CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20718/S2

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

SEP 20 1999

NDA 20-718/S-002

COR Therapeutics, Inc.
Attention: Ms. Ellen L. Martin
256 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Martin:

Please refer to your supplemental new drug application dated October 9, 1998, received October 13, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Integrilin (eptifibatide) Injection, 20 mg/10 mL and 75 mg/100 mL Vials.

We acknowledge receipt of your submission dated August 20, 1999 that constituted a complete response to our August 9, 1999 action letter.

This supplement provides for final printed labeling revised to include information describing the PURSUIT six-month follow-up data.

Your original October 9, 1998 submission proposed the following labeling changes:

1. The reference to Figure 1 was deleted in the paragraph immediately preceding Table 2 in the **CLINICAL STUDIES** section.

2. Figure 1 in the **CLINICAL STUDIES** section was revised to include the six-month PURSUIT data and moved so that it immediately preceded the discussion of the IMPACT II study in the **CLINICAL STUDIES** section. In addition, the following paragraph was added to precede Figure 1 immediately:

   A secondary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (as reported by investigators) within 6 months of randomization. As shown in the Kaplan-Meier curve in Figure 1, investigators reported a reduction in death or MI from 13.6% with placebo to 12.1 % with eptifibatide (p=0.021 log rank) within 6 months of randomization.

3. The following paragraph regarding the assessment of stroke at six months was inserted between the first and second paragraphs of the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection:

   Investigator's assessment of all strokes within 6 months of randomization was 0.8% in patients receiving eptifibatide 180/1.3, 1.3% in patients receiving eptifibatide 180/2.0, and 1.5% in placebo patients.

In our May 4, 1999 approvable letter for this supplement, we noted that this application was approvable, provided the following changes were made:

1. Figure 1 remained as it was in the approved labeling and was not revised or relocated. The reference to Figure 1 in the current text remained, as well.

2. The revised Figure 1 and the paragraph proposed to precede the revised Figure 1 immediately were not included in labeling, as they were not acceptable. We asked you to provide the five-month endpoint data for the PURSUIT study, noting that after the five-month data were reviewed by the Division, a determination would be made as to how this might be included in labeling.

3. The paragraph regarding the assessment of stroke at six months that was inserted between the first and second paragraphs in the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection was not included in labeling, as it was not acceptable.

In your May 7, 1999 submission you concurred with all of the labeling changes specified in the May 4, 1999 approvable letter, with one exception. You proposed to add the following paragraph to the **CLINICAL STUDIES** section of the package insert, immediately preceding the IMPACT II study description:

> 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 of randomization. Based upon data available from 96.9 percent 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 percent with eptifibatide 180/2.0 (p=0.021 log rank) at the six-month timepoint.

In our August 9, 1999 approvable letter for this supplement, we indicated that this supplement was approvable, provided you submit final printed labeling revised as follows:

> The paragraph added to the **CLINICAL STUDIES** section, immediately preceding the IMPACT II study description, was replaced with the following paragraph:
>
> > Follow-up data were available through 165 days for 10,611 patients enrolled in the PURSUIT trial (96.9 percent of the initial enrollment). This follow-up included 4566 patients who received eptifibatide at the 180/2.0 dose. As reported by the investigators, the occurrence of death from any cause or new myocardial infarction for patients followed for at least 165 days was reduced from 13.6 percent with placebo to 12.1 percent with eptifibatide 180/2.0.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the final printed labeling included in your August 20, 1999 submission. Accordingly, the supplemental application is approved effective on the date of this letter.

We note your commitment, as agreed to by Ms. Arleen Glenn, Associate Director of Regulatory Affairs, COR Therapeutics, Inc., in a September 3, 1999 telephone conversation with Ms. Colleen LoCicero, Regulatory Health Project Coordinator, Division of Cardio-Renal Drug Products, to amend the labeling, at your next printing, to present the serum creatinine values consistently throughout the package insert (i.e., express the values as either all whole numbers or all decimal numbers), and to report this change in your next annual report.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact:

Ms. Colleen LoCicero
Regulatory Health Project Coordinator
(301) 594-5334

Sincerely yours,

/S/ 9/20/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20718/S2

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

AUG - 9 1999

NDA 20-718/S-002

COR Therapeutics, Inc.
Attention: Ms. Ellen L. Martin
256 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Martin:

Please refer to your supplemental new drug application dated October 9, 1998, received October 13, 1998, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Integrilin (eptifibatide) Injection.

We acknowledge receipt of your submissions dated May 7 and 19, and June 3, 1999.

This supplement provides for labeling amended to include information describing the PURSUIT six-month follow-up data.

Your original October 9, 1998 submission proposed the following labeling changes:

1. The reference to Figure 1 was deleted in the paragraph immediately preceding Table 2 in the **CLINICAL STUDIES** section.

2. Figure 1 in the **CLINICAL STUDIES** section was revised to include the six-month PURSUIT data and moved so that it immediately preceded the discussion of the IMPACT II study in the **CLINICAL STUDIES** section. In addition, the following paragraph was added to immediately precede Figure 1:

> A secondary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (as reported by investigators) within 6 months of randomization. As shown in the Kaplan-Meier curve in Figure 1, investigators reported a reduction in death or MI from 13.6% with placebo to 12.1 % with eptifibatide (p=0.021 log rank) within 6 months of randomization.

3. The following paragraph regarding the assessment of stroke at six months was inserted between the first and second paragraphs of the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection:

> Investigator's assessment of all strokes within 6 months of randomization was 0.8% in patients receiving eptifibatide 180/1.3, 1.3% in patients receiving eptifibatide 180/2.0, and 1.5% in placebo patients.

In our May 4, 1999 approvable letter for this supplement, we noted that this application was approvable, provided the following changes were made:

1. Figure 1 should remain as it is in the current, approved labeling and should not be revised or relocated. The reference to Figure 1 in the current text should remain, as well. We noted that Figure 1 in the approved labeling plots the Kaplan-Meier curve for events adjudicated by the Clinical Endpoints Committee within 30 days of randomization, and that the events adjudicated by the Clinical Events Committee were the protocol specified endpoints to be analyzed in the primary analysis.

2. The revised Figure 1 and the paragraph proposed to precede the revised Figure 1 immediately should not be included in labeling, as they are not acceptable. We noted that 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 labeling that describes six-month outcome endpoints depended on data from greater than 98% of the patients. It would be unreasonable to permit labeling suggesting complete six-month follow-up when, in fact, one-sixth of the patients had less than six months of follow-up information. We further noted that the new Figure 1 is also not acceptable because it depends on events reported by investigators and not events adjudicated by the Clinical Events Committee. We asked you to please provide the five-month endpoint data for the PURSUIT study, noting that after the five-month data are reviewed by the Division, a determination will be made as to how this might be included in labeling.

3. The paragraph regarding the assessment of stroke at six months that was inserted between the first and second paragraphs in the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection should not be included in labeling, as it is not acceptable. We noted that this statement implies a clinical benefit with regard to the effect of Integrilin 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.

In your May 7, 1999 submission you concurred with all of the labeling changes specified in the May 4, 1999 approvable letter, with one exception. You proposed to add the following paragraph to the **CLINICAL STUDIES** section of the package insert, immediately preceding the IMPACT II study description:

> 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 of randomization. Based upon data available from 96.9 percent 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 percent with eptifibatide 180/2.0 (p=0.021 log rank) at the six-month timepoint.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

The paragraph you propose to add to the **CLINICAL STUDIES** section, immediately preceding the IMPACT II study description, should be replaced with the following paragraph:

> Follow-up data were available through 165 days for 10,611 patients enrolled in the PURSUIT trial (96.9 percent of the initial enrollment). This follow-up included 4566 patients who received eptifibatide at the 180/2.0 dose. As reported by the investigators, the occurrence of death from any cause or new myocardial infarction for patients followed for at least 165 days was reduced from 13.6 percent with placebo to 12.1 percent with eptifibatide 180/2.0.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit 20 copies of the final printed labeling ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with this change prior to approval of these supplemental applications.

If you have any questions, please contact:

Colleen LoCicero
Regulatory Health Project Coordinator
(301) 594-5312.

Sincerely yours,

/S/ 8/9/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-718/S-002
NDA 20-718/S-003

MAY 4 1999

COR Therapeutics, Inc.
Attention: Ellen L. Martin
256 East Grand Avenue
South San Francisco, CA 94080

Dear Ms. Martin:

Please refer to your supplemental new drug applications dated October 9, 1998 (S-002) and November 18, 1998 (S-003), received October 13, 1998 and November 19, 1998, respectively, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Integrilin (eptifibatide) Injection.

We acknowledge receipt of your submission dated February 19, 1999.

These supplements propose the following changes to the labeling:

S-002

1. In the paragraph immediately preceding Table 2 in the **CLINICAL STUDIES** section, the reference to Figure 1 has been deleted.

2. Figure 1 in the **CLINICAL STUDIES** section has been revised to include the six-month PURSUIT data and moved so that it immediately precedes the discussion of the IMPACT II study in the **CLINICAL STUDIES** section. In addition, the following paragraph has been added to immediately precede Figure 1:

> A secondary endpoint of the study was the occurrence of death from any cause or new myocardial infarction (as reported by investigators) within 6 months of randomization. As shown in the Kaplan-Meier curve in Figure 1, investigators reported a reduction in death or MI from 13.6% with placebo to 12.1% with eptifibatide (p=0.021 log rank) within 6 months of randomization.

3. The following paragraph regarding the assessment of stroke at six months has been inserted between the first and second paragraphs in the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection:

> Investigator's assessment of all strokes within 6 months of randomization was 0.8% in patients receiving eptifibatide 180/1.3, 1.3% in patients receiving eptifibatide 180/2.0, and 1.5% in placebo patients.

S-003

4. The sentence immediately preceding Table 1 in the **CLINICAL PHARMACOLOGY/Pharmacodynamics** subsection has been changed from the following:

[ ]

to the following:

> Table 1 shows the effects of the two doses of eptifibatide used in the clinical studies on *ex vivo* platelet aggregation induced by 20 μM ADP in PPACK-anticoagulated platelet-rich plasma and on bleeding time of the doses of eptifibatide used in the two principal clinical studies.

5. The two dose regimens (135/0.5 and 180/2.0) in Table 1 in the **CLINICAL PHARMACOLOGY/Pharmacodynamics** subsection have been single- and double-asterisked, respectively, and the following statements added in smaller print immediately following Table 1:

> * 135 μg/kg bolus followed by a continuous infusion of 0.5 μg/kg/min
>
> ** 180 μg/kg bolus dose followed by a continuous infusion of 2.0 μg/kg/min

6. Table 3 in the **CLINICAL STUDIES** section has been revised to include 30-day endpoint data and the two sentences immediately preceding Table 3 have been replaced with the following:

> Treatment with eptifibatide prior to determination of patient management strategy reduced clinical events regardless of whether patients ultimately underwent diagnostic catheterization, revascularization (i.e., PCI, or CABG surgery) or continued to receive medical management alone. Table 3 shows the incidence of death or MI within 72 hours and within 30 days of randomization.

7. The seventh bulleted statement in the **CONTRAINDICATIONS** section has been changed from the following:

[ ]

to the following:

> Serum creatinine $\geq$ 4.0 mg/dL. In patients with serum creatinine levels between 2.0 g/dL and 4.0 mg/dL, the 135 μg/kg bolus and 0.5 μg/kg/min infusion should be administered.

8. The second, third, and fourth sentences in the **PRECAUTIONS/Maintaining Target aPTT and ACT** subsection have been deleted, and the first and second paragraphs combined.

9. The following sentence has been added following the first sentence in the **PRECAUTIONS/Renal Insufficiency** subsection:

> For patients with serum creatinine > 2 and < 4 mg/dL, eptifibatide should be administered as a 135 μg/kg bolus followed by a 0.5 μg/kg/min infusion.

10. The first paragraph of the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection has been changed from the following:

[ ]

to the following:

> 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 within 30 days of randomization. The overall incidence of stroke was 0.5% in patients receiving eptifibatide 180/1.3, 0.7% in patients receiving eptifibatide 180/2.0, and 0.8% in placebo patients within 30 days of randomization.

11. The following paragraphs have been added following Table 6 in the **PRECAUTIONS/Maintaining Target aPTT and ACT** subsection:

> During PCI, the PURSUIT study stipulated a target ACT of between 300 and 350 seconds. Patients receiving an eptifibatide 180 μg/kg bolus followed by a 2 μg/kg/min infusion experienced an increased incidence of bleeding relative to placebo, primarily at the femoral access site.
>
> PRIDE was a randomized, placebo-controlled, multicenter trial conducted in 126 patients with coronary artery disease undergoing PCI. The pharmacodynamics of 3 dosing regimens of eptifibatide were assessed: a 135 μg/kg bolus followed by a 0.75 μg/kg/min infusion, a 180 μg/kg bolus followed by a 2 μg/kg/min infusion, and a 250 μg/kg bolus followed by a 3 μg/kg/min infusion. All infusions were continued for 24 hours post-PCI. Patients receiving an eptifibatide 180 μg/kg bolus followed by a 2 μg/kg/min infusion and heparin targeted at an ACT of 200-250 seconds experienced a similar incidence of bleeding as patients receiving placebo in conjunction with heparin, the administration of which was targeted at an ACT of 300-350 seconds. The study was not powered to assess the impact of lower heparin doses on clinical efficacy.
>
> The aPTT or ACT should be checked prior to arterial sheath removal. The sheath should not be removed unless the aPTT is < 45 seconds or the ACT is < 150 seconds.

We have completed the review of these applications, as amended, and they are approvable. Before these applications may be approved, however, it will be necessary for you to submit final printed labeling revised as follows:

S-002

1. Figure 1 should remain as it is in the current, approved labeling and should not be revised or relocated. The reference to Figure 1 in the current text should remain, as well. Figure 1 of the approved labeling 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.

2. The revised Figure 1 and the paragraph proposed to precede the revised Figure 1 immediately are not acceptable and should not be included in labeling. 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 labeling that describes six-month outcome endpoints depended on data from greater than 98% of the patients. It would be unreasonable to permit labeling suggesting complete six-month follow-up when, in fact, one-sixth of the patients had less than six months of follow-up information. The new Figure 1 is also 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 study. After the five-month data are reviewed by the Division, a determination will be made as to how it might be included in labeling.

3. The paragraph regarding the assessment of stroke at six months that was inserted between the first and second paragraphs in the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection is not acceptable and should not be included in labeling. This statement implies a clinical benefit with regard to the effect of Integrilin 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.

S-003

4. The proposed text " and within 30 days of randomization" in the last sentence preceding Table 3 in the **CLINICAL STUDIES** section is not acceptable and should not be included in labeling. In addition, the revised Table 3, which includes 30-day endpoint data, is not acceptable and should not be included in labeling. Table 3 from the current, approved labeling should be retained. At the time of approval, 30-day data were 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. Inclusion in labeling of a 30-day post-hoc analysis of PCI and no PCI subgroups is not justified.

5. The serum creatinine values in the sentence added to the **PRECAUTIONS/Renal Insufficiency** subsection should be written as 2.0 mg/dL and 4.0 mg/dL.

6. The paragraph describing the PRIDE study (the second paragraph following Table 6) that is proposed to be added to the **PRECAUTIONS/Maintaining Target aPTT and ACT** subsection is not acceptable and should not be included in labeling. 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 support the lower heparin dose regimen for abciximab and do not provide support for a lower heparin dose with eptifibatide.

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made. It would be helpful to provide a double-column document with current labeling in the left column and labeling changes noted in the right column for this and future labeling submissions.

Please submit 20 copies of the final printed labeling (to each application) ten of which are individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of these drugs becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please contact:

Ms. Colleen LoCicero
Consumer Safety Officer
(301) 594-5312

Sincerely yours,

/S/ 5/4/99

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research