

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

**APPLICATION NUMBER
20-718/S-010**

Correspondence

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (650) 246-7776

Attention: Michael Marsman

Company Name: COR Therapeutics

Phone: (650) 244-6929

Subject: NDA 20-718/S-010 request for information

Date: 3/13/01

Pages including this sheet: 2

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Mike,

To facilitate the Division's review of this supplemental application, please complete the accompanying table and submit to the application the completed table. Please provide incidence as the number of events, the number of patients who used the given stent, and the percentage. If you have any questions, please let me know.

Regards,
Colleen

Table 3.3.10.4 Incidence of Primary Endpoint by Stent Use^{a,b}.

Stent Type	Placebo	Eptifibatide	% Reduction Relative/Absolute
DUET (n=479)	X/Y (z%)		
NIR (n=375)			
gix (n=239)			
MULTI-LINK (n=138)			
Cross-Flex (n=122)			

a. Primary endpoint Death/MI/UTVR/TBO at 48 hrs.

b. All events as adjudicated by the Central Events Classification Committee (CEC).

**APPEARS THIS WAY
ON ORIGINAL**

**APPEARS THIS WAY
ON ORIGINAL**

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (650) 246-7776

Attention: Mike Marsman

Company Name: COR Therapeutics

Phone: (650) 244-6929

Subject: NDA 20-718/S-010 request for information

Date: 3-9-01

Pages including this sheet: 1

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Mike,

Dr. Throckmorton has the following request regarding this supplemental application:

Please submit the demographics of the stents used in the ESPRIT study. Additionally, for any stent used in a substantial number of subjects (500 or more), please provide an analysis of the primary endpoints by treatment group.

If you have any questions, please let me know.

Regards,
Colleen

djsk

**DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION**



US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

This document is intended only for the use of the party to whom it is addressed and may contain information that is privileged, confidential, and protected from disclosure under applicable law. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to: CDER, DCRDP (HFD-110); 5600 Fishers Lane; Rockville, MD 20857

Transmitted to FAX Number: (650) 246-7776

Attention: Mike Marsman

Company Name: COR Therapeutics

Phone: (650) 244-6929

Subject: request from Dr. Throckmorton

Date: 1/25/01

Pages including this sheet: 2

From: Colleen LoCicero
Phone: 301-594-5332
Fax: 301-594-5494

Mike,

Attached is a request from Dr. Throckmorton for some information relating to NDA 20-718/S-010.

Regards,
Colleen

cc: NDA 20-718/S-010
HFD-110
HFD-110/LoCicero

Mike:

1.25.01

Three questions regarding the ESPRIT study, along with some tables I'd like filled in. Thanks.

1. Please provide the incidence of the primary endpoint stratified by use of clopidogrel or ticlopidine.
2. The clinical events were initially reviewed by the Cardiology Fellow, but 5% were to be re-audited by Faculty. What faculty, and what were the results of those re-audits? Section 16.1.9.10.19.
3. Please give me data on Death/MI endpoint using investigator-designated MIs at 48 hours and 30 days.
4. Please fill in missing values.

Table 6.2.3.12.1.1 Demographics of ESPRIT^a.

Baseline Characteristic	Placebo N = 1024	Eptifibatide N=1040
Age, years		
Mean (sd)	6211	6211
Age Group, n (%)		
< 65 years		
65 - 74 years		
75 years		
Gender, n (%)		
Male	742 (72.5%)	760 (73.1%)
Female	282 (27.5%)	280 (26.9%)
Race, n (%)		
White	930 (90.8%)	927 (89.1%)
Black	43 (4.2%)	52 (5.0%)
Hispanic	21 (2.1%)	21 (2.0%)
Asian	11 (1.1%)	16 (1.5%)
Other	19 (1.8%)	43 (4.1%)
Weight, kg		
Mean (sd)	86.618	85.118
Enrollment by Nation		
U.S.		
Canada		

a. Data from ESPRIT study report, table 11-1.



LoCoco

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JUL 12 2000

NDA 20-718/S-010

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

Dear Dr. Marsman:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Integrilin (eptifibatide) Injection

NDA Number: 20-718

Supplement Number: S-010

Therapeutic Classification: Standard (S)

Date of Supplement: June 29, 2000

Date of Receipt: June 30, 2000

This supplement proposes the following changes:

1. The addition of a new "front loaded" dosing regimen for patients undergoing percutaneous coronary intervention (PCI).
2. The substitution of the ESPRIT dosing regimen for the IMPACT II dosing recommendation for use in PCI.
3. A change in the recommended target range for the activated clotting time (ACT) during PCI.
4. The movement of information regarding renal insufficiency and thrombocytopenia from the CONTRAINDICATIONS section to the WARNINGS section of the package insert.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 29, 2000 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 30, 2001 and the secondary user fee goal date will be June 30, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal Service:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products,
HFD-110
Attention: Division Document Room,
HFD-110
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products,
HFD-110
Attention: Division Document Room,
HFD-110
1451 Rockville Pike
Rockville, Maryland 20852-1420

If you have any questions, please call:

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

Sincerely yours,

/s/

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research



ORIGINAL

June 29, 2000

Food and Drug Administration
Center for Drug Evaluation and Research
Cardio-Renal Drug Products, HFD-110
WOC2, 5th Floor
1451 Rockville Pike
Rockville, MD 20852

~~NDA 20-718 REF. NO. 010~~
NDA Supplement ~~98 SE2~~
Check & per/CSO

SUBJECT: INTEGRILIN[®] (eptifibatide) Injection
NDA 20-718
CLINICAL SUPPLEMENT

References:

1. Protocol number 98-025, "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" (IND ~~Serial No. 242, submitted 12/15/98~~)
2. Pre-supplement meeting with the Cardio-Renal Division at FDA, April 19, 2000
3. Protocol number 96-023b, "A Randomized Open Label Evaluation of the Pharmacodynamics and Safety of Four Dosing Regimens of Integrilin in Patients undergoing Percutaneous Coronary Intervention: A Sub-study of the PRIDE Protocol (IND ~~Serial No. 209, submitted 4/18/97~~)

This supplement is being submitted to support revisions to the current product labeling for INTEGRILIN[®] (eptifibatide) Injection (Rev. #6) in the following key areas:

1. The addition of a new "front loaded" dosing regimen designed to provide inhibition of platelet aggregation at the critical timepoint during percutaneous coronary intervention (PCI) consisting of a 180 µg/kg bolus, an infusion of 2 µg/kg/min, and a second 180 µg/kg bolus 10 minutes after the first bolus (180/2.0/180). The addition of this double bolus dosing regimen is based on results of the ESPRIT clinical study, which unequivocally demonstrated a reduction in ischemic events in patients who received eptifibatide while undergoing percutaneous coronary intervention (PCI) with stent

placement. A statistically significant reduction was observed at 48 hours for the primary endpoint of death, myocardial infarction (MI), urgent target vessel revascularization (UTVR) and/or need for "bail-out" to open label GP IIb/IIIa inhibition due to a thrombotic complication of PCI (TBO) among patients who received eptifibatide. Statistically significant reductions were maintained for eptifibatide-treated patients in the incidence of the key secondary endpoint (a composite of death, MI and/or UTVR) at 30 days and the prespecified composite endpoint of death and/or MI at both 48 hours and 30 days. Further, the results of the study demonstrated a strong safety profile for the INTEGRILIN dosing regimen used in ESPRIT.

2. The substitution of the ESPRIT 180/2.0/180 dosing regimen for the IMPACT II dosing recommendation of a 135 µg/kg bolus followed by a 0.5 µg/kg/min infusion for use in PCI. This change is based on the results of the ESPRIT Study, which show that the new proposed regimen of 180/2/180, which achieves early and persistent high level GP IIb/IIIa receptor blockade, is safe and effective in patients undergoing contemporary PCI.
3. A change in the recommended target range for the activated clotting time (ACT) during PCI to 200-300 seconds based on the ESPRIT Study.
4. The movement of information regarding renal insufficiency and thrombocytopenia from the **Contraindications** section to the **Warnings** section since there is no evidence for specific harm in patients with either one of these disorders.

Other minor revisions have been made as noted in the proposed revised labeling included herein (Vol. 1, Section 2A).

In addition to the final study report for the ESPRIT clinical study, which supports most of the changes being requested in this submission, this supplement also contains the final study report for the PRIDE Sub-study, which evaluated the pharmacokinetic and pharmacodynamic effects of a double-bolus dosing regimen of eptifibatide. This study demonstrated that a second bolus of eptifibatide was necessary to achieve inhibition of platelet aggregation and receptor occupancy at early time points that were similar to those achieved at steady-state. The information from the PRIDE Sub-study contributed to the design of the ESPRIT clinical trial.

In support of the proposed labeling revisions described above, COR is supplementing NDA 20-718 as indicated in the enclosed "Overall Table of Contents". This Table of Contents, including the sections not being amended, was agreed to in a meeting with the Cardio-Renal Division held at FDA on April 19, 2000. At this same meeting, it was agreed that case report form (CRF) tabulations would not be included in this supplement. Furthermore, in a June 23, 2000 telephone conversation between Colleen LoCicero of FDA and Arleen Glenn of COR,

it was agreed that CRFs for deaths and discontinuations due to adverse events would be included as part of the ESPRIT electronic study report on CD-ROM and not as paper copies.

In addition to the paper copies of the supplement, also enclosed are CD-ROMs containing the following documentation:

- ESPRIT Study and PRIDE Sub-study final study reports in PDF (one disc, 2 copies)
- Case Report Forms for deaths and discontinuations due to adverse events in PDF (one disc, 2 copies)
- The electronic data sets and user manual (two discs, 2 copies of each)

For ease of review, the ESPRIT Study and PRIDE Sub-study reports on CD-ROM include "hyperlinks" between the tables of contents and the sections listed in the tables of contents, and between text and referenced tables and listings.

COR is requesting a six-month priority review of the enclosed clinical supplement.

As was pointed out in the filings made to the Division during the time period when the ESPRIT trial was on a clinical hold (Serial Nos. 251 and 252, dated 3/04/99 and 3/12/99 respectively), GP IIb/IIIa inhibitors in PCI are not as widely utilized as one might assume, given their compelling contribution to an improved outcome. This situation exists for a number of reasons, not the least of which are concerns about the risk of bleeding and the cost factor. The compelling results of the ESPRIT clinical study not only confirm the benefits of INTEGRILIN[®], but establish a new dosing regimen for INTEGRILIN in PCI that is both safe and compatible with current procedures, i.e., stent placement. Furthermore, this dosing regimen was based on careful analysis of the pharmacokinetics and pharmacodynamics of the drug so that high level blockade of platelet GP IIb/IIIa receptors was achieved early (i.e. at the time of stent placement) and maintained throughout the entire infusion period. COR's request for a priority review is therefore based on the following:

- ESPRIT has significantly added to the body of knowledge that small molecule, reversible GP IIb/IIIa inhibitors in PCI reduce thrombotic events;
- Currently, GP IIb/IIIa inhibitors are not routinely used in PCI, primarily because of expense. ESPRIT was undertaken with INTEGRILIN as a more cost-effective therapy than the current standard, to demonstrate superiority to placebo in reducing adverse outcomes in patients undergoing contemporary PCI; and
- Based on INTEGRILIN's demonstration of efficacy and an excellent benefit to risk profile, along with the lower cost of therapy, GP IIb/IIIa usage should now be made available to the large majority of patients undergoing PCI who are not currently afforded the benefit of treatment.

In accordance with Section 306(k) of the Food, Drug and Cosmetics Act, COR certifies that, with respect to this NDA supplement, it did not and will not knowingly use the services of any persons that have been debarred under the provisions of Section 306(a) or (b) of the Act.

Please be advised that material and data in this supplement are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j).

The Applicant contact is:

Michael R. Marsman, Pharm.D.

Director, Regulatory Affairs

Phone: (650) 244-6929

FAX: (650) 246-7776

Address:

COR Therapeutics Inc.

256 East Grand Avenue

South San Francisco, CA 94080

Please contact me at (650) 244-6929 regarding any questions or clarifications that may arise during the review process.

Sincerely,



Michael R. Marsman, Pharm.D.

Director, Regulatory Affairs

Cc: Colleen LoCicero, Project Coordinator, HFD-110