CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
20-718/S-010

Administrative Documents

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

Date: March 12, 2001

To: Douglas Throckmorton, M.D., DCRDP

From: Andrew Haffer, Pharm.D., DDMAC

Re: Comments on proposed labeling changes for Integrilin

Cor is proposing to revise the approved product labeling (PI) for Integrilin to reflect the results of the ESPRIT trial. DDMAC has reviewed the proposed labeling changes and offers the following comments. If you have any questions about these comments please do not hesitate to call.

Page 4

DRAFT

Page 12

Page 16

Page 17

2 pages redacted from this section of the approval package consisted of draft labeling

COR

COR THERAPEUTICS, INC.

August 7, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Document Control Room
1451 Rockville Pike
Rockville, MD 20851

RE: NDA 20-718/S-010, INTEGRILIN® (eptifibatide) Injection
Patent Certification

COR Therapeutics Inc. (COR) declares that the INTEGRILIN® (eptifibatide) Injection product is the subject of NDA 20-718/S-010. COR further declares that the content of NDA 20-718/S-010 is already covered by the previously submitted patents listed below.

- Patent #5,807,825 (Method of Use) – Expires September 15, 2015
- Patent #5,756,451 (Drug Substance) – Expires November 11, 2014
- Patent #5,686,570 (Drug Substance) – Expires November 11, 2014

COR has no new patents specifically directed to the dosage regimen or indication in Supplement No. 010 to NDA 20-718/S-010.

Please contact me at 650-244-6929 if you have any questions or require additional information.

Sincerely,

Michael R. Marsman, Pharm.D.
Director, Regulatory Affairs

Desk Copy: Colleen Locicero, Project Manager

Marzam Holoback
Food and Drug Administration, HFD-090
5600 Fishers Lane, Rockville, MD 20857

Copy sent to Marzam Holoback, HFD-090 on 8/8

256 E. Grand Avenue • South San Francisco • California 94080 • 650 244 6800 • Fax 650 244 9208

EXCLUSIVITY SUMMARY FOR NDA # 20-718/SE2-010

Trade Name: Integrilin

Generic Name: eptifibatide

Applicant Name: COR Therapeutics, Inc.

HFD #-110

Approval Date If Known:

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /___/ NO /_X_/

b) Is it an effectiveness supplement?

YES /_X_/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE2

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X_/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

---

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO- please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO / X /

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-718, Integrilin (eptifibatide) Injection

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been

sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain: _____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Protocol 98-025, entitled "Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (the 'ESPRIT' Study): A Phase III Study in Patients Undergoing Percutaneous Coronary Intervention with Stent Implantation."

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Protocol 98-025, the 'ESPRIT' study

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND #(_____) YES /X_/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO / X /

If yes, explain: _____

Colleen LoCicero
Regulatory Health Project Manager
April 26, 2001

Raymond Lipicky, M.D. 4/30/01
Division Director

cc: Original NDA
Division File
HFD-93 Mary Ann Holovac

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	020718	**Trade Name:**	INTEGRILIN (EPTIFIBATIDE)1V2.0MG/ML/0.75
Supplement Number:	010	**Generic Name:**	INTRIFIBAN
Supplement Type:	SE2	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	AS AN ADJUNCT TO ASPIRIN AND HEPARIN IN PATIENTS UNDERGOING PTCA FOR THE PREVENTION PF ACUTE CARDIAC ISCHEMIC COMPLICATIONS (DEATH/MYOCARDIAL INFARCTION/NEED FOR
Action Date:	6/30/00		

Indication # 1: 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, including those undergoing intracoronary stenting. 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 IMPACT II, PURSUIT, and ESPRIT studies of eptifibatide, most patients received heparin and aspirin, as described in CLINICAL TRIALS.

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): Full waiver of pediatric study requirement for this supplemental application was granted by Division on August 28, 2000.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
0 months	Adult	Waived	

This page was last edited on 4/27/01

/S/

Signature

4/27/01

Date

L. Colleen

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 20-718/S-010

AUG 28 2000

COR Therapeutics, Inc.
Attention: Michael R. Marsman, Pharm.D.
256 East Grand Avenue
South San Francisco, CA 94080

Dear Dr. Marsman:

Please refer to your correspondence dated August 4, 2000, requesting a waiver for pediatric studies under 21 CFR 314.55(c).

We have reviewed the information you have submitted and agree that a waiver is justified for Integrilin (eptifibatide) Injection for the treatment of patients undergoing PCI, including those undergoing intracoronary stenting, for the pediatric population.

Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55 at this time.

If you have questions, please contact:

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

Sincerely,

/S/

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION — **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : April 26, 2001

FROM : Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval of NDA 20-718/S-010, eptifibatide, COR Therapeutics, Secondary Medical Review and Division Director summary.

TO : NDA File

Introduction

This is the secondary medical review and summary document for S-010. The primary Medical and Statistical reviews being conducted by Dr.'s Throckmorton and Hung, and Clinical Pharmacology review conducted by Dr. Robbie.

There are no changes to the formulation or manufacture process, consequently no review by the chemists was needed. We elected to no have any clinical inspections. This study qualifying for such exclusion according to the draft MAPP which was discussed in detail with Division Directors at a recent meeting. We have suitably noted that one center was disqualified, not because of its conduct of the ESPRIT trial, rather because of the local institution deciding that the investigator did not perform appropriately while conducting another trial.

Eptifibatide is an approved drug, the patient population studied in the trial known as ESPRIT is a population previously unstudied, namely patients who have a stent placed by percutaneous means, for whatever reason. A new dosing regimen of eptifibatide and of heparin was studied in a placebo controlled trial.

I can add little detail to the medical, statistical or clinical pharmacology reviews.

Results

This was a multicenter, double-blind, placebo controlled trial that enrolled 1024 patients to the placebo arm and 1040 patients to the eptifibatide arm (there were only two arms). The trial was stopped prematurely by the DSMB, based upon their judgement of overwhelming efficacy, after analyzing results from only 1758 total patients (about 85% of patients in the final database). All analyses were intent-to-treat (all patients randomized), irrespective of dropouts); one patient in each arm was (two patients total) was lost to follow up within the 30 day trial duration. One center was disqualified from having data included in the results. Neither the loss to follow-up nor the one center disqualification makes any difference to the results.

The primary endpoint was the composite of death, myocardial infarction , urgent target vessel revascularization and thrombotic "bail-out" 48 hours after randomized treatment. For the primary endpoint there were 108 events in the placebo group and 69 events in the placebo group, $p = 0.0015$. Indeed, eptifibatide was superior to placebo, unquestionably.

At 30 days, there were 107 events in the placebo group and 71 events in the eptifibatide group, $p = 0.0034$. So, the effect persists.

There are 32 pages of medical review and 19 pages of statistical review that address the question of whether one should take this result at face value (unplanned analyses of efficacy, a center that was disqualified because the local institution found problems with the investigator, subgroups, etc. Both reviews conclude that the face value look reasonably reflects the findings of the trial and no need for detail.

Bleeding events were more common in the ebtifibatide group than in the placebo group, from 2 to 3 times more common, depending upon what bleeding criterion one examines, although major bleeding was a problem in only 1.3% of patients randomized to eptifibatide; an acceptable incidence. In particular there were three retroperitoneal bleeds in the eptifibatide group (none in placebo) and two intracranial bleeds in the eptifibatide group (1 in placebo). Thrombocytopenia (platelet count <100,000 was more common in the eptifibatide group 9 in the eptifibatide group (4 in placebo). Discontinuations due to adverse events were 5.8% in the eptifibatide group vs. 2 % in the placebo group. Clearly, epitifibatide has a down side.

Dose

Not unusually, dose could be a major item for discussion. The **approved** dosing for eptifibatide are:

Acute Coronary Syndrome

180 micrograms/kg bolus, followed by an infusion of **2** micrograms/kg/min (for up to 72 hours)

PCI

135 micrograms/kg bolus. Followed by an infusion of **0.5** micrograms/kg/min for 20-24, **Heparin** therapy aimed at an ACT of 300-350 seconds.

Dosing used in the ESPRIT study (note patients were a mixture of Acute Coronary Syndrome and PCI) was

180 micrograms/kg bolus, followed b **2.0** micrograms/kg/minute and a **second 180** micrograms/kg bolus 10 minutes after the first bolus (with the continuous infusion running). **Heparin** therapy was aimed at an ACT of 200-300 seconds.

The major difference between regimens studied was in the target ACT, 200-300 seconds for ESPRIT and 300-350 seconds in prior studies. There was certainly at least comparable efficacy in ESPRIT, thus the target ACT should be 200-300 for all indications.

The second 19- micrograms/kg bolus (10 minutes following the 1 st bolus) is intended to minimize the nadir in plasma concentrations (and consequently the platelet inhibition effect) is not a material change in dosing of eptifibatide.

Since there were no plasma concentrations of eptifibatide measured in ESPRIT, Dr. Robbie used available data from other studies to simulate the ESPRIT eptifibatide dosing regimen and found the dosing regimen to acceptably produce a concentration above 1600 nanograms/ml. So, the additional bolus makes pharmacokintic sense. The previously recommended dosing regimens for PCI (empirically based upon IMPACT II) seems to me to be superceded by the ESPRIT dosing regimens that are applicable to PCI with or without stent placement.

Although the trials still do not give a firm basis for recommending any particular dosing regimen, they certainly point out that there is no need to have 3 empirical regimens in the Dosing and Administration Section, they are amply documented in the rest of labeling.

So, now there are 2 dosing regimens (I could argue for only one – that of ESPRIT) that appear in the Dosing and Administration section. One for Acute Coronary Syndrome and another for PCI. The lower ACT (and presumably the dose of heparin needed to achieve it) is included in both. I think that is appropriate and in keeping with the data.

Summary

Everything is in apparent order. My mark-up of the package insert has been circulated. An approvable letter can be drafted.

Memo to the file

Date:	February 6, 2001
From:	Colleen LoCicero Regulatory Health Project Manager, HFD-110
To:	NDA 20-718/S-010
Subject:	Dr. Robbie's request

I telephoned Dr. Michael Marsman of COR Therapeutics, Inc. on February 6, 2001 to convey the following request from Dr. Gabriel Robbie, the assigned Clinical Pharmacology/Biopharmaceutics reviewer for NDA 20-718/S-010 (the ESPRIT supplement):

1. Dr. Robbie requests that COR provide details of the standard curve range, quality control sample information, and intra-and inter-day assay variability for Study 96-023b.

I recommended that COR direct any questions they may have with respect to this request to Dr. Robbie himself. COR may respond via facsimile, but should follow up the facsimile with official correspondence to the file. Dr. Marsman inquired as to whether he should also follow up a February 5, 2001 facsimile he sent to Dr. Douglas Throckmorton, the primary medical reviewer for NDA 20-718/S-010, with official correspondence to the file. I recommended that Dr. Marsman do so. I agreed to verify with Dr. Throckmorton that he received the February 5, 2001 facsimile and notify Dr. Marsman if Dr. Throckmorton had not received it.

JAN 24 2000

Minutes of a teleconference

Date of teleconference:	January 12, 2000
Product:	Integrilin (eptifibatide) Injection
/NDA #:	20-718
Sponsor:	COR Therapeutics, Inc.
Purpose:	to discuss desired format for electronic submission of ESPRIT data
Teleconference Chair:	James Hung, Ph.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	

FDA

James Hung, Ph.D.	Acting Team Leader, Statistical, Division of Biometrics I (HFD-710)
Douglas Throckmorton, M.D.	Medical Officer, Division of Cardio-Renal Drug Products (HFD-110)
Colleen LoCicero	Regulatory Health Project Coordinator, HFD-110

COR Therapeutics, Inc.

Sally Greenberg, Ph.D.	Director, Biostatistics
Arleen Glenn	Associate Director, Regulatory Affairs

Background

COR requested this meeting to discuss the desired format for the electronic submission of the ESPRIT study data.

The teleconference

COR is currently developing the software for the submission of the ESPRIT study data and would like the Division's input on what to include in the electronic submission.

Dr. Throckmorton noted that, if they haven't already done so, COR should refer to the Agency's guidance on electronic submissions. Dr. Hung stated that he would like the following items included in the electronic submission:

1. the raw SAS data sets
2. the annotated case report forms (with the SAS variables)
3. the analysis data set
4. the SAS program used to convert and generate the analysis data set from the raw data set plus the user manuals

5. the SAS program used to analyze the data plus the user manuals

The sponsor plans to submit the SAS datasets as SAS transport files and all of this on CD-ROM. The sponsor was encouraged to contact Dr. Hung if they have additional questions. Dr. Hung noted that it might be helpful to send him a sample of the data tables, etc. prior to submitting the entire data set so that he can review and comment on them. Dr. Throckmorton recommended against submitting a lengthy study report, noting that we primarily need COR's assessment of the primary endpoint(s) and data.

The sponsor noted that the ESPRIT study is presently ongoing, but that they anticipate breaking the blind in March.

Signature, Teleconference Recorder: /S/ Colleen LoCicero

Concurrence, Teleconference Chair: /S/ James Hung, Ph.D

drafted: 1/13/00 finaled: 1/21/00

rd:

Throckmorton 1/14/00
Hung 1/14/00

Minutes of a teleconference

Date of teleconference:	May 31, 2000
Application:	NDA 20-718
Product:	Integrilin (eptifibatide) Injection
Sponsor:	COR Therapeutics, Inc.
Purpose:	to discuss the misunderstanding surrounding the interim analyses of the ESPRIT data and the early termination of the ESPRIT study
Teleconference Chair:	Douglas Throckmorton, M.D.
Teleconference Recorder:	Colleen LoCicero
Participants:	
FDA	
Douglas Throckmorton, M.D.	Medical Officer, Division of Cardio-Renal Drug Products (HFD-110)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
COR	
Charles Homcy, M.D.	Executive Vice President, Research and Development
Michael Kitt, M.D.	Vice President, Medical Affairs
Todd Lorenz, M.D.	Vice President, Medical Affairs
Sally Greenberg, Ph.D.	Director, Biostatistics
Arleen Glenn	Associate Director, Regulatory Affairs

Background

COR requested this teleconference to discuss the misunderstanding surrounding the reasons for the unplanned interim analyses of the ESPRIT data and the early termination of the ESPRIT study that transpired during the April 19, 2000 meeting between the Agency and COR.

The teleconference

COR believed it critical to ensure that the Agency understands that COR was not involved in any way with the decision to perform the interim analyses of the ESPRIT data or the decision to terminate the ESPRIT study early. These were the decisions of the DSMC, with no input from COR.

Additionally, COR noted that while the DSMC did review the data which led to these decisions because of ethical concerns, they were not the ethical concerns raised by the Agency when the ESPRIT study was submitted, but ethical concerns of their own. This has become apparent from the minutes of the DSMC meetings.

During the April 19, 2000 meeting between the Agency and COR, it was the Agency's understanding, based on statements made by COR, that the Agency's early concerns with the ESPRIT study were a factor in the decision to look at the ESPRIT data and perform the initial unplanned interim analysis. It is our understanding now that this was not the case. However, since minutes are to reflect the conversation of the meeting, it would not be appropriate to remove the statements regarding the Agency's early ethical concerns from the minutes. However, as the Agency has already indicated to COR, an addendum to the minutes can be made to clarify the sponsor's position regarding the circumstances surrounding the decision to perform the interim analyses and terminate the study early. The Division believed COR's proposed addendum, submitted May 26, 2000, was acceptable. All agreed that the addendum was the appropriate approach to take to address any miscommunication that might have occurred during the meeting.

Dr. Throckmorton confirmed that the Agency understands that COR was not involved in the decision to perform the unscheduled interim analysis or stop the study; a position COR intends to support in their supplemental NDA application.

Revisions to the April 19, 2000 meeting minutes, which will incorporate the May 23, 2000 changes proposed by Dr. Throckmorton and the May 26, 2000 addendum proposed by COR, will be finalized and forwarded to COR, as well as filed in the Division archives with the original minutes.

Signature, Teleconference Recorder: /S/ Colleen LoCicero

Concurrence, Teleconference Chair: /S/ Douglas Throckmorton, M.D.

cc: orig IND
NDA 20-718
HFD-110
HFD-110/Matthews
HFD-110/LoCicero

drafted: 6/5/00 finaled: 6/6/00

rd:
Throckmorton 6/6/00

Minutes of a meeting

Date of meeting:	April 19, 2000
Application #:	NDA 20-718
Product:	Integrilin (eptifibatide) Injection
Sponsor:	COR Therapeutics, Inc.
Purpose:	pre-NDA supplement
Meeting Chair:	Shaw Chen, M.D., Ph.D.
Meeting Recorder:	Colleen LoCicero
Participants:	
FDA	
Shaw Chen, M.D., Ph.D.	Team Leader, Medical, Division of Cardio-Renal Drug Products (HFD-110)
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Douglas Throckmorton, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Acting Team Leader, Statistical, Division of Biometrics I (HFD-710)
Gabriel Robbie, Ph.D.	Clinical Pharmacologist and Biopharmaceutist, Division of Pharmaceutical Evaluation I (HFD-860)
Colleen LoCicero	Regulatory Health Project Manager, HFD-110
COR	
Michael Kitt, M.D.	Vice President, Medical Affairs
Todd Lorenz, M.D.	Vice President, Medical Affairs
Sally Greenberg, Ph.D.	Director, Biostatistics
Arleen Glenn	Associate Director, Regulatory Affairs

Background

The sponsor requested this meeting to discuss their anticipated August submission of an efficacy supplement based on the ESPRIT study results. The sponsor proposed to present a synopsis of the decision to stop the ESPRIT study early, and to discuss the format of the upcoming submission, the proposed presentation of the safety data, labeling changes and table of contents, and an electronic submission.

The meeting

Discussion Point #1: The decision to terminate study early

An interim look at efficacy was not provided for prospectively in the ESPRIT study protocol. COR noted that the ESPRIT protocol provided for a look at the efficacy data by the DSMC only if the safety to efficacy ratio appeared not to be what was expected. Slower than expected enrollment concerned COR, because of the ethical issues raised by the Agency when the study was submitted, prompting them to have the DSMC conduct an unplanned look at efficacy. COR noted that the DCRI statistician, who is not a voting member of the DSMC, prepared the integrated data summary. COR added that they did not have access to the ESPRIT data until after the decision to stop the study was made.

Because COR did not prospectively plan for an interim analysis or provide for early study termination in the study protocol, and subsequently performed two interim analyses and lowered the bound for the stopping rules, it will be necessary for them to provide us with all the information they can obtain surrounding the DSMC's decision to stop the study early. This would include, but not be limited to, relevant DSMC minutes and all of the data the Committee reviewed prior to making the decision to stop the study. COR should identify which data prompted the DSMC to stop the study. The Agency will perform our own analysis of these data. The Division requested that COR obtain from DCRI the exact (electronic) dataset used by the DSMC to make the decision to stop the study early and include this dataset in the application.

COR should also provide a justification for the first interim analysis. Prior to the start of ESPRIT, the Agency decided that ESPRIT was an ethical study. The Division did not believe, therefore, that COR's concern with low enrollment and the risk/benefit ratio was an acceptable reason for performing the initial unscheduled interim analysis.

A letter from Dr. Califf of DCRI summarizing the thinking of the DSMC and their rationale for stopping the study early would not hurt COR's cause, but it might not be particularly helpful either.

Discussion Point #2: Preferred analysis method for presentation of data in label

Four percent of the ESPRIT study subjects underwent bailout treatment, which was provided for in the ESPRIT protocol. COR asked whether the Agency would prefer that the data presented in the tables in the proposed label be analyzed by treatment strategy (separate by bail-out, placebo or eptifibatide) or intent-to-treat. For consistency, COR would prefer to analyze these data by intent to treat, as this was how they presented these data to the American College of Cardiology and how these data are presented on the Duke Clinical Research Institute (DCRI) website. COR noted that the difference between the two analyses is not significant (0.1%). Dr. Throckmorton noted that there was much discussion, when the ESPIRT protocol was initially submitted to the Agency, about the bailout treatment. Dr. Throckmorton would like to see both analyses, but

believed it preferable to analyze the data presented in the tables of the proposed label by intent-to-treat. He noted, however that he could not speak for Dr. Temple.

Discussion Point #3: Proposed labeling revisions

The sponsor proposes to revise the **DOSAGE AND ADMINISTRATION** section of the package insert to

DRAFT

ESPRIT study. They propose to

. On the surface, this appears to be acceptable, however, it will depend on the data. Also, for the PCI indication, the sponsor intends to
ESPRIT study and

The sponsor is not proposing any changes to the eptifibatide dosing for the ACS indication in the package insert. However, COR intends to recommend
to reflect

The sponsor would prefer to
package insert. However, they would be willing to
depending on the Agency's preference. The Division recommended that COR not spend much time on the proposed labeling, noting that we are very proactive with respect to labeling and will, most likely, extensively revise the labeling.

The Division believed there should be some consistency across Centers with respect to the heparin dosing for these products.

Discussion Point #4: Format/content of application

COR is not planning to submit an Integrated Summary of Safety or Efficacy for the supplement. The Division agreed that this was acceptable.

COR noted their previous telephone conversation with Drs. Hung and Throckmorton to discuss the format/content of the statistical portion of the supplement (see attached minutes). As previously agreed, all pertinent statistical information/data will be provided on CD-ROM. Dr. Hung believed the sponsor's proposals for the datasets, software, and documentation of the electronic submission to be acceptable. COR agreed to include in the application the dataset from DCRI upon which the DSMC based their decision to stop the study early.

Case report tabulations (CRT) include all labs and observations for each study subject that experiences an adverse event. All of the information in the CRT would also be included in the raw data sets. The Division agreed that the raw data would be sufficient and that it would not be necessary for COR to include the CRT in this supplement. Dr. Stockbridge suggested that COR request a waiver of the CRT requirement.

The sponsor would prefer to provide only paper copies of the case report forms. The Division believed this to be acceptable.

An electronic submission would probably facilitate the review of this supplement, but should not delay its submission.

Signature, Meeting Recorder: /S/ Colleen LoCicero

Concurrence, Meeting Chair /S/ Shaw Chen, M.D., Ph.D.

Addendum:

Following the meeting, Ms. Glenn contacted Ms. LoCicero to ask whether it was necessary to submit a formal request for a waiver of the CRT requirement, since the Division agreed to waive this requirement at the meeting and there would be official minutes of the meeting. Ms. Glenn referred to 21 CFR 314.50(f)(1), noting that this section seems to imply that an agreement by the Agency at a pre-(s)NDA meeting that it is not necessary for the sponsor to submit the CRT effectively waives this requirement. The CFR makes no mention of the need to follow this up with a letter, presumably because the minutes of the meeting would serve as official documentation of the agreement. Ms. LoCicero agreed to verify this with Ms. Natalia Morgenstern, Cardio-Renal, Chief, Project Management Staff, and get back to Ms. Glenn. Ms. LoCicero telephoned Ms. Glenn on May 5, 2000 to report that, as confirmed by Ms. Morgenstern, the minutes of the pre-(s) NDA meeting would serve as official documentation that the requirement to submit the case report tabulations had been waived. Therefore, it would not be necessary for the sponsor to submit a waiver request letter.

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

drafted: 5/9/00 finaled: 5/15/00

rd:
Robbie 5/11/00
Hung 5/15/00
Throckmorton 5/12/00
Stockbridge 5/12/00
Chen 5/15/00

Corrections to meeting minutes

Date of meeting:	April 19, 2000
Date of minutes:	May 16, 2000
Application:	NDA 20-718
Product:	Integrilin (eptifibatide) Injection
Sponsor:	COR Therapeutics, Inc.

The following corrections should be made to the original minutes of the April 19, 2000 meeting regarding NDA 20-718 between COR Therapeutics and the Division:

1. The third sentence in the first paragraph under Discussion Point #1 (The decision to terminate study early) should be changed from the following:

   > Slower than expected enrollment concerned COR, because of the ethical issues raised by the Agency when the study was submitted, prompting them to have the DSMC conduct an unplanned look at efficacy.

   to the following:

   > Slower than expected enrollment concerned the DSMC, because of the ethical issues raised by the Agency when the study was submitted (see Addendum).

2. The first sentence in the second paragraph under Discussion Point #1 should be changed from the following:

   > Because COR did not prospectively plan for an interim analysis or provide for early study termination in the study protocol, and subsequently performed two interim analyses and lowered the bound for the stopping rules, it will be necessary for them to provide us with all the information they can obtain surrounding the DSMC's decision to stop the study early.

   to the following:

   > Because COR did not prospectively plan for an interim analysis or provide for early study termination in the study protocol, and subsequently DCRI, at the DSMC's request, performed two interim analyses and lowered the bound for the stopping rules, it will be necessary for COR to provide us with all the information they can obtain surrounding the DSMC's decision to perform the interim analysis and stop the study early.

3. The first sentence in the third paragraph under Discussion Point #1 ("COR should also provide a justification for the first interim analysis.") should be deleted from the minutes.

4. The last sentence in the third paragraph under Discussion Point #1 should be changed from the following:

> The Division did not believe, therefore, that COR's concern with low enrollment and the risk/benefit ratio was an acceptable reason for performing the initial unscheduled interim analysis.

to the following:

> The Division did not believe, therefore, that concern with low enrollment was a clearly acceptable reason for performing the initial unscheduled interim analysis.

5. The last paragraph under Discussion Point #1 should be changed from the following:

> A letter from Dr. Califf of DCRI summarizing the thinking of the DSMC and their rationale for stopping the study early would not hurt COR's cause, but it might not be particularly helpful either.

to the following:

> A letter from Dr. Califf of DCRI summarizing the thinking of the DSMC and their rationale for performing the unscheduled interim analysis and stopping the study early would not hurt COR's cause, but it might not be particularly helpful either.

6. The last sentence in the first paragraph under Discussion Point #3 (Proposed labeling revisions) should be changed from the following:

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to the following:

Draft

Additionally, the following paragraphs should be added as an Addendum to the minutes:

COR wishes to emphasize that it had no prior knowledge or insight into why the DSMC decided to initiate an interim analysis. In fact, the rationale behind their decision becomes clear upon reading the minutes of the DSMC meetings (all of which will be included in the ESPRIT final study report). Multiple issues came into play, but the deliberation on this topic began (December 16, 1999) when a DSMC member raised the concern that safety considerations dictated that an analysis of ischemic events be undertaken, i.e., an efficacy analysis. It is true that slower than expected enrollment allowed a meaningful analysis to be performed in that sufficient quality data would be available.

COR did not intend to communicate to the Division that either the ethical basis for the study or slow enrollment motivated the DSMC's actions. As was learned later from the minutes of the DSMC's sessions, members of the DSMC believed that it was reasonable to review ischemic events as part of the safety review to determine if an overwhelming treatment benefit was being achieved. To reiterate, COR had no knowledge of the events as they transpired in real time.

Signature, Minutes Recorder: /S/ Colleen LoCicero

Concurrence, Meeting Chair: /S/ w Chen, M.D., Ph.D.

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

rd:
Throckmorton 6/1/00

RHPM Review of Final Printed Labeling
NDA 20-718/S-010 and S-013

Date of labeling submission:	May 14, 2001
Date labeling reviewed:	May 29, 2001
Product:	Integrilin (eptifibatide) Injection
Sponsor:	COR Therapeutics, Inc.

Background

As agreed to by the Agency, the sponsor has provided a single final printed labeling submission in response to the approvable letters issued for S-010 (on April 30, 2001) and S-013 (on March 28, 2001). The labeling incorporates the changes specified in both approvable letters.

S-010 provided for labeling revised to reflect the findings of the ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy) study, including revised dosing recommendations for patients undergoing Percutaneous Coronary Intervention (PCI) and a revised recommended target range for activated clotting time (ACT) during PCI. The approvable letter for S-010 specified that the sponsor submit final printed labeling identical to the marked-up draft labeling that accompanied the letter.

S-013 provided for the addition of information to the package insert on bleeding events from post-marketing adverse event reports. (The addition of this information was requested by the Division at a November 8, 2000 meeting with the sponsor). The approvable letter for S-013 specified that the sponsor submit final printed labeling identical to the February 12, 2001 submitted draft labeling, with the exception of the revisions listed in the letter and the corrections to the dosing charts the sponsor committed verbally to make.

Evaluation

I reviewed the submitted final printed labeling in its entirety, comparing it to the labeling that accompanied the April 30, 2001 approvable letter for S-010, the February 12, 2001 submitted draft labeling for S-013, and the changes, as specified in the March 28, 2001 approvable letter, that were to be made in the final printed labeling for S-013.

The May 14, 2001 submitted final printed labeling differs from what was specified in the approvable letters for S-010 and S-013, as follows:

1. The heading of the section describing the IMPACT II study in the **CLINICAL STUDIES/Percutaneous Coronary Intervention** subsection does not include a hyphen between "Thrombosis" and "II".

2. Throughout the package insert, all quotation marks are consistently presented as double quotation marks ("). During the review of S-010, the Division requested that

the sponsor present "bail out" consistently, using single quotation marks (') exclusively or double marks (") exclusively throughout the package insert and not a combination of both. The sponsor agreed to do this in the final printed labeling for S-010. The sponsor has taken this one step further and presented all quotation marks consistently as double marks throughout the package insert.

3. The first sentence in the **CONTRAINDICATIONS** section is bolded.

4. In the last sentence of the **PRECAUTIONS/Renal Insufficiency** subsection, "in vitro" is not italicized.

5. The study headings and "Patients" subheadings in Table 7 have been moved from the center to the left side of the table.

6. The dosing chart heading has been moved from the left side to the center of the table.

7. "354" has been changed to "254" in the entry in the second column and next to the last row of the dosing chart.

Recommendation

As the submitted final printed labeling is exactly as requested in the approvable letters for S-010 and S-013, with the exception of a few, minor, editorial revisions, I recommend the Division issue an approval letter for these supplemental applications.

6/8/01

Colleen LoCicero, RHPM

RHPM Package Overview

Date:	April 26, 2001
Application:	NDA 20-718/S-010 Integrilin (eptifibatide) Injection
Applicant:	COR Therapeutics, Inc.
Classification:	6S
User Fee Goal dates:	April 30, 2001 (primary) June 30, 2001 (secondary)

Background

This supplemental application proposes revised dosing recommendations for Integrilin in patients undergoing Percutaneous Coronary Interventions (PCI), based on the findings of the ESPRIT ("Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (the 'ESPRIT' Study); A Phase III Study in Patients Undergoing Percutaneous Coronary Intervention with Stent Implantation") study. Throughout the labeling, additional changes have been proposed to reflect the ESPRIT findings.

Labeling

The sponsor's proposed revised labeling was included in the original supplement submission. For a detailed explanation of the sponsor's proposed changes, refer to the RHPM review of draft labeling that follows this overview.

Dr. Throckmorton, the primary medical reviewer, reviewed and revised the sponsor's proposed labeling. He included his marked-up version of the proposed labeling in his April 6, 2001 review of the application. Dr. Throckmorton has indicated that he included in the marked-up labeling the changes proposed by Dr. Andrew Haffer of the Division of Drug Marketing, Advertising, and Communication (DDMAC) in Dr. Haffer's March 12, 2001 memorandum regarding the proposed labeling.

Although Dr. Lipicky states in his April 26, 2001 memorandum that he could argue for a single dosing regimen in the labeling (that of ESPRIT), he indicates that the draft labeling that will accompany the approvable letter will include two regimens. The two regimens are those proposed by the sponsor in their revised labeling, one for Acute Coronary Syndrome and the other for Percutaneous Coronary Intervention. The marked up package insert to which Dr. Lipicky refers in his review is a copy of Dr. Throckmorton's marked up labeling on which Dr. Lipicky has indicated his concurrence with Dr. Throckmorton's proposed changes and the changes proposed by COR that Dr. Throckmorton did not change.

A copy of the Division's revised version of the sponsor's proposed labeling that will accompany the approvable letter is located in the labeling section of the Action Package.

Exclusivity

The sponsor did not include in the supplemental application a request for exclusivity for the proposed new dosing regimen. The Action Package contains a completed exclusivity checklist for this supplemental application.

Pediatric Rule

In response to the sponsor's August 4, 2000 request for a waiver from the pediatric study requirement for this supplemental application, the Division granted a full waiver of the pediatric study requirement on August 28, 2000. A copy of the August 28, 2000 letter is located in the pediatric section of the Action Package.

Financial Disclosure

The sponsor has provided the financial disclosure information required under 21 CFR 54.4. The sponsor's financial disclosure information consists of a completed Form FDA 3454 (Certification of Financial Interests and Arrangements of Clinical Investigators) with attachments. Dr. Throckmorton indicates in his April 25, 2001 memo concerning the financial disclosure information that he finds no investigator to be the recipient of significant payments as defined under 21 CFR 54.2(f). He adds that he does not find any evidence of inappropriate or suspect financial arrangements between the sponsor and the ESPRIT investigators.

DSI

The Division elected not to request any clinical audits of the ESPRIT study, as noted in Dr. Lipicky's April 26, 2001 review of this supplemental application.

Chemistry

There are no Chemistry, Manufacturing, and Controls issues for this supplemental application, with the exception of the August 4, 2000 claim for categorical exclusion from environmental assessment the sponsor submitted in accordance with 21 CFR 25.15(a). In his April 27, 2001 review of this submission, Mr. Advani finds the claim of categorical exclusion satisfactory.

Statistical

Dr. Hung's January 24, 2001 review of this supplemental application concludes that the ESPRIT results demonstrate a statistically significant greater reduction of the primary efficacy endpoint and key secondary endpoint for Integrilin than placebo in patients undergoing PCI with stent implantation. He notes that the adjudicated events show great

internal consistency. He further notes that the investigator's reported events demonstrate a much smaller effect of eptifibatide that is not statistically significant.

Clinical Pharmacology/Biopharmaceutics

In his February 1, 2001 review of this supplemental application, Dr. Robbie states that the sponsor should have collected plasma samples from a representative subgroup of PCI patients in ESPRIT, rather than simulating plasma concentrations. However, he concludes that, based on expected plasma concentrations following treatment with the new double bolus dose regimen simulated by OCPB (The Office of Clinical Pharmacology and Biopharmaceutics), the proposed new regimen is acceptable. He notes that the new regimen is expected to maintain plasma concentrations above the target concentration of 1600 ng/ml during the entire treatment. In his review, Dr. Robbie requests that COR provide the details of the standard curve range, quality control sample information, and intra- and inter-day assay variability for Study 96-023b.

On February 6, 2001, I communicated, via telephone, Dr. Robbie's request for details of STUDY 96-023b to Dr. Michael Marsman of COR Therapeutics, Inc. On March 14, 2001, COR submitted the requested information in an amendment to the supplemental application. In his March 20, 2001 review of this amendment, Dr. Robbie finds the quality control and standard curve data acceptable.

DDMAC review

In his memorandum of March 12, 2001 to Dr. Throckmorton, Dr. Andrew Haffer of DDMAC provides his recommendations regarding the sponsor's proposed changes to the Integrilin labeling. Dr. Throckmorton has indicated to me verbally that he incorporated Dr. Haffer's recommendations into the marked-up version of the labeling that accompanies his (Dr. Throckmorton's) review.

Primary Medical

In his April 6, 2001 review of this supplemental application, Dr. Throckmorton concludes that the ESPRIT results provide robust support for the use of eptifibatide in patients undergoing PCI with stent placement using the revised dosing regimen, including the use of a lower dose heparin. He notes that he has revised the sponsor's proposed labeling and includes a copy of his marked-up version of the proposed labeling in his review.

Safety Update

In his April 26, 2001 review of the 120-day safety update, Dr. Throckmorton indicates that the update does not affect his original conclusions regarding the safety of Integrilin when used as described in the ESPRIT study.

Secondary Medical

In his review of this supplemental application, Dr. Lipicky indicates that on the primary endpoint, eptifibatide was unquestionably superior to placebo and that the effect persisted at 30 days. He continues that the major item for discussion is dose. Although Dr. Lipicky states that he could argue for a single dosing regimen in labeling (that of ESPRIT), he does not do so, indicating later in the memorandum that the **DOSAGE AND ADMINISTRATION** section will include two dosing regimens, one for Acute Coronary Syndrome and one for Percutaneous Coronary Intervention. He recommends that an approvable letter be drafted.

RHPM Summary

All primary and secondary reviews are completed. To my knowledge, there are no outstanding issues that would preclude taking an action on this application. As requested by Dr. Lipicky, I have prepared an approvable letter (based on enclosed marked-up draft labeling) for his signature.

S 5/1/01

Colleen LoCicero, RHPM

RHPM Review of Draft Labeling
NDA 20-718/SE2-010

Date labeling submitted:	June 29, 2000
Date labeling reviewed:	September 22, 2000
Product:	Integrilin (eptifibatide) Injection
Sponsor:	COR Therapeutics, Inc.

Background

This supplemental application proposes revised dosing recommendations for Integrilin in patients undergoing Percutaneous Coronary Interventions (PCI) based on the ESPRIT study results, which are included in the submission. The recommended target range for activated clotting time (ACT) during PCI has been revised and additional changes have been made throughout the labeling to reflect the ESPRIT study results. Finally, information on renal insufficiency and thrombocytopenia has been moved from the **CONTRAINDICATIONS** to the **WARNINGS** section of the package insert.

Evaluation

I reviewed the submitted draft labeling in its entirety and noted the following changes from the last approved labeling (labeling approved March 3, 2000 for SCM-007).

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

to the following:

> Table 1 shows the effects of dosing regimens of eptifibatide used in the IMPACT II and PURSUIT studies on *ex vivo* platelet aggregation induced by 20 μM ADP in PPACK-anticoagulated platelet-rich plasma and on bleeding time.

2. The following paragraph has been added to the **CLINICAL PHARMACOLOGY/Pharmacodynamics** subsection immediately following Table 1:

3. The third sentence in the **CLINICAL PHARMACOLOGY/Pharmacokinetics** subsection has been changed from the following:

to the following:

4. The following sentence has been inserted between the third and fourth sentences in the **CLINICAL PHARMACOLOGY/Pharmacokinetics** subsection:

5. The following text has been added to the end of the fourth sentence in the **CLINICAL PHARMACOLOGY/Excretion and Metabolism** subsection:

   ; another 8 patients with serum creatinine between 2.0 and 4.0 mg/dL were enrolled in the ESPRIT study and received the full 180/180 µg/kg double bolus regimen with an infusion adjusted down from 2.0 to 1.0 µg/kg/min.

6. The reference at the end of the last sentence in the **CLINICAL PHARMACOLOGY/Excretion and Metabolism** subsection has been changed from "see **CONTRAINDICATIONS**" to "see **WARNINGS.**"

7. The third sentence in the **CLINICAL PHARMACOLOGY/Special Populations** subsection:

has been replaced with the following:

8. The first sentence in the **CLINICAL STUDIES** section has been changed from the following:

to the following:

> Eptifibatide was studied in three placebo-controlled, randomized studies, one (PURSUIT) in patients with acute coronary syndrome (unstable angina (UA) or non-Q-wave myocardial infarction (NQMI)), and two (ESPRIT and IMPACT II) in patients about to undergo a percutaneous coronary intervention (PCI).

9. The following sentence has been added to the **CLINICAL STUDIES** section, immediately following the first sentence:

10. The following heading has been inserted between the first and second paragraphs of the **CLINICAL STUDIES** section:

> **Acute Coronary Syndrome**

11. The following heading has been added between the second and third paragraphs of the **CLINICAL STUDIES** section:

> **PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using INTEGRILIN Therapy)**

12. "**PURSUIT**" is no longer bolded in the first sentence of the third paragraph of the **CLINICAL STUDIES** section.

13. The paragraph immediately following Figure 1 in the **CLINICAL STUDIES** section has been deleted.

14. In the second sentence of the second paragraph following Table 3 in the **CLINICAL STUDIES** section, the comma has been removed from "4,566."

15. The following heading has been added between the second and third paragraphs following Table 3 in the **CLINICAL STUDIES** section:

Percutaneous Coronary Intervention

16. The first sentence of the third paragraph following Table 3 in the **CLINICAL STUDIES** section has been changed from the following:

to the following:

17. The following sentence has been added between the second and third sentences in the fourth paragraph following Table 3 in the **CLINICAL STUDIES** section:

Forty-one percent of the patients underwent PCI for ongoing ACS.

18. In the "Eptifibatide (135/0.5)" column and "Death or MI/6 months" row (the next to the last row) of Table 4 in the **CLINICAL STUDIES** section, the parentheses that enclose 10.6% are incomplete.

19. The paragraph on the subpopulations studied in the IMPACT II study that immediately precedes Table 5 and Table 5 (Clinical Events at 30 Days in the IMPACT II Study, Stratified by Acuity at Time of Randomization) of the **CLINICAL STUDIES** section have been replaced with the following text and new Table 5:

ESPRIT (Enhanced Suppression of the Platelet IIb/IIIa Receptor with INTEGRILIN Therapy)

2 pages redacted from this section of the approval package consisted of draft labeling

20. The first sentence in the second bulleted indication in the **INDICATIONS AND USAGE** section has been changed from the following:

to the following:

> For the treatment of patients undergoing PCI, including those undergoing intracoronary stenting.

21. The last sentence of the **INDICATIONS AND USAGE** section has been changed from the following:

to the following:

> In the IMPACT II, PURSUIT and ESPRIT studies of eptifibatide, most patients received heparin and aspirin, as described in CLINICAL TRIALS.

22. The sixth and seventh bulleted statements in the **CONTRAINDICATIONS** section

23. The first sentence in the second paragraph of the **WARNINGS/Bleeding** subsection has been changed from the following:

to the following:

24. The following text has been added as the last two paragraphs of the **WARNINGS** section:

> **Renal insufficiency.** Eptifibatide is cleared in part by the kidney and its plasma concentration is expected to increase with decreasing renal function.

> **Platelet Count <100,000/mm^3.** Because it is an inhibitor of platelet aggregation, caution should be exercised when administering eptifibatide to patients with a platelet count <100,000/mm^3; there has been no clinical experience with eptifibatide initiated in patients with a platelet count <100,000/mm^3.

25. The second sentence in the **PRECAUTIONS/Bleeding Precautions/Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI)** subsection has been changed from the following:

to the following:

> After PCI, eptifibatide infusion should be continued until hospital discharge or up to 18-24 hours, whichever comes first.

26. The third sentence in the **PRECAUTIONS/Bleeding Precautions/Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI)** subsection

27. The former fourth sentence (it is now the third sentence) in the **PRECAUTIONS/Bleeding Precautions/Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI)** subsection has been changed from the following:

to the following:

> Heparin use is discouraged after the PCI procedure.

28. The last three sentences of the **PRECAUTIONS/Bleeding Precautions/Care of the Femoral Artery Access Site in Patients Undergoing Percutaneous Coronary Intervention (PCI)** subsection have been changed from the following:

to the following:

> Early sheath removal is encouraged while eptifibatide is being infused. Prior to removing the sheath it is recommended that heparin be discontinued for 3-4 hours and an aPTT of <45 seconds or ACT < 150 seconds be achieved. In any case, both heparin and eptifibatide should be discontinued and sheath hemostasis should be achieved at least 2-4 hours before hospital discharge.

29. The first sentence in the **PRECAUTIONS/Bleeding Precautions/Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents** subsection has been changed from the following:

to the following:

> In the IMPACT II, PURSUIT and ESPRIT studies, eptifibatide was used concomitantly with heparin and aspirin (see CLINICAL STUDIES).

30. The following sentence was added between the first and second sentences in the **PRECAUTIONS/Bleeding Precautions/Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents** subsection:

31. The next to the last sentence in the first paragraph of the **PRECAUTIONS/Bleeding Precautions/Use of Thrombolytics, Anticoagulants, and Other Antiplatelet Agents** subsection has been changed from the following:

to the following:

> Because eptifibatide inhibits platelet aggregation, caution should be employed when it is used with other drugs that affect hemostasis, including **thrombolytics, oral anticoagulants, non-steroidal anti-inflammatory drugs, and dipyridamole.**

32. The first sentence immediately following Table 6 in the **PRECAUTIONS/Bleeding Precautions/Maintaining Target aPTT and ACT** subsection has been changed from the following:

to the following:

> The ESPRIT study stipulated a target ACT of 200 to 300 seconds during PCI.

33. The second sentence following Table 6 in the **PRECAUTIONS/Bleeding Precautions/Maintaining Target aPTT and ACT** subsection has been revised from the following:

to the following:

> Patients receiving eptifibatide 180/2.0/180 (mean ACT 284 seconds) experienced an increased incidence of bleeding relative to placebo (mean ACT 276 seconds), primarily at the femoral artery access site. At these lower ACTs, bleeding was less than previously reported with eptifibatide in the PURSUIT and IMPACT II studies.

34. The first two sentences of the **PRECAUTIONS/Renal Insufficiency** subsection have been revised from the following:

to the following:

Based on results of the PURSUIT and ESPRIT studies and the fact that the drug is cleared equally by renal and nonrenal mechanisms, dose adjustment is unnecessary for patients with mild to moderate renal impairment (serum creatinine <2.0 mg/dL). For patients with serum creatinine between 2.0 mg/dL and 4.0 mg/dL, the infusion dose should be reduced to 1.0 µg/kg/min while the bolus dose(s) should remain unchanged.

35. The last sentence in the **PRECAUTIONS/GeriatricUse** subsection has been changed from the following:

to the following:

No dose adjustment was made for elderly patients, but patients over 75 years of age had to weigh at least 50 kg to be enrolled in the PURSUIT study; no such limitation was stipulated in the ESPRIT study (see also ADVERSE REACTIONS).

36. The first two paragraphs of the **ADVERSE REACTIONS** section have been changed from the following:

to the following:

These 16,782 patients had a mean age of 62 years (range 20 to 94 years). Eighty-nine percent of the patients were Caucasian, with the remainder being predominantly Black (5%) and Hispanic (5%). Sixty-eight percent were men.

Because of the different regimens used in PURSUIT, IMPACT II and ESPRIT, data from the three studies were not pooled.

37. The first sentence in the **ADVERSE REACTIONS/Bleeding** subsection has been revised to include the ESPRIT study, as follows:

The incidences of bleeding events and transfusions in the PURSUIT, IMPACT II and ESPRIT studies are shown in Table 7.

38. Table 7 in the **ADVERSE REACTIONS** section has been revised to include information on the ESPRIT study as follows:

Table 7

Bleeding Events and Transfusions in the PURSUIT, ESPRIT and IMPACT II Studies

39. The two paragraphs immediately following Table 7 in the **ADVERSE REACTIONS** section have been revised from the following:

to the following:

> The majority of major bleeding events in the ESPRIT study occurred at the vascular access site (1 and 8 patients, or 0.1% and 0.8% in the placebo and eptifibatide groups, respectively). Bleeding at "other" locations occurred in 0.2% and 0.4% of patients, respectively.
>
> In the PURSUIT study, the greatest increase in major bleeding in eptifibatide-treated patients compared to placebo-treated patients was associated with bleeding at the femoral artery access site (2.8% versus 1.3%). Oropharyngeal (primarily gingival), genito-urinary, gastrointestinal, and retroperitoneal bleeding were also seen more commonly in eptifibatide-treated patients compared to placebo-treated patients.
>
> Among patients experiencing a major bleed in the IMPACT II study, an increase in bleeding on eptifibatide versus placebo was observed only for the femoral artery access site (3.2% versus 2.8%).

40. The paragraph immediately preceding Table 8 in the **ADVERSE REACTIONS** section has been changed from the following:

to the following:

> Table 8 displays the incidence of TIMI major bleeding according to the cardiac procedures carried out in the PURSUIT study. The most common bleeding complications were related to cardiac revascularization (CABG-related or femoral artery access site bleeding). A corresponding table for ESPRIT is not presented as every patient underwent PCI in the ESPRIT study and only 11 patients underwent CABG.

41. .

42. The following paragraph has been added to immediately follow Table 8 in the **ADVERSE REACTIONS** section:

43. The last two paragraphs of the **ADVERSE REACTIONS/Bleeding** subsection have been changed from the following:

to the following:

> In the PURSUIT and ESPRIT studies, the risk of major bleeding with eptifibatide increased as patient weight decreased. This relationship was most apparent for patients weighing less than 70 kg.
>
> Bleeding adverse events resulting in discontinuation of study drug were more frequent among patients receiving eptifibatide than placebo (4.6% versus 0.9% in ESPRIT, 8% versus 1% in PURSUIT, 3.5% versus 1.9% in IMPACT II).

7 pages redacted from this section of the approval package consisted of draft labeling

Dr. Throckmorton has recommended this sentence be struck from the labeling and Dr. Lipicky has agreed. Therefore, this sentence will be struck through in the marked-up draft labeling that will accompany the approvable letter.

3. Remove the first or third sentence of the **ADVERSE REACTIONS/Allergic Reactions** subsection, as they are duplicate sentences.

4. Change the comma following the word "eptifibatide" in the text added to the end of the first paragraph of the **ADVERSE REACTIONS/Allergic Reactions** subsection to a period.

During the April 17th discussion, I also noted the addition of the word " to the drugs listed in the first sentence of point #2 under the **DOSAGE AND ADMINISTRATION /Instructions for Administration** subsection. Dr. Marsman could not say whether this was inadvertent or intentional and agreed to follow up on this. On April 18, 2001, Dr. Marsman left a voicemessage indicating that the addition of was inadvertent and that COR would remove this word from the final printed labeling.

Medical Review

In his April 6, 2001 review of this supplemental application, Dr. Throckmorton indicates that he has made some changes to the sponsor's proposed revised labeling and has included in his review a marked up version of the sponsor's proposed labeling. Dr. Throckmorton has indicated that he incorporated into this marked up labeling the changes recommended by Dr. Andrew Haffer of the Division of Drug Marketing, Advertising, and Communication (DDMAC) in his March 12, 2001 memorandum to Dr. Throckmorton regarding this supplemental application.

DDMAC

As indicated in the section above describing Dr. Throckmorton's medical review, Dr. Andrew Haffer of DDMAC recommended several changes to the sponsor's proposed labeling in a March 12, 2001 memorandum to Dr. Throckmorton. Dr. Throckmorton has indicated that he incorporated Dr. Haffer's recommendations in the marked up labeling Dr. Throckmorton included in his review.

Statistical

Dr. Hung does not include any labeling recommendations in his review of this application.

Clinical Pharmacology/Biopharmaceutics

Dr. Robbie did not include any labeling recommendations in his review of this application. However, upon circulation of the draft approvable letter and labeling, Dr. Robbie proposed a few changes to the

CLINICAL PHARMACOLOGY/Pharmacodynamics and **Pharmacokinetics** subsections.

Secondary Medical Review

Although Dr. Lipicky indicates in his April 26, 2001 memorandum that he could argue for a single dosing regimen (that of ESPRIT) in labeling, he does not do so. He indicates later in the memorandum that the **DOSAGE AND ADMINISTRATION** section will include two dosing regimens, one for Acute Coronary Syndrome and the other for Percutaneous Coronary Intervention. The marked up labeling to which he refers in his memorandum is a copy of Dr. Throckmorton's marked up labeling on which Dr. Lipicky has noted his concurrence with the proposed changes (Dr. Throckmorton's changes and the sponsor's changes that Dr. Throckmorton did not change).

Conclusion

As recommended by Dr. Lipicky, I will prepare an approvable letter (based on enclosed marked up draft labeling) for Dr. Lipicky's signature. The labeling that will accompany the letter will be Dr. Throckmorton's marked up version, with the changes discussed (mostly editorial) with Dr. Marsman and Dr. Robbie's changes.

/S/ 5/1/01

Colleen LoCicero, RHPM

71 pages redacted from this section of the approval package consisted of draft labeling