)	-29.8
30 Days	369 (7.8%)	291 (6.2%)	-20.5
6 Months	461 (9.9%)	387 (8.3%) [b]	-16.2

a. From NDA 20-718 addendum, table 4
b. Kaplan-Meier estimate of incidence using available information from each patient.
c. Calculated as the difference between placebo and eptifibatide divided by the placebo rate (X100).

PURSUIT Trial Results: 6 Month Incidence of Death/MI/ Recurrent Vascularization

The sponsor also reported the incidence of the combined endpoint of Death/MI/ Recurrent Vascularization through 6 months. These results are shown below. At the end of 6 months the use of eptifibatide was associated with a 2.7% decrease in the incidence of the endpoint, a difference which was nominally significant, without correction for the post-hoc nature of the analysis and any penalty for multiple looks.

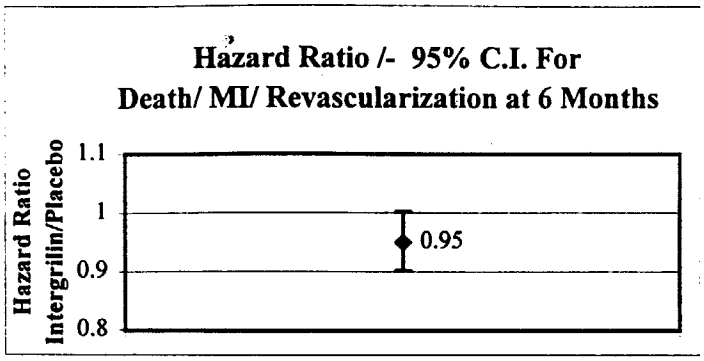
Table R5 Incidence of Death, MI, and Recurrent Revascularization in the 'All-Randomized' population from the PURSUIT trial[a].

Time	Placebo N=4739	Eptifibatide 180/2.0 N=4722	p Value	% Change in Incidence [c]
6 Months	2874 (60.8%)	2779 (59.1%)	0.051	-2.7%

a. From NDA 20-718 addendum, table 4
b. Kaplan-Meier estimate of incidence using available information from each patient.
c. Calculated as the difference between placebo and eptifibatide divided by the placebo rate.

The figure below shows the hazard ratio for the incidence of Death/MI/Revascularization (including PTCA, stent, CABG, and rehospitalization) at six months in the 'All Randomized' population, along with the 95% confidence intervals.

PURSUIT Trial Results: 6 Month Incidence of Death/MI/ Recurrent Vascularization



PURSUIT Trial Results: 6 Month Result Sub-Group Analyses

1) Region

The results when analyzed according to region are shown below for the incidence of Death/MI at the end of 30 days and 6 months. As discussed above, these data are from the investigator-identified endpoints rather than the centrally-adjudicated endpoints.

Table R6 Incidence of Death/MI in the 'All-Randomized' population from the PURSUIT trial by region[b].

	North America	Western Europe	Eastern Europe	Latin America
30-Days				
Placebo	180 (9.4%)	183 (9.9%)	89 (11.5%)	23 (11.7%)
Eptifibatide 180/2.0	129 (6.8%)	154 (8.3%)	78 (10.2%)	19 (9.5%)
6 Months				
Placebo	252 (13.2%)	242 (13.1%)	120 (15.5%)	29 (14.8%)
Eptifibatide 180/2.0	205 (10.8%)	216 (11.7%)	117 (15.4%)	32 (16.2%)

a. Reduction in incidence with eptifibatide relative to placebo in absolute percentage terms. MIs are investigator-adjudicated.

b. From NDA 20-718 addendum, text table 3, and from primary review of PURSUIT by Dr. Hammond.

2) Gender

The results when analyzed according to gender are shown below for the incidence of Death/MI at the end of 30 days and 6 months. As discussed above, these data are from the investigator-identified endpoints rather than the centrally-adjudicated endpoints. As previously noted, there was a higher incidence of the primary endpoint in the females receiving eptifibatide at the end of 30 days.

Table R7 Incidence of Death/MI in the 'All-Randomized' population from the PURSUIT trial by gender[b].

	Placebo		Eptifibatide 180/2.0	
	Female	Male	Female	Male
30-Days	146 (8.5%)	329 (10.9%)	14 (8.7%)	236 (7.7%)
6 Months	210 (12.3%)	433 (14.4%)	202 (12.3%)	368 (12.0%)

a. Reduction in incidence with eptifibatide relative to placebo in absolute percentage terms. MIs are investigator-adjudicated.

b. From NDA 20-718 addendum, text table 3, and from primary review of PURSUIT by Dr. Hammond.

PURSUIT Trial Results: 6 Month Result Sub-Group Analyses (cont)

As observed previously, this gender discrepancy was driven by the results from Europe and South America.

Table R8 Incidence of Death/MI through 6 months in the 'All-Randomized' population from the PURSUIT trial by gender and region[a].

		Placebo	Eptifibatide	p Value
Worldwide	Female	210 (12.3%)	202 (12.3%)	0.993
	Male	433 (14.4%)	368 (12.0%)	0.004
North America	Female	92 (13.7%)	64 (9.8%)	0.030
	Male	160 (12.9%)	141 (11.3%)	0.174
South America	Female	6 (8.5%)	13 (17.1%)	0.135
	Male	23 (18.4%)	19 (15.6%)	0.508
Western Europe	Female	58 (9.9%)	71 (12.5%)	0.155
	Male	184 (14.6%)	145 (11.4%)	0.011
Eastern Europe	Female	54 (14.3%)	54 (15.5%)	0.621
	Male	66 (16.6%)	63 (15.2%)	0.504

a. Data from NDA 20-718 addendum, text table 7. Nominal p Values per sponsor.

3) Efficacy Results in Patients with and without Percutaneous Coronary Intervention

The sponsor also summarized the 6 month incidence of MI/Death according to the receipt of PCI within 72 hours of start of drug administration. The sponsor notes that at all timepoints, the incidence of Death/MI was consistently less in patients treated with eptifibatide compared with placebo, regardless of whether the patient underwent PCI in the first 72 hours. The percent reduction in the incidence, however, tended to wane at the 6 month measurement period.

Table R9 Incidence of Death/MI for patients who underwent PCI within 72 hours of enrollment[a].

Endpoint	Time	Placebo n=631	Eptifibatide n=619	% Change in Incidence [b]
Death/MI	96 hours	70 (11.1%)	32 (5.2%)	-53.1%
	7 days	75 (11.9%)	37 (6.0%)	-49.6%
	30 days	81 (12.8%)	45 (7.3%)	-43.0%
	6 months	101 (16.0%)	72 (11.7%)	-26.9%

a. Data from NDA 20-718 addendum, text table 8.

b. Calculated as the difference between placebo and eptifibatide divided by the placebo rate (X100).

Table R10 Incidence of Death/MI for patients who did not underwent PCI within 72 hours of enrollment[a].

Endpoint	Time	Placebo n=4108	Eptifibatide n=4103	% Change in Incidence [b]
Death/MI	96 hours	171 (4.2%)	126 (3.1%)	-26.2%
	7 days	250 (6.1%)	191 (4.7%)	-23.0%
	30 days	395 (9.6%)	335 (8.2%)	-14.6%
	6 months	542 (13.3%)	498 (12.2%)	-8.3%

a. Data from NDA 20-718 addendum, text table 9.

b. Calculated as the difference between placebo and eptifibatide divided by the placebo rate (X100).

PURSUIT Trial Results: 6 Month Safety Evaluation

The only safety marker collected through six months was the investigator's reported incidence of stroke. These data are shown below. There was no numerical difference in stroke incidence (investigator-reported).

Table R11 Incidence of strokes through 6 months in the PURSUIT trial[a].

Time	Placebo n=4696	Eptifibatide n=4679
30 Days (Centrally-adjudicated)	39 (0.8%)	32 (0.7%)
30 Days (Investigator-reported)	44 (0.9%)	33 (0.7%)
6 Months (Investigator-reported)	70 (1.5%)	52 (1.3%)

a. Data from NDA supplement, Table 11.

(1) INCLUSION OF SIX-MONTH FOLLOW-UP DATA IN LABELING (CONT)

Comparison of proposed language with the language regarding long-term results presented in the labels of other IIb/IIIa inhibitors.

Tirofiban (Aggrastat)

The CLINICAL STUDIES section of the approved tirofiban label presents six-month data in the clinical descriptions of two trials submitted as part of the NDA: PRISM-PLUS and RESTORE.

PRISM-PLUS

The PRISM-PLUS trial enrolled patients with UAP/NQWMI, including patients who were to be managed medically and those that underwent PCI, including PTCA and stent placement. In the PRISM-PLUS trial, the incidence of the following composite endpoint at six months was a pre-specified 'exploratory' endpoint: death, rehospitalizations for myocardial ischemia/infarction, and any revasculalization procedures. Per the sponsor, 'investigators were asked only to document the date of the 6-month follow-up, whether the patient had died, whether the patient had been admitted to the hospital with a cardiac ischemic syndrome, and, if yes, whether this syndrome was unstable angina or a myocardial infarction. '...These blinded data were not monitored, reviewed, or adjudicated, but were entered directly into the database as recorded by the investigator on the case report form.' This case report form was the only piece of information submitted to the sponsor. Complete 180 day follow-up data were available for 1892 of 1915 (98.8%) of the randomized patients. The remainder were lost to follow-up (17), refused follow-up (1), or were not contacted by the investigators (5).

In the approved Aggrastat label, the risk reduction for the primary endpoint (refractory ischemia, new myocardial infarction and death) at 30 days and 6 months for PRISM-PLUS is presented in a Kaplan-Meier curve.

Table C1 Incidence of the primary endpoint (RIC/MI/Death) and it components at 180 days in the PRISM-PLUS trial[a,c,d].

Endpoint	Tirofiban n=345		Tirofiban +Heparin n=773	Heparin n=797	p Value (T+H vs H)[b]
Composite endpoint at 180 days	105 (30.4%)		214 (27.7%)	256 (32.1%)	0.055
MI/Death at 180 days	55 (15.9%)		95 (12.3%)	122 (15.3%)	0.063
MI at 180 days (fatal/ nonfatal)	35 (10.1%)		64 (8.3%)	84 (10.5%)	0.100
Death at 180 days	25 (7.2%)		53 (6.9%)	56 (7.0%)	0.85

a. Data from NDA 20-912, volume 1.42, tables 17-20 and volume 1.59, reference 55, table 1. Intent-to-treat population is used.

b. p Value using Pearson's chi square by FDA analysis.

c. RIC: refractory ischemic conditions included: (1) prolonged or repetitive anginal chest pain with ischemic ST-T changes on electrocardiogram despite optimal medical therapy, (2) hemodynamic instability in the setting of recurrent angina or ischemic electrocardiographic changes or (3) severe, prolonged or repetitive chest pain leading to an urgent invasive intervention within 12 hours of symptom onset.

d. The primary efficacy endpoint of the trial was the composite occurrence of refractory ischemic conditions, new myocardial infarction, or death within 7 days of start of study drug.

RESTORE

The RESTORE trial enrolled subjects undergoing PTCA or atherectomy within 72 hours of presentation with an acute coronary ischemic syndrome (UAP/NQWMI). In the 'RESTORE trial, the incidence of the following composite endpoint at six months was a pre-specified secondary endpoint: death from any cause, nonfatal MI, CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia, or insertion of a coronary endovascular stent because of procedure failure. Per the sponsor, the six month data was to be obtained at the 6 month visit. 'An actual clinic appointment was preferred, but the investigators were also permitted to contact the patient by telephone, especially in cases where the patient lived a long distance from the investigative site. If the patient or family reported that an event occurred, the investigator obtained the information that was needed by the Endpoint Committee for the adjudication process (e.g., ECGs, CK-MB data, PTCA reports, discharge summaries, etc.), exactly as had been done for the 30 day endpoints. There was a 6-month endpoint case report form. Following the collection of these data, the endpoints occurring between days 31 and 180 were adjudicated by the Endpoint Committee in blinded fashion. At the 6 month endpoint, data were available on 1,057 of 1,071 (99%) of the tirofiban-treated patients, and 1,050 of 1,070 (98%) of the placebo-treated patients.

In the approved Aggrastat label, the risk reduction in the composite primary/secondary endpoint (death, nonfatal myocardial infarction and all repeat cardiac revascularization) at 30 days and 6 months is presented in a Kaplan-Meier curve.

The table below summarizes the 6 month data from the RESTORE trial. Note that at 6 months, the there is a nominal increase in mortality in the tirofiban group relative to placebo.

Table C2 Incidence of the combined endpoint and its components at 180 days in the RESTORE trial[a].

	Tirofiban n=1071	Placebo n=1070	Odds Ratio & 95% CI	p Value[b]
Combined endpoint at 180 days (secondary endpoint)[c]	258 (24.1%)	290 (27.1%)	0.853 0.702, 1.037	0.110
CABG at 180 days	59 (5.5%)	73 (6.8%)	0.793 0.556, 1.130	0.199
Repeat PTCA at 180 days[d]	168 (15.7%)	183 (17.1%)	0.902 0.717, 1.135	0.378
MI (fatal & non-fatal) at 180 days	67 (6.3%)	81 (7.6%)	0.809 0.578, 1.132	0.216
Death at 180 days	19 (1.8%)	15 (1.4%)	1.274 0.644, 2.521	0.487

a. Data from NDA 20-912, volume 1.55, tables 18-22. Intent-to-treat population is used.

b. p Value per the sponsor based on logistic regression analysis, and confirmed by FDA analysis (Dr. James Hung).

c. Combined endpoint was a composite of the following: death from any cause; nonfatal myocardial infarction; CABG or repeat percutaneous intervention of the target vessel for recurrent ischemia; or insertion of a stent because of procedural failure.

d. Includes both PTCA and atherectomy.

Abciximab (Reopro)

In the approved Reopro label, six month (or longer) follow-up data is included from three clinical trials: EPIC, EPILOG, and CAPTURE.

EPIC

The EPIC trial enrolled high-risk patients undergoing PTCA. In the EPIC trial, 6 month data was not part of any pre-specified endpoint. However, six month data was collected and reviewed by an independent clinical endpoints committee, which remained blinded to treatment and required consensus of at least two reviewers for classification of each clinical event. The only unblinding, per the sponsor, occurred for 36 patients who underwent emergency CABG and 46 patients with bleeding complications in during study drug administration. Follow-up was available for all but 21 of the 2099 patients who entered the EPIC trial: 17 refused follow-up, 3 had moved to other countries, and 1 'was devastated by a hurricane.'

In the approved Reopro label, the long-term data from EPIC are described as follows in the approved label: 'The primary endpoint event rates in the bolus plus infusion treatment group were reduced mostly in the first 48 hours and this benefit was sustained through blinded evaluations at 30 days, six months and three years. At the six-month follow-up visit this event rate remained lower in the bolus plus infusion arm (12.3%) than in the placebo arm (17.6%) (p=0.006 vs. placebo).

EPIC (cont)

Median long-term follow up was 3.1 years (99% of patients had follow up between 2.5 and 3.5 years). Using Kaplan-Meier estimates, at 3 years the absolute reduction in events was maintained with an event rate of 19.6% in the bolus plus infusion arm and 24.4% in the placebo arm (p=0.027 vs. placebo).'

The results from the EPIC trial at 1 year are shown below. Numerical data for the 6 month time point are not available at this time (they are presented as a Kaplan-Meier curve in the available articles and in the approved label).

Table C3 Incidence of the combined endpoint and its components at 365 days in the EPIC trial[a].

	Abciximab n=708	Placebo n=696	Odds Ratio & 95% CI	p Value
Combined endpoint at 365 days[b]	216 (30.8%)	266 (38.6%)	0.75 0.63-0.90	0.75
MI (fatal & non-fatal) at 365 days	55 (7.9%)	77 (11.2%)	0.69 0.49-0.97	0.032
Death at 365 days	30 (4.2%)	31 (4.5%)	0.95 0.58-1.57	0.841
Revascularization at 365 days	178 (25.6%)	221 (32.6%)	0.75 0.62-0.91	0.004

a. Data from published results, JAMA (1997) 278:479-484.
b. Combined endpoint: Death/MI/Revascularization.

EPILOG

EPILOG enrolled patients undergoing either urgent or elective PTCA. In the EPILOG trial, the incidence of the following composite endpoint at six months was a non-primary endpoint: death, MI, and repeat coronary intervention (urgent and non-urgent. Per the primary Medical Reviewer for abciximab, Dr. Dina Stolman, the six-month data was obtained in double-blind fashion, and clinical events were centrally-adjudicated.

In the approved Reopro label, the trial results are described in as follows in the CLINICAL STUDIES section: 'At the six-month follow-up visit, the event rate for death, MI, or repeat (urgent or non-urgent) intervention remained lower in the Abciximab treatment arms (22.3% and 22.8%, respectively, for the standard- and low-dose heparin arms) than in the placebo arm (25.8%) and the event rate for death, MI, or urgent intervention was substantially lower in the Abciximab treatment arms (8.3% and 8.4%, respectively, for the standard- and low-dose heparin arms) than in the placebo arm (14.7%).'

The table below summarizes the 6 month data from the EPILOG trial, shown for the standard-dose heparin group.

Table C4 Incidence of the combined endpoint and its components at 180 days in the EPILOG trial[a].

	Abciximab n=918	Placebo n=939	p Value
Combined endpoint at 180 days[b]	203 (22.3%)	241 (25.8%)	0.04
MI (fatal & non-fatal) at 180 days	48 (5.3%)	93 (9.9%)	<0.001
Death at 180 days	13 (1.4%)	15 (1.6%)	0.74
Revascularization at 180 days	167 (18.4%)	180 (19.4%)	0.52

a. Data from published results, NEJM (1997) 336:1689-96.
b. Combined endpoint: Death/MI/Revascularization.

CAPTURE

In the CAPTURE trial, abciximab was administered prior to PTCA. The incidence of the following composite at 30 days was the pre-specified primary endpoint: death, MI, or urgent intervention (angioplasty, CABG, stent placement, or IABP). In this trial, clinical outcomes at 6 months were not a pre-specified primary or secondary endpoint, but patient data was collected through 6 months in blinded fashion. A Clinical Endpoint Committee reviewed all case-report forms, ECGs, and supporting documents for confirmation that patients met endpoint criteria. All but one patient had six-month follow-up data.

In the approved Reopro label, the six month data for CAPTURE are presented as follows: 'At six months of follow up, the composite endpoint of death, MI, or repeat intervention (urgent or non-urgent) was not different between the Abciximab and placebo groups (Abciximab 31.0%, placebo 30.8%, p=0.77).'

The data from the CAPTURE trial at six months is summarized below. None of the p Values were significant at the nominal p <0.01 (two-sided). Note that there was a numerical increase in the incidence of death in the abciximab group relative to placebo at 180 days.

Table C5 Incidence of the combined endpoint and its components at 180 days in the CAPTURE trial[a].

	Abciximab n=630	Placebo n=635	p Value
Combined endpoint at 180 days[b]	193 (31.0%)	193 (30.8%)	NS
MI (fatal & non-fatal) at 180 days	41 (6.6%)	59 (9.3%)	NS
Death at 180 days	17 (2.8%)	14 (2.2%)	NS
Revascularization at 180 days	156 (25.4%)	154 (24.9%)	NS

a. Data from published results, Lancet (1997) 349:1429-1435.
b. Combined endpoint: Death/MI/Revascularization.

The following table summarizes the salient features of the current and proposed language describing 6-month data in the current and proposed labels for abciximab, tirofiban and eptifibatide.

Comparison with Other Approved IIb/IIIa Labels (Reopro, Aggrastat)

Drug/ Trial	6-Month Information in Label[e]	Blinded?	Centrally-Adjudicated?	% Follow-Up	Pre-specified Endpoint?
Abciximab					
EPIC	MI/Death/Revascularization in writing	Y	Y	99%	N
EPILOGUE	MI/Death/Revascularization in writing	Y	Y	>95%[b]	N
CAPTURE	MI/Death/Urgent Intervention in writing	Y	Y	99%	N
Tirofiban					
PRISM-PLUS	MI/Death/Refractory Ischemia in K-M Curve	Y	N	98.8%	Y
CAPTURE	MI/Death/Revascularization in K-M Curve	Y	Y	99%	Y
Integrilin					
PURSUIT	Death/MI in writing and K-M Curve	Y[g]	N[c]	76.7%[f]	N[d]
(proposed)					

b. Per Primary Medical Reveiwer in CBER, Dr. Stolman.
c. CRFs were reviewed centrally and events excluded if sufficient data existed. This occurred in <2% of the events submitted by investigators per the sponsor.
d. The following was a pre-specified composite endpoint at 6 months: Death/MI/recurrence of ischemic symptoms, repeat attempts at coronary intervention and readmission for ischemic symptoms.
e. Results are all included in the Clinical Trials Section.
f. Follow-up for ≥150 days 98%, including patients known to have died.
g. The sponsor does not specify maintaining the blind with regard to treatment in any document reviewed. However, the six-month CRFs identify the patients only by number/treatment site, with no treatment group identified. This suggests the maintenance of the blinding.

MEDICAL REVIEWER'S COMMENTS FOR SIX-MONTH FOLLOW-UP DATA FROM THE PURSUIT TRIAL

The sponsor proposes to add language regarding the results of the 6-month follow-up from the PURSUIT trial to the Integrilin label. The proposed text is found on page 2 of this review. There are several issues relevant to a decision to include the 6-month results in the label: adequacy of the data collection, the results of the data analysis, and comparison of the proposed label change with other approved labels for IIb/IIIa inhibitors.

Adequacy of the data collection

The 6-month data from the PURSUIT trial was collected by individual investigators in blinded fashion. This data consisted primarily of a standard case report form. If no events were identified, no further investigation occurred, and the patient was designated as being event-free. If an event was identified as occurring, further documentation was requested by the sponsor and reviewed. In the rare cases where an event identified by the investigator was found not to have occurred, it was censored from the analysis. Otherwise, the event was considered to have taken place. Within this framework, follow-up data are available for a lower percentage of patients than is available for any of the other 6-month trial data included in the labels of other IIb/IIIa inhibitors. While >98% of both treatment groups had a final contact >120 days after enrollment or were known to have died, the percentage of patients with ≥180 only averaged 83% in the two treatment groups. Another 15% had follow-up for between 150 and 180 days. Given that the number of patients with 150-180 days of follow-up was equal in both groups, the primary effect of this shorter follow-up in these patients is to decrease the number of observed events in both groups.

Results of the data analysis

At the end of six months, the trend of eptifibatide effect on the incidence of death/MI is consistent from 96 hours through 6 months, with the magnitude of the effect slowly decreasing with time. The submitted data are consistent with a persistent effect of eptifibatide to decreased the incidence of death/MI in the patient population studied through 6 months (see table R1).

Eptifibatide had similar effects in the various subgroups at both 30 days and 6 months. Importantly, the observed variability in the effect of eptifibatide in women persisted (see tables R7, R8). For instance, the rate of death/MI in woman after six months was numerically equivalent in the placebo and eptifibatide patients. However, for the women in the North American subset, a nominally significant effect of eptifibatide on the incidence of death/MI was detected (13.7% vs. 9.8% for placebo, p = 0.030). A similar difference was detected in the Western Europe cohort.

Finally, note that there was a numerically higer incidence of death in the eptifibatide group at the 6 month follow-up (Table R3, 6.2% in placebo, 6.4% in eptifibatide).

Comparison of the proposed label changes with other approved labels for IIb/IIIa inhibitor

Both tirofiban and abciximab include 6 month data in their approved labels.

For abciximab, the 6 month data included in the label was not a pre-specified primary endpoint in any of the three trials with information in the label (EPIC, EPILOGUE, CAPTURE). For all three trials, the 6 month data were collected in blinded fashion and centrally-adjudicated. For two trials with available specific information (EPIC, CAPTURE), follow-up data through 6 months were available on >99% of the enrolled patients. No specific information about the adequacy of the follow-up is available for EPILOGUE, but per the primary reviewer (Dr. Stolman) it was >95%.

For tirofiban, the six month data from the PRISM-PLUS trial were a pre-specified 'exploratory' endpoint. The six month data were a pre-specified secondary endpoint from the RESTORE trial. In the PRISM-PLUS trial, the data through 6 months were collected in blinded fashion by individual investigators for 98.8% of the enrolled patients, and were not centrally-adjudicated. In the RESTORE trial, the data were collected by individual investigators for >98% of the enrolled patients, along with further clinical information for any event. The endpoints occurring between days 31 and 180 were then adjudicated by the Endpoint Committee in blinded fashion.

Reviewer's Conclusions

1. The collection of six-month data in the PURSUIT trial was less than perfect, especially with regard to the the reliance on investigators for evaluating clinical events and the extent of the 180 day follow-up. In comparison with other trials that are included in currently approved labels, the data collection are less stringent than for some (EPIC, CAPTURE, RESTORE), but apparently equal to the PRISM-PLUS trial. In the PRISM-PLUS trial, similar to PURSUIT, the only data collected were the occurrence of death or clinical cardiac events, as judged by the investigators. In one respect, however, PURSUIT was more 'rigorous' than PRISM-PLUS: PURSUIT investigators also collected other clinical details (e.g., ECGs, hospital summaries).

2. The follow-up available for the PURSUIT trial is significantly less complete than that available for the other trials. This is because the Duke Clinical Center felt that 'a follow-up interval of 120 days would be adequate to characterize the long-term result.' As a result, not all patients have 180 day data (see Table D2: 6 Month Follow-up in the PURSUIT). The result is that while >98% of both treatment groups had a final contact >120 days, only 83% of the patients had follow-up for ≥180 days.

3. That the six month data from PURSUIT was not a pre-specified endpoint is similar to the data included in the Reopro label from the EPIC and EPILOGUE trials. The PURSUIT results suggest a durable, if declining, effect of eptifibatide on the combined endpoint of death/MI through 6 months. It is notable that the nominal incidence of mortality is higher in the eptifibatide group at the end of six months, relative to placebo. A similar trend was seen for some (RESTORE, CAPTURE), but not all (EPIC, EPILOGUE, PRISM-PLUS) of the other trials with IIb/IIIa antagonists.

4. The decision to include the six month data from PURSUIT in the approved label, then, revolves around the importance of the full 180 day follow-up. The other deficiencies noted for the PURSUIT data are similar to those seen with other trials that have been previously included in labeling. Given the inclusion of the PRISM-PLUS trial in approved labeling, precedent would suggest that the PURSUIT data should also be included in the Aggrastat label, but only for the 150 day data where there is follow-up for >98% of the subjects. The sponsor should be required to submit the 150 day follow-up, to be analyzed for inclusion in the approved Integrilin label, and should not be allowed to include the incomplete 180 day follow-up data in the label.

(2) INCLUSION OF 'SUGGESTED' LOWER HEPARIN DOSE USED WITH EPTIFIBATIDE IN LABELING

The sponsor proposes the following changes in the PRECAUTIONS section of the Integrilin label, discussing the use of a lower 'target ACT' in the PRIDE trial. (words removed are 'lined-out' while new proposed language is underlined) .

PRECAUTIONS

Lower ACT in trials using Abciximab

A lower target ACT was used in the EPILOG trial with another GP IIb/IIIa antagonist, abciximab (target ACT ≥200 seconds). This trial had three comparator arms: placebo +standard-dose heparin, abciximab +standard-dose heparin, and abciximab + low-dose heparin. In that trial, a clinically significant effect of abciximab to reduce the incidence of death/MI/ urgent revascularization was seen for both the low- and standard-dose heparin groups. The incidence of the primary endpoint at the end of 30 days (Death/MI/Urgent Revascularization) and each of its components are shown below. No significant differences between the low and standard-dose heparin arms was seen except in the incidence of 'Urgent Revascularization', which favored the low-dose heparin/abciximab arm.

Table S1 Efficacy endpoints from the EPILOG trial using abciximab and varying doses of heparin[a].

Endpoint	Placebo +Standard Dose Heparin n=939	Abciximab + Standard Dose Heparin n=935	p Value[b]	Abciximab + Low Dose Heparin n=918	p Value[b]
Composite[c]	109 (11.7%)	49 (5.4%)	<0.001	48 (5.2%)	<0.001
Death	7 (0.8%)	4 (0.4%)	0.39	3 (0.3%)	0.21
MI	81 (8.7%)	35 (3.8%)	<0.001	34 (3.7%)	<0.001
Urgent Revasc.	48 (5.2%)	21 (2.3%)	<0.001	15 (1.6%)	<0.001
Death/ MI	85 (9.1%)	38 (4.2%)	<0.001	35 (3.8%)	<0.001

a. Data from EPILOG trial publication for the 30-day time point: NEJM (1997) 336:1689-96.
b. p Value compared with placebo group.
c. Death, MI, Urgent revascularization.

Bleeding rates using Integrilin and two different target ACTs in the PRIDE study

The sponsor has submitted analyses from the eptifibatide NDA database supporting the safety of a lower target ACT in patients receiving eptifibatide. First, in the PRIDE study (Platelet Aggregation and Receptor Occupancy with Integrilin Dynamic Evaluation), 45 patients were randomized to receive eptifibatide in conjunction with a lower dose of heparin, using a target ACT of 200 seconds. The table below shows the dose groups in the PRIDE study, along with the target ACTs for each one. The sponsor is proposing dosing regimen 'C' (eptifibatide 180/2.0) for the labeling change.

Bleeding rates using Integrilin and two different target ACTs in the PRIDE study (cont)

Table S2 Dosing regimens in the PRIDE study[a].

Dose Group	Study Drug Bolus (µg/kg)	Study Drug Infusion (µg/kg-min)	Infusion Duration (hours)	Heparin Regimen	ASA Regimen
A	Placebo	Placebo	24-72	Standard. Target ACT 300-350 sec	81-325 mg/day
B	135	0.75	24-72	Standard. Target ACT 300-350 sec	81-325 mg/day
C	180	2.0	24-72	Low-dose. Target ACT 200-250 sec	81-325 mg/day
D	250	3.0	24-72	Low-dose. Target ACT 200-250 sec	81-325 mg/day

a. from Medical Officer review and NDA volume 2.33 page 21.

Bleeding rates using Integrilin and two different target ACTs in the PRIDE study (cont)

While the PRIDE trial was not designed to assess the influence of Integrilin on clinical outcomes, these events were recorded during the trial. The table below summarizes these events. Statistical comparisons would not be meaningful given the small number of events. It is worth noting, however, that the 135/0.75 group (which had a higher target ACT) had no clinical events recorded, compared with 6 for the 180/2.0 and 1 for the 250/3.0 groups (both of which used a target ACT of 200 seconds). This difference extended to the 30 day results. Shading has been used to emphasize the comparison used by the sponsor to argue for the reduced ACT target.

Table S3 Clinical endpoints from the PRIDE trial at 24 hours and 30 days.

Endpoint	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=43	Integrilin 250/3.0 n=42
Through 24 hours post-infusion				
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Definite/Possible MI	1 (6%)	0 (0.0%)	1 (2.3%)	0 (0.0%)
Definite/Possible Ischemia	3 (18%)	0 (0.0%)	5 (11.6%)	1 (2.4%)
CABG				
Urgent or Elective	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Repeat PTCA	1 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Hemorrhagic Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Through 30 days post-infusion				
Death	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Definite/Possible MI	1 (6%)	0 (0.0%)	1 (2.3%)	0 (0.0%)
Definite/Possible Ischemia	3 (18%)	0 (0.0%)	6 (14%)	1 (2.4%)
CABG				
Urgent or Elective	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Repeat PTCA/atherectomy	2 (12%)	0 (0%)	1 (2.3%)	2 (5.1%)
Hemorrhagic Stroke	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

a. From Medical Officer review and NDA.

Next, the sponsor summarized the safety of the different eptifibatide doses. For purposes of this discussion, the emphasis will be on the bleeding adverse events.

TIMI Scale Bleeding

The table below summarizes the bleeding AEs in the PRIDE trial according to the TIMI scale. There was an increase in both minor and insignificant bleeding in the Integrilin groups, especially the highest Integrilin dose group. The grey columns reflect the comparison emphasized by the sponsor for the labeling change. Per the sponsor, 'the incidence of clinically notable bleeding events were similar between the two treatment groups, although the incidence of mild and insignificant bleeding events was higher with the eptifibatide 180/2.0 regimen.' (NDA supplement, page 153). It can also be said that the incidence of bleeding in the two 'low-ACT' eptifibatide groups is not markedly different from that seen in the eptifibatide 135/0.75 group ('high-ACT').

Bleeding rates using Integrilin and two different target ACTs in the PRIDE study (cont)

Table S4 TIMI scale bleeding during hospitalization in the PRIDE trial[a].

Bleeding Classification	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42
Major	1 (6%)	0 (0%)	1 (2%)	0 (0%)
Minor	0 (0%)	0 (0%)	1 (2%)	4 (9.5%)
Insignificant	3 (18%)	6 (27%)	13 (29%)	9 (21%)
None	12 (70%)	15 (68%)	25 (56%)	27 (64%)
No data	1 (6%)	1 (4%)	5 (11%)	2 (5%)

a. Data from medical officer review and NDA volume 2.33, table 7-1.

Bleeding Sites (per investigator)

The investigators were asked to identify any bleeding site. No severe bleeding was identified from any site, and the femoral artery access site accounted for >75% of the reported bleeding sites. There was an increased incidence of groin bleeding, gross hematuria, hematemesis, oral bleeding, hemoptysis, and epistaxis identified in the Integrilin groups, relative to placebo, especially the highest dose group (250/3.0). No intracranial bleeding was reported.

Table S5 Bleeding sites identified by the PRIDE study investigators[a].

Bleeding Classification	Placebo n=17	Integrilin 135/0.75 n=22	Integrilin 180/2.0 n=45	Integrilin 250/3.0 n=42
Groin	2 (12%)	4 (18%)	13 (29%)	10 (24%)
Gross hematuria	0 (0%)	0 (0%)	0 (0%)	2 (5%)
Hematemesis	0 (0%)	0 (0%)	1 (2%)	2 (5%)
Gastrointestinal	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Oral	0 (0%)	0 (0%)	0 (0%)	2 (14%)
Hct drop only	0 (0%)	1 (4%)	0 (0%)	0 (0%)
Hemoptysis	0 (0%)	0 (0%)	0 (0%)	1 (2%)
Epistaxis	0 (0%)	0 (0%)	0 (0%)	1 (2%)

a. Data from medical officer review and NDA volume 2.33, table 7-2, expressed as % of total subjects with available data.

Transfusions

Three subjects received transfusions: one placebo subject (8014); one in the Integrilin 180/2.0 group and one in the Integrilin 250/3.0 group.

Incidence of bleeding grouped according to ACT in the PURSUIT trial

The final piece submitted by the sponsor is support of the lower ACT is a subset analysis of the PURSUIT trial, looking at bleeding risk according to ACT attained. Recall that in this trial, all patients had a target ACT of 300 seconds. Note also that the eptifibatide group in this analysis includes both doses used in the PURSUIT trial (180/2.0 and 180/1.3).

Table S6 Occurrence of bleeding by Peak ACT in patients undergoing percutaneous coronary intervention in the PURSUIT trial[a].

Endpoint		ACT ≤200 N=44	ACT201-250 N=60	ACT 251-300 N=131	ACT 301-350 N=199	ACT >350 N=282
Major Bleed	Placebo	0 (0%)	1 (3.0%)	4 (5.3%)	8 (8.2%)	5 (4.7%)
	Eptifibatide	0 (0%)	1 (3.7%)	4 (7.4%)	9 (9.2%)	18 (10.8%)
Minor Bleed	Placebo	0 (0%)	4 (12%)	13 (17.3%)	11 (11.3%)	15 (14.2%)
	Eptifibatide	6 (35.3%)	4 (14.8%)	11 (20.4%)	29 (29.6%)	40 (24.0%)
RBC Txf	Placebo	0 (0%)	2 (6.1%)	2 (2.6%)	7 (7.1%)	5 (4.6%)
	Eptifibatide	0 (0%)	2 (7.4%)	2 (3.7%)	10 (10.1%)	17 (10.1%)

a. Data from NDA supplement, page 153.

MEDICAL OFFICER'S CONCLUSIONS REGARDING ADJUSTMENT OF SUGGESTED HEPARIN DOSE USED WITH EPTIFIBATIDE

The sponsor proposes inclusion of a lower 'target ACT' and lower overall heparin dose in conjunction with eptifibatide in the label. The full text of the proposed changes are found on page 9 of this review.

The submitted data are inadequate to support a labeling change suggesting a lower target ACT, which would lead to a lower heparin dose. Such a change requires data showing that lowering the heparin dose used in conjunction with eptifibatide would: 1) not adversely affect the efficacy of eptifibatide regarding the incidence of death/MI, and 2) not adversely affect the incidence of adverse events following eptifibatide (that is, not decrease efficacy).

First, the data in support of the efficacy of the lower heparin dose in conjunction with a IIb/IIIa inhibitor come from a trial using abciximab, a product with similar, but not identical, properties to eptifibatide. In the EPILOG trial, the use of abciximab in combination with a lower dose of heparin had similar efficacy to abciximab used in combination with standard heparin dosing targets, as measured by a decrease in either death/MI or death/MI/urgent revascularization. The sponsor has offered no data to support the notion that this same phenomenon will be seen with eptifibatide. Given the differences in the two products (abciximab is an irreversible inhibitor of platelet aggregation and has putative effects on other receptor systems beyond the IIb/IIIa receptor with a much longer pharmacodynamic half-life), there is no proof that using eptifibatide in conjunction with lower doses of heparin will not be less effective than eptifibatide plus standard dose heparin. There is also no precedent for using the efficacy data of one drug (abciximab in this case, from the EPILOGUE trial) to support a label change for another one (eptifibatide). The PRIDE trial cannot be used to support this efficacy question, as the trial was severely underpowered to detect any meaningful differences in efficacy endpoints (126 total enrolled in four treatment groups).

Second, with regard to the safety of the lower dose of heparin, the sponsor submitted the results of the PRIDE trial, emphasizing the comparison between the eptifibatide plus low-dose heparin and placebo. In fact, the PRIDE trial examined three doses of eptifibatide/heparin and compared them with control. The primary intent of the PRIDE trial was pharmacokinetic, and the trial was severely underpowered to detect any meaningful differences in bleeding rates or with regard to any meaningful efficacy endpoints (126 total enrolled in four treatment groups).

These small numbers limit our ability to detect true effects on significant clinical outcomes. My conclusion from my original review of PRIDE follows: 'Few clinical events (MI, death, urgent revascularization, stroke, recurrent ischemia) occurred in the 30 day follow-up of the PRIDE trial, precluding any meaningful statistical analysis of the effect of Integrilin on these event rates. There was a lower incidence rate for definite/possible cardiac ischemia in the combined Integrilin group (6.4%) than in the placebo (18%) at 30 days. No other differences in the incidence rates of the clinical events listed were noted.'

In conclusion, then, the submitted material do not adequately support the inclusion of any language regarding the possible use of lower heparin doses in conjunction with eptifibatide in this clinical setting.

(3) MISCELLANEOUS OTHER PROPOSED LABELING CHANGES

1) Changes in language regarding use of eptifibatide with and without procedures.

The sponsor proposes changes in the description of the use of eptifibatide with and without PCI in the PURSUIT trial. The change in language is below.

In the attached letter, the sponsor argues for the new inclusion of the 30 day data, 'which was the primary endpoint time period from the PURSUIT study.' No other justification for the data inclusion was given.

Medical Officer's conclusions regarding changes in language regarding use of eptifibatide with and without procedures.

The rewording to make clear that patients in the PURSUIT trial received eptifibatide prior to the determination of management strategy is acceptable, and clarifies the relationship between drug administration and the determination of management strategy in the PURSUIT trial.

The proposed addition of the 30 day data should not be approved, as it adds no useful purpose and rests on post-hoc data analysis. The 72 hour timepoint was included in part to convey the fact that the effect of eptifibatide was established within 72 hours (during the drug infusion), regardless of management strategy. The argument that the 30 day timepoint should be included because it was the primary endpoint is of course misleading: the analysis according to management strategy was included in the original protocol in a broad secondary endpoint as follows: 1. Incidence of death and/or MI at 30 days in subsets of the population (e.g., stratified by age).

2) Changes in language regarding the dosing of eptifibatide in renal insufficiency.

The sponsor argues that, as written, 'these sections were not clear as to whether patients with Acute Coronary Syndrome who would normally be administered a 180 μg/kg bolus and 2 μg/kg/min infusion but who had a serum creatinine between 2.0 mg/dl and 4.0 mg/dl should receive a 135 μg/kg bolus and a 0.5 μg/kg/min infusion.

CONTRAINDICATIONS

PRECAUTIONS: Renal Insufficiency

Medical Officer's conclusions regarding changes in language regarding the dosing of eptifibatide in renal insufficiency:

Both of these proposed changes improve the label clarity and should be approved. The use of two different styles of number presentation (2 and 2.0) should be corrected in the final label.

3) Addition of the rates of intracranial hemorrhage within 30 days and stroke within 6 months.

The sponsor proposes to add these pieces of data 'as a result of questions from physicians and other health professionals.'

ADVERSE REACTIONS: Intracranial Hemorrhage and Stroke

Medical Officer's conclusions regarding addition of the rates of intracranial hemorrhage within 30 days and stroke within 6 months to labeling.

The addition of the timing for the ICH data clarifies the label, and should be approved.

Following a review of the 150-day data (or wherever follow-up is >98%), language regarding the overall equivalence of the incidence of stroke and ICH in the Integrilin and placebo populations may be approvable.

OVERALL RECOMMENDATION OF MEDICAL OFFICER:

1. The proposed inclusion of the
not approvable due to the inadequate nature of the full 6-month follow-up. The sponsor should submit the 150 day follow-up data for evaluation and possible inclusion in the label.

2. The proposed label changes regarding the is not approvable, and no data regarding the PRIDE trial should be included in the label. While it is reasonable, indeed even probable, that the lower dose of heparin will lead to fewer adverse events (in particular bleeding adverse events), these submitted data are inadequate to support either their inclusion in the label or a change in the current eptifibatide label to suggest a lower heparin dose.

3. To support a change in the heparin dose in conjunction with eptifibatide, the sponsor should obtain data using low-dose heparin in conjunction with eptifibatide 180/ 2.0 from a sufficiently powered trial to demonstrate the efficacy and safety of that regimen.

4. The proposed changes in the description of the use of eptifibatide with and without medical intervention are approvable, but the 30 day data regarding the subsets should not be included in the label.

5. The proposed changes in labeling for renal insufficiency is approvable.

6. The proposed changes in labeling to detail the timing of the data on ICH is approvable,

cc: ORIG: NDA 20-718
HFD-110 Division File
HFD-110/Project Manager Colleen Locicero
HFD-110/Medical Officer Douglas Throckmorton
HFD-110/Team Leader Charles Ganley

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APR 1 1999

Secondary Medical Review

NDA #: 20-718/SLR-002 and 20-718/SLR-003	NDA Volume:	Drug Name: eptifibatide
Sponsor: Cor Therapeutics	Type of Document: Labeling Supplement	Reviewer: Ganley
Correspondence Date: 9/9/98	Date Received: 9/10/98	Date Completed: 3/30/99

Dr. Throckmorton has reviewed labeling supplements for eptifibatide. The proposed changes are listed in the following Tables. The labeling submission SLR-003 changed some of the proposed changes requested in SLR-002. All comments after the Tables should be included in an action letter.

Table 1. Changes in CLINICAL STUDIES section, PURSUIT subsection.

Current Labeling	Proposed Labeling
CLINICAL STUDIES section, PURSUIT subsection: .... The reduction in the incidence of endpoint events in patients receiving eptifibatide was evident early during treatment, and this reduction was maintained through at least 30 days (see Figure 1). Table 2 also shows the incidence of the components of the primary endpoint, death (whether or not preceded by an MI) and new MI in surviving patients at 30 days. Table 2. (not shown) Figure 1 (not shown) The effect of eptifibatide.....these possible factors are unknown. Treatment with eptifibatide reduced clinical events in patients undergoing PCI during drug administration and in those receiving medical management alone. Table 3 shows the incidence of death or MI within 72 hours of randomization. Table 3 (not shown). All of the effect of eptifibatide was established within 72 hours (during the period of drug infusion), regardless of management strategy. Moreover, for patients undergoing early PCI, a reduction in events was evident prior to the procedure.	CLINICAL STUDIES section, PURSUIT subsection:

Current Labeling	Proposed Labeling

Figure 1 plots the Kaplan-Meier curve for events adjudicated by the Clinical Endpoints Committee within 30 days of randomization. The events adjudicated by the Clinical Events Committee were the protocol specified endpoints to be analyzed in the primary analysis. Figure 1 and references to figure 1 in the text should not be eliminated from the label.

The changes in text beginning with "Treatment with eptifibatide..." and ending with "...a reduction in events was evident prior to the procedure" are acceptable with the following exceptions.

At the time of approval, 30 day data was purposely left out of Table 3 because Figure 1 included information for the 30 day endpoint. Table 3 emphasizes the treatment effect within the first 72 hours of randomization irrespective of whether a PCI was performed or not. A 30 day post-hoc analysis of PCI and no PCI subgroups is not justified.

The proposed addition of the text

is not acceptable. The six month data included the status of only 83% of the patients randomized to the placebo or high dose eptifibatide treatment groups. For other approved drugs with similar pharmacologic action (e.g. abciximab, tirofiban), the label that describes 6 month outcome endpoints depended on data from greater than 98% of the patients. It would be unreasonable to permit labeling suggesting complete 6 month follow-up when in fact one-sixth of the patients had less than 6 months of follow-up information. is not acceptable because it depends on events reported by investigators and not events adjudicated by the Clinical Events Committee. Please provide the five month endpoint data for the Pursuit trial. After the five month data is reviewed by the Division, a determination will be made as to how it should be included in labeling.

Table 2. Changes in the PRECAUTIONS section, Maintaining Target aPTT and ACT subsection.

Current Labeling	Proposed Labeling
In the PRECAUTIONS section, Maintaining Target aPTT and ACT subsection: The aPTT should be maintained between 50 and 70 seconds unless PCI is to be performed. During PCI, the ACT should be maintained between 300 and 350 seconds. The aPTT should be checked prior to arterial sheath removal: the sheath should not be removed unless the aPTT is <45 seconds. In patients treated with heparin, bleeding can be minimized by close monitoring of the aPTT. Table 6 displays the risk of major bleeding according to the maximum aPTT attained within 72 hours in the PURSUIT study. Table 6 (not shown)	In the PRECAUTIONS section, Maintaining Target aPTT and ACT subsection:

Current Labeling	Proposed Labeling

The proposed changes to the PRECAUTIONS section, Maintaining Target aPTT and ACT subsection are acceptable with the exception of the paragraph describing the PRIDE study. The PRIDE Study description does not provide any meaningful information for the proper use of this drug product and should not be included in the labeling. The inclusion of this information could erroneously lead a prescriber of eptifibatide to conclude that lower targeted ACT is acceptable despite the lack of clinical efficacy data. The data from the EPILOG study supports the lower heparin dose regimen for abciximab and does not does not provide support of a lower heparin dose with eptifibatide.

Table 2. Changes in the PRECAUTIONS section, Maintaining Target aPTT and ACT subsection.

Current Labeling	Proposed Labeling
CONTRAINDICATIONS • Serum creatinine ≥ 2.0 mg/dl (for the 180 µg/kg bolus and the 2 µg/kg/min infusion) or ≥ 4.0 mg/dl (for the 135 µg/kg bolus and the 0.5 µg/kg/min infusion).	CONTRAINDICATIONS

The proposed change to the CONTRAINDICATIONS section is acceptable.

Table 3. Changes in the PRECAUTIONS section, Renal Insufficiency subsection.

Current Labeling	Proposed Labeling

The proposed addition to the PRECAUTIONS section is acceptable. The serum creatinine values should be written as 2.0 mg/dl and 4.0 mg/dl.

Table 4. Changes in the ADVERSE REACTIONS section, Intracranial Hemorrhage and Stroke subsection.

Current Labeling	Proposed Labeling
UNDER the ADVERSE REACTIONS section, Intracranial Hemorrhage and Stroke subsection: Intracranial hemorrhage was rare in the PURSUIT clinical study, with only 3 patients in the placebo group, 1 patient in the group treated with eptifibatide 180/1.3 and 5 patients in the group treated with eptifibatide 180/2.0 experiencing a hemorrhagic stroke. The overall incidence of stroke was 0.5% in patients receiving eptifibatide 180/1.3, 0.7% in patients receiving 180/2.0, and 0.8% in placebo patients. In the IMPACT II study, intracranial hemorrhage was experienced by 1 patient treated with eptifibatide 135/0.5, 2 patients treated with eptifibatide 135/0.75 and 2 patients in the placebo group. The overall incidence of stroke was 0.5% in patients receiving 135/0.5 eptifibatide, 0.7% in patients receiving 135/0.75, and 0.7% in placebo group.	

The proposed addition of <u>within 30 days of randomization</u> to the label are acceptable. The addition of the statement '

' is not acceptable. This statement implies a clinical benefit with regard to the effect of Integrelin on stroke. There is no evidence in the database that supports this claim especially in view of the fact that the six month follow-up was incomplete and endpoints were not validated by a clinical endpoints committee.

When submitting revised labeling in the future, the sponsor should provide a double column document with current labeling provided in the left column and revised labeling provided in the right column.

/S/

Charles J. Ganley, M.D.

cc: orig.
HFD-110
HFD-110 /project manager / ganley / throckmorton

JUL - 8 1998

MEDICAL OFFICER REVIEW

NDA #:	20-718
DRUG NAME:	Integrilin
SPONSOR:	COR Therapeutics
TYPE OF DOCUMENT:	Supplement (SLR-001)
DATE RECEIVED:	6-10-98
DATE COMPLETED:	7-8-98
MEDICAL OFFICER:	Isaac W. Hammond, MD, Ph.D.

Review of the antigenicity statement to the allergic reaction portion of the adverse events section of the labeling is acceptable. The numbers included in both the allergic reaction portion and the antigenicity statement have been verified and found to be consistent with the data submitted in the NDA submission.

The following re-statement of the antigenicity statement is suggested.

> The potential for development of antibodies to eptifibatide has been studied in 433 subjects. Epitifibatide was non-antigenic in 412 patients receiving a single administration of epitifibatide (135 µg/kg bolus followed by a continuous infusion of either 0.5 µg/kg/min or 0.75 µg/kg/min), and in 21 subjects to whom eptifibatide (135 µg/kg bolus followed by continuous infusion of 0.75 µg/kg/min) was administered twice, 28 days apart. In both cases, plasma for antibody detection was collected approximately 30 days after each dose. The development of antibodies to eptifibatide at higher doses has not been evaluated.

RECOMMENDED REGULATORY ACTION

The new labeling for integrilin is acceptable with the minor changes suggested. Will recommend approval.

/S/

Isaac W. Hammond, M.D., Ph.D.

cc: orig.
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HFD-110 / CSO / C. GANLEY/ I. Hammond