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APPLICATION NUMBER: NDA 20718/S2

ADMINISTRATIVE DOCUMENTS

RHPC Review of FPL
NDA 20-718/S-002

Date of Supplement: October 9, 1998
Date FPL submitted: August 20, 1999
Date of Review: September 1, 1999
Applicant Name: COR Therapeutics, Inc.
Product Name: Integrilin (eptifibatide) Injection, 20 mg/10 mL and
75 mg/100 mL Vials

Evaluation:

This submission provides for final printed labeling as requested in the Agency's August 9, 1999 approvable letter. The supplement provides for the addition to labeling of information describing the PURSUIT six-month follow-up data. The original October 9, 1999 submission proposed the following 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 the Agency's May 4, 1999 approvable letter for this supplement, which also responded to S-003, we noted that the labeling proposed in S-002 was approvable, provided the following changes were made:

1. Figure 1 remained as it was in the current, 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 requested that COR provide the five-month endpoint data for PURSUIT, 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 unacceptable.

In their May 7, 1999 submission, the sponsor concurred with all of the labeling changes specified in the May 4, 1999 approvable letter, with one exception. They 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.

On August 9, 1999, the Agency issued an approvable letter for this supplement. In this letter, the Agency stated that before the application could be approved, it would be necessary for the sponsor to submit final printed labeling revised so that the paragraph the sponsor proposed to add 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.

I reviewed the submitted final printed labeling in its entirety and found it to be identical in content to the labeling requested in the Agency's August 9, 1999 approvable letter. The sponsor, however, did not incorporate into the labeling a minor change the Agency

requested in our July 21, 1999 approval letter for S-003 and S-004. In this letter, the Agency requested that, at the time of the sponsor's next printing, they revise the package insert to present the serum creatinine values consistently throughout (i.e., express the values as either all whole numbers or all decimal numbers throughout the package insert). In a September 2, 1999 voicemail and subsequent September 3, 1999 telephone conversation, Ms. Arleen Glenn, Associate Director for Regulatory Affairs, COR Therapeutics, Inc., indicated that COR's failure in this submission to amend the labeling to present the serum creatinine values consistently throughout the package insert was an oversight. Ms. Glenn stated that COR will amend the package insert accordingly (present the serum creatinine values consistently throughout the package insert) and report this change in their next annual report, as permitted under 21 CFR 314.70(d)(3). She added that this would be done immediately so that the next package inserts issued would include this change.

Recommendation:

I recommend that the Division issue an approval letter for this supplement, as set forth under 21 CFR 314.70(b)(3)(i). The approval letter should note COR's agreement to amend the labeling to present the serum creatinine values consistently throughout the package insert at the time of their next printing and to report this change in their next annual report.

/s/

Colleen LoCicero, RHPC

cc: orig NDA 20-718
HFD-110
HFD-110/LoCicero
HFD-110/ABlount
HF-2/MedWatch

RHPC Review of Draft Labeling
NDA 20-718/SE8-002

Date of Supplement: October 9, 1998
Date of Amendments: May 7, 1999
May 19, 1999
June 3, 1999
Date of Review: July 30, 1999
Applicant Name: COR Therapeutics, Inc.
Product Name: Integrilin (eptifibatide) Injection, 20 mg/10 mL and
75 mg/100 mL Vials

Evaluation:

This supplement provides for labeling amended to include information describing the PURSUIT six-month follow-up data. The original October 9, 1998 submission proposed the following 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 the Agency's May 4, 1999 approvable letter for this supplement, which also responded to S-003, we note that the labeling proposed in S-002 is approvable, provided the following changes are made:

1. Figure 1 remains as it is in the current, approved labeling and is not revised or relocated. The reference to Figure 1 in the current text remains, as well. *We note 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 are not included in labeling, as they are not acceptable. *We note that the six-month data included the status of only 83% of the patients randomized to the placebo or high-dose eptifibatide treatment groups. We further note that for other approved drugs with similar pharmacologic action (e.g., abciximab, tirofiban), the labeling that describes the 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 state that the new Figure 1 is not acceptable also because it depends on events reported by investigators and not events adjudicated by the Clinical Events Committee. We request that COR provide the five-month endpoint data for PURSUIT, 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 is not included in labeling, as it is unacceptable. *We note that this statement implies a clinical benefit with regard to the effect of Integrilin on stroke, and that 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 the sponsor's May 7, 1999 submission, they concur will all of the labeling changes specified in the May 4, 1999 approvable letter, with one exception. They propose 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.

Medical/Statistical Assessment

Following COR's May 7, 1999 submission, the Division requested a copy from COR of the SAS data set that summarizes the six-month follow-up data from PURSUIT. Dr. James Hung performed a statistical analysis of these data. In his June 7, 1999 review of this submission, Dr. Hung notes that, based on the SAS database provided by the sponsor, his analysis at 146 days and six-months suggest that eptifibatide seems to reduce death/MI events reported by the investigators after 30 days. He further notes that the validity of these analyses depends on the assumption that there was no bias in the investigator assessment of the endpoint. He concludes that whether data collection beyond 30 days not blinded to treatment caused some bias that is not assessable is an important point of concern.

In his June 24, 1999 review of this supplement, Dr. Throckmorton recommends approval of the paragraph COR proposes to add to the CLINICAL STUDIES section, provided the reference to the incidence of death or myocardial infarction as a secondary endpoint is removed from the paragraph.

On July 28, 1999, the Division held an internal meeting to discuss this supplement. This meeting was attended by Drs. Lipicky, Fenichel, Chen, and Throckmorton, and Ms. Morgenstern and LoCicero from the Division of Cardio-Renal Drug Products, and Ms. Norden from the Division of Drug Marketing, Advertising, and Communication. In the meeting, Ms. Norden noted that the number of patients stated in the proposed paragraph as having been followed for 165 days or longer (n=10,611) includes patients from both PURSUIT dose groups (the 180/2.0 regimen and the 180/1.3 regimen). She further noted that the paragraph, as proposed, seems to imply that all 10,611 patients received the 180/2.0 dose. Those in attendance agreed that the paragraph, as proposed, was misleading in this respect and that the paragraph should be revised accordingly. Those in attendance also agreed with Dr. Throckmorton's recommendation to remove from the paragraph the reference to the incidence of death or myocardial infarction as a secondary endpoint, because it was not pre-specified as such. For this reason also, it was agreed that the p-value should be omitted from the proposed paragraph.

It was agreed that Dr. Throckmorton would revise the proposed paragraph to address the Agency's concerns. It was also agreed that the Agency should issue an approvable letter to COR for this supplement. The approvable letter should propose that COR replace the paragraph they propose to add to the CLINICAL STUDIES section of the labeling (immediately preceding the description of the IMPACT II study) with Dr. Throckmorton's revised paragraph that is as follows:

Follow-up data were available through 165 days for 10,611 patients enrolled in the PURUIT 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.

Recommendation:

I recommend that the Division issue an approvable letter for this supplement in accordance with 21 CFR 314.70(b)(3). The letter should request that the sponsor submit final printed labeling revised as described above.


Colleen LoCicero, RHPC

cc: orig NDA 20-718
HFD-110
HFD-110/LoCicero
HFD-110/ABlount

SEP 21 1999

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	<u>20718</u>	Trade Name:	^{02-9/21/99} <u>INTEGRILIN (EPTIFIBATIDE) 1V2.0MG/ML/0.75</u>
Supplement Number:	<u>2</u>	Generic Name:	INTRIFIBAN ^{02-9/21/99} <u>eptifibatide</u>
Supplement Type:	<u>SE8</u>	Dosage Form:	<u>INJ</u>

Regulatory Action: AP

Proposed Indication:

-For the treatment of patients with acute coronary syndrome (UA/NQMI), including patients who are to be managed medically and those undergoing percutaneous coronary intervention (PCI). In this setting, Integrilin has been shown to decrease the rate of a combined endpoint of death or new myocardial infarction. -For the treatment of patients undergoing PCI. In this setting, Integrilin has been shown to decrease the rate of a combined endpoint of death, new myocardial infarction, or need for urgent intervention. In the clinical studies of eptifibatide, most patients received heparin and aspirin, as described in CLINICAL TRIALS.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

 NeoNates (0-30 Days) Children (25 Months-12 years)
 Infants (1-24 Months) Adolescents (13-16 Years)

Label Adequacy Does Not Apply
Formulation Status -
Studies Needed -
Study Status -

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This is an SE8, labeling supplement containing new clinical data. This supplement provided for the addition to labeling of the six-month follow-up data from one of the trials that supported approval of the orig. NDA.

Not applicable.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER,

01/2
MAY 4 1999

CSO Labeling Review
NDA 20-718/SE8-002 & SLR-003

Date of Submissions: October 9, 1998 (SE8-002)
 November 18, 1998 (SLR-003)
 February 19, 1999 (SLR-003-BL)

Date of Review: April 8, 1999

Applicant Name: COR Therapeutics, Inc.

Product Name: Integrilin (eptifibatide) Injection

Background:

The original October 9, 1998 submission includes draft labeling with proposed revisions based upon new clinical data, the PURSUIT six-month follow-up data, that are included in the submission. The submission also includes additional labeling revisions that do not require the review of new clinical data. In the November 18, 1998 submission, the sponsor requests to withdraw the labeling revisions that do not require the review of new clinical data from the October 9, 1998 submission and resubmit them in this submission. The sponsor requests further to revise the **DOSAGE and ADMINISTRATION** and **PRECAUTIONS** sections of the draft labeling included in the November 18, 1998 submission in the February 19, 1999 submission.

The Division met on March 23, 1999 to discuss the labeling changes proposed in these submissions. It was agreed that Dr. Ganley would incorporate the decisions made at this meeting in the secondary medical review of these submissions, and that these decisions then be conveyed to the sponsor in an approvable letter.

Evaluation:

The changes proposed in these submissions are as follows:

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 the 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 μ M 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 have been added in smaller print immediately following Table 1:

* 135 μ g/kg bolus followed by a continuous infusion of 0.5 μ g/kg/min

** 180 μ g/kg bolus dose followed by a continuous infusion of 2.0 μ g/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:

[REDACTED]

to the following:

Serum creatinine ≥ 4.0 mg/dL. In patients with serum creatinine levels between 2.0 mg/dL and 4.0 mg/dL, the 135 $\mu\text{g}/\text{kg}$ bolus and 0.5 $\mu\text{g}/\text{kg}/\text{min}$ 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 $\mu\text{g}/\text{kg}$ bolus followed by a 0.5 $\mu\text{g}/\text{kg}/\text{min}$ infusion.

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

[REDACTED]

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 a 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.

Medical Review:

In his review, dated April 1, 1999, Dr. Ganley states that his comments regarding the proposed labeling changes should be included in the action letter for these supplements.

S-002

In his April 1 review, Dr. Ganley notes that Figure 1 in the **CLINICAL STUDIES** section of the current text, which plots the Kaplan-Meier curve for events adjudicated by

the Clinical Endpoints Committee within 30 days of randomization, and references in the text to Figure 1 should not be eliminated from the labeling. The revised Figure 1, which includes investigator-reported events at up to six months, and the paragraph proposed to immediately precede it are not acceptable because the six-month data included the status of only 83% of the patients randomized to the placebo or high-dose eptifibatid treatment groups. Dr. Ganley notes that 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. He further notes that the revised Figure 1 is also not acceptable because it depends on events reported by investigators and not events adjudicated by the Clinical Events Committee. He requests that the sponsor 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 to include this in labeling.

Furthermore, Dr. Ganley states that 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, as it implies a clinical benefit with regard to the effect of Integrilin on stroke.

S-003

I discussed the changes to the **CLINICAL PHARMACOLOGY/Pharmacodynamics** subsection with Dr. Ganley and he believed they were acceptable.

Dr. Ganley notes that the paragraph proposed to precede Table 3 in the **CLINICAL STUDIES** section is acceptable, with the exception of the text "and within 30 days of randomization" in the last sentence. The last sentence of the paragraph should read as follows:

Table 3 shows the incidence of death or MI within 72 hours.

The revised Table 3, which includes 30-day endpoint data, is not acceptable. Table 3 in the current, approved labeling should be retained, as it emphasizes the treatment effect within the first 72 hours of randomization irrespective of whether a PCI was performed or not. Dr. Ganley notes that a 30-day post-hoc analysis of PCI and no PCI subgroups is not justified.

Dr. Ganley believes the change made to the text regarding serum creatinine levels in the **CONTRAINDICATIONS** section is acceptable.

The text added to the **PRECAUTIONS/Renal Insufficiency** subsection is acceptable, except that the serum creatinine values should be written as 2.0 mg/dL and 4.0 mg/dL.

Dr. Ganley believes the changes to the first paragraph in the **ADVERSE REACTIONS/Intracranial Hemorrhage and Stroke** subsection are acceptable.

Dr. Ganley notes that the text added to the **PRECAUTIONS/Maintaining Target aPTT and ACT** subsection is acceptable, with the exception of the paragraph describing the PRIDE study (the second paragraph following Table 6).

Finally, Dr. Ganley suggests that COR 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 to facilitate the review of the submissions.

Recommendation:

The Division should issue an approvable letter for these supplements. The letter should include Dr. Ganley's comments on the proposed changes and request that the sponsor submit FPL identical to the draft labeling as stated in the letter.



Colleen LoCicero, CSO

cc: orig NDA 20-718
HFD-110
HFD-110/LoCicero
HFD-110/SBenton