DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration
CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396 Expiration Date: April 30, 2009.

#### TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

tors	See "FDA-3454 Attachment-H7T-MC-TABR"	
iga	· · · · · · · · · · · · · · · · · · ·	· · · · · · · · · · · · · · · · · · ·
vesi		×
al In		2
nic		
Ü	· ·	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
William Macias, M.D.	Senior Medical Fellow II (Medical Director)
FIRM / ORGANIZATION	
Eli Lilly and Company	
SIGNATURE	DATE
hill have	10/12/2007
Paperwork Red	luction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing netructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville. MD 20857

FORM FDA 3454 (4/06)

PSC Graphics: (301) 443-1090 EF

# \_\_ Page(s) Withheld

10 PS 8 2 2 3

\_ Trade Secret / Confidential (b4)

\_\_\_\_ Draft Labeling (b4)

\_\_\_ Draft Labeling (b5)

\_\_\_\_ Deliberative Process (b5)

 $\underline{X}$  Personal Privacy (b6)

CE		Food and Drug Adr	ND HUMAN SERVICES ninistration		Form Approved: OMB No. 0910-0396 Expiration Date: April 30, 2009.	8
ARR	ANGEMEN	TS OF CLIN	CAL INVESTI	GATORS		
			TO BE COMPLETED BY	APPLICANT		
uppot o ertificatio	of this application is made in c	on, I certify to ompliance with	one of the statem 21 CFR part 54 ar	ents below as a d that for the pu	below (if appropriate)) submitted in appropriate. I understand that this rposes of this statement, a clinical as defined in 21 CFR 54.2(d).	
			Please mark the applic	able checkbox.	]	
wi th sti to th	with the listed cli his form) where tudy as defined the sponsor w he sponsor as (	nical investigato by the value of co in 21 CFR 54.2 hether the inves defined in 21 CF	rs (enter names of compensation to the a). I also certify that tigator had a propri R 54.2(b) did not	clinical investigate investigator could t each listed clinic etary interest in the disclose any suc	ered into any financial arrangement ors below or attach list of names to d be affected by the outcome of the cal investigator required to disclose his product or a significant equity in h interests. I further certify that no orts as defined in 21 CFR 54.2(f).	
	See "FDA-34	454 Attachment-H	7T-EW-TACS"			
in the second			· · · · · · · · · · · · · · · · · · ·	· ·		
al leave						
ĉ	ō				**	
ap in fir in	pplicant, 1 certinvestigators, the nancial arrange nvestigator for d	fy that based on e listed clinical in ement with the s conducting the s	n information obtain vestigators (attach ponsor of a covere tudy could be affe	ined from the sp list of names to ed study whereby cted by the outco	by a firm or party other than the onsor or from participating clinical this form) did not participate in any the value of compensation to the ome of the study (as defined in 21 the compart in the propert of	
ap in fir C th ot ] (3) As ap (a	pplicant, 1 certi nvestigators, the nancial arrange nvestigator for o CFR 54.2(a)); has covered stud ther sorts (as d as the applican pplicant, 1 certi attach list of nati	fy that based of a listed clinical in ment with the s conducting the s ad no proprietan dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the	n information obtain vestigators (attach ponsor of a covere tudy could be affe- y interest in this pr 21 CFR 54.2(b)); a 54.2(f)). ting a study or stu- cted with due dilig	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored rence to obtain fin nation required ur	onsor or from participating clinical this form) did not participate in any y the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to	
ap in fir C th ot (a (a do NAME	pplicant, 1 certi nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certi attach list of nan o so. The reaso	fy that based of a listed clinical in ment with the s conducting the s ad no proprietan dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the	n information obtain vestigators (attach ponsor of a covere tudy could be affer y interest in this pro- 21 CFR 54.2(b)); a 54.2(f)). ting a study or stat cted with due dilig sponsor the inform	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fin hation required ur obtained is attac	onsor or from participating clinical this form) did not participate in any the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators inder 54.4 and it was not possible to hed.	
ap in fir C th ot (a (a (a MAME William M	pplicant, 1 certi nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); has the covered stud- ther sorts (as d as the applican pplicant, 1 certi attach list of nan- o so. The reason Macias, M.D.	fy that based of a listed clinical in ment with the s conducting the s ad no proprietan dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the	n information obtain vestigators (attach ponsor of a covere tudy could be affer y interest in this pro- 21 CFR 54.2(b)); a 54.2(f)). ting a study or stat cted with due dilig sponsor the inform	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fin hation required ur obtained is attac	onsor or from participating clinical this form) did not participate in any y the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to	
ap in fir C th ot (3) As ap (a do NAME William M	pplicant, 1 certi nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certi attach list of nan o so. The reaso	fy that based of a listed clinical in ment with the s conducting the s ad no proprietan dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the	n information obtain vestigators (attach ponsor of a covere tudy could be affer y interest in this pro- 21 CFR 54.2(b)); a 54.2(f)). ting a study or stat cted with due dilig sponsor the inform	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fin hation required ur obtained is attac	onsor or from participating clinical this form) did not participate in any the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators inder 54.4 and it was not possible to hed.	
ap in fir C th ot (3) As ap (a do NAME William M	pplicant, 1 certi nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certi attach list of nan to so. The reason Macias, M.D. and Company	fy that based of a listed clinical in ment with the s conducting the s ad no proprietan dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the	n information obtain vestigators (attach ponsor of a covere tudy could be affer y interest in this pro- 21 CFR 54.2(b)); a 54.2(f)). ting a study or stat cted with due dilig sponsor the inform	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fin hation required ur obtained is attac	onsor or from participating clinical this form) did not participate in any the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators inder 54.4 and it was not possible to hed.	•
ap in fir C th ot (a (a (a (a (a (a (a (a (a (a (a (a (a	pplicant, 1 certi nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certi attach list of nan to so. The reason Macias, M.D. and Company	fy that based o e listed clinical ir ement with the s conducting the s ad no proprietary dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the on why this inforr	n information obtain vestigators (attach ponsor of a covera- tudy could be affer y interest in this pr 21 CFR 54.2(b)); 54.2(f)). ting a study or stu- cted with due dilig sponsor the inform nation could not be	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored rence to obtain fination required ur obtained is attac	onsor or from participating clinical this form) did not participate in any the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to hed.	
ap in fir in Cl th ot (1) (3) As ap (3) (3) As ap (3) (3) As ap (3) (3) As ap (3) As (3) As (3) As (3) As (3) As (3) As (3) As (3) As (3) As (3) (3) As (3) (3) (3) (3) (3) (3) (3) (3) (3) (3)	pplicant, 1 certin nestigators, the nancial arrange nestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certin attach list of nan to so. The reason Macias, M.D. AGANIZATION and Company RE	fy that based o e listed clinical ir ement with the s conducting the s ad no proprietar dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the on why this inforr why this inforr pr. and a person is no dy valid OMB control to average I hour per sources, gathering an tion of information.	n information obtain vestigators (attach ponsor of a covere tudy could be affer y interest in this pro- 21 CFR 54.2(b)); a 54.2(f)). ting a study or stat cted with due dilig sponsor the inform	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fination required ur obtained is attac TITLE Senior Medical F	onsor or from participating clinical this form) did not participate in any the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to hed.	
ap in fir in Cl th ot (1) (3) As ap (3) (3) As ap (3) (3) As ap (3) (3) As ap (3) As (3) As (3) As (3) As (3) As (3) As (3) As (3) As (3) As (3) (3) As (3) (3) (3) (3) (3) (3) (3) (3) (3) (3)	pplicant, 1 certin nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certin attach list of nan to so. The reason Macias, M.D. AGANIZATION and Company RE	fy that based o e listed clinical ir ement with the s conducting the s ad no proprietar dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the on why this inforr why this inforr pr. and a person is no dy valid OMB control to average I hour per sources, gathering an tion of information.	aperwork Reduction trequired to respond to mation could be affect (a table of the standard (b table of the standard (c table of the standard) (c table of ta	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fination required ur obtained is attac TITLE Senior Medical F	onsor or from participating clinical this form) did not participate in any the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to hed. DATE IO $II2$ $I2007Department of Health and Human ServicesFood and Drug Administration5600 Fishers Lane, Room 14C-03$	1-1090 EF
ap in fir in C th ot (1) (3) As ap (1) (3) As ap (1) (3) As ap (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)	pplicant, 1 certin nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certin attach list of nan to so. The reason Macias, M.D. AGANIZATION and Company RE	fy that based o e listed clinical ir ement with the s conducting the s ad no proprietar dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the on why this inforr why this inforr pr. and a person is no dy valid OMB control to average I hour per sources, gathering an tion of information.	aperwork Reduction trequired to respond to mation could be affect (a table of the standard (b table of the standard (c table of the standard) (c table of ta	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fination required ur obtained is attac TITLE Senior Medical F	onsor or from participating clinical this form) did not participate in any $\gamma$ the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators inder 54.4 and it was not possible to hed. DATE 10 / 12 / 200 7 Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857	1-1090 EF
ap in fir in C th ot (1) (3) As ap (1) (3) As ap (1) (3) As ap (1) (1) (1) (1) (1) (1) (1) (1) (1) (1)	pplicant, 1 certin nvestigators, the nancial arrange nvestigator for of CFR 54.2(a)); ha ne covered stud ther sorts (as d as the applican pplicant, 1 certin attach list of nan to so. The reason Macias, M.D. AGANIZATION and Company RE	fy that based o e listed clinical ir ement with the s conducting the s ad no proprietar dy (as defined in efined in 21 CFF t who is submit fy that I have a mes) or from the on why this inforr why this inforr pr. and a person is no dy valid OMB control to average I hour per sources, gathering an tion of information.	aperwork Reduction trequired to respond to mation could be affect (a table of the standard (b table of the standard (c table of the standard) (c table of ta	ined from the sp list of names to ed study whereby cted by the outco oduct or significa and was not the udies sponsored ence to obtain fination required ur obtained is attac TITLE Senior Medical F	onsor or from participating clinical this form) did not participate in any $\gamma$ the value of compensation to the ome of the study (as defined in 21 int equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators inder 54.4 and it was not possible to hed. DATE 10 / 12 / 200 7 Department of Health and Human Services Food and Drug Administration 5600 Fishers Lane, Room 14C-03 Rockville, MD 20857	►1090 EF

# \_\_\_\_ Page(s) Withheld

\_ Trade Secret / Confidential (b4)

\_\_\_\_ Draft Labeling (b4)

\_\_\_ Draft Labeling (b5)

\_ Deliberative Process (b5)

 $\underline{\chi}$  Personal Privacy (b6)

			TO BE COMPLE	TED BY APPLICANT	
suppo certific	rt of ation	this application, I is made in compl	inical studies (or specific certify to one of the s iance with 21 CFR part	c clinical studies listed statements below as a 54 and that for the pu	below (if appropriate)) submitted in appropriate. I understand that this urposes of this statement, a clinical as defined in 21 CFR 54.2(d).
			Please mark the	e applicable checkbox.	
⊠ (1)	with this stuc to the	the listed clinical form) whereby the dy as defined in 21 he sponsor whethe sponsor as define	investigators (enter name value of compensation CFR 54.2(a). I also cert or the investigator had a ed in 21 CFR 54.2(b) di	tes of clinical investigat to the investigator coul ify that each listed clini proprietary interest in t d not disclose any suc	ered into any financial arrangement tors below or attach list of names to id be affected by the outcome of the ical investigator required to disclose his product or a significant equity in ch interests. I further certify that no orts as defined in 21 CFR 54.2(f).
	ators	See "FDA-3454 A	ttachment-H7T-EW-TAAV	N"	
	Clinical Investigators		· · ·		3
	Clinica		· · · · · · · · · · · · · · · · · · ·		
(2)	app inve	estigators, the liste	at based on information ed clinical investigators (	attach list of names to	consor or from participating clinical this form) did not participate in any
□ (2)	app inve fina inve CFI the othe As app (atta	licant, I certify that estigators, the liste incial arrangement estigator for condu R 54.2(a)); had no covered study (as er sorts (as defined the applicant who licant, I certify that ach list of names)	at based on information ed clinical investigators ( it with the sponsor of a c ucting the study could be proprietary interest in t is defined in 21 CFR 54.2 d in 21 CFR 54.2(f)).	attach list of names to covered study whereby e affected by the outco his product or significa 2(b)); and was not the or studies sponsored e diligence to obtain f information required up	this form) did not participate in any y the value of compensation to the ome of the study (as defined in 21 ant equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to
(3)	app inve fina inve CFI the othe As app (atta do s	licant, I certify that estigators, the liste incial arrangement estigator for condu R 54.2(a)); had no covered study (as er sorts (as defined the applicant who plicant, I certify that ach list of names) so. The reason wh	at based on information ed clinical investigators ( it with the sponsor of a c ucting the study could be proprietary interest in t is defined in 21 CFR 54.2 d in 21 CFR 54.2(f)).	attach list of names to covered study whereby e affected by the outco his product or significa 2(b)); and was not the or studies sponsored e diligence to obtain f information required un to be obtained is attac	this form) did not participate in any y the value of compensation to the ome of the study (as defined in 21 ant equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to shed.
(3) NAME Willia FIRM	app inve fina inve CFI the othe As app (att do s	licant, I certify that estigators, the liste incial arrangement estigator for condu R 54.2(a)); had no covered study (as er sorts (as defined the applicant who licant, I certify that ach list of names)	at based on information ed clinical investigators ( it with the sponsor of a c ucting the study could be proprietary interest in t is defined in 21 CFR 54.2 d in 21 CFR 54.2(f)).	attach list of names to covered study whereby e affected by the outco his product or significa 2(b)); and was not the or studies sponsored e diligence to obtain f information required un to be obtained is attac	this form) did not participate in any y the value of compensation to the ome of the study (as defined in 21 ant equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to
I (3) NAME Willia FIRM Eli Li	app inve fina inve CFI the othe As app (att do s	licant, I certify that estigators, the listed incial arrangement estigator for condu R 54.2(a)); had no covered study (as er sorts (as defined the applicant who plicant, I certify that ach list of names) so. The reason wh actias, M.D. ANIZATION d Company	at based on information ed clinical investigators ( it with the sponsor of a c ucting the study could be proprietary interest in t is defined in 21 CFR 54.2 d in 21 CFR 54.2(f)).	attach list of names to covered study whereby e affected by the outco his product or significa 2(b)); and was not the or studies sponsored e diligence to obtain f information required un to be obtained is attac	this form) did not participate in any y the value of compensation to the ome of the study (as defined in 21 ant equity interest in the sponsor of recipient of significant payments of by a firm or party other than the rom the listed clinical investigators nder 54.4 and it was not possible to shed.

# Page(s) Withheld

\_\_\_\_ Trade Secret / Confidential (b4)

\_\_\_\_ Draft Labeling (b4)

\_ Draft Labeling (b5)

\_\_\_ Deliberative Process (b5)

 $\times$  Personal Privacy (b6)



### DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration Rockville, MD 20857

NDA 22-307

Eli Lilly and Company Attention: Elizabeth C. Bearby, Pharm.D. Director, U.S. Regulatory Affairs Lilly Corporate Center Indianapolis, IN 46285

Dear Dr. Bearby:

Please refer to your December 26, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Effient (prasugrel) 5 and 10 mg Tablets.

#### **RISK EVALUATION AND MITIGATION STRATEGY REQUIREMENTS**

Section 505-1 of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if FDA determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)).

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Effient (prasugrel) to ensure that the benefits of the drug outweigh the risk of major bleeding.

Your proposed REMS must include the following:

Medication Guide: As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Effient (prasugrel) poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Effient (prasugrel). FDA has determined that Effient (prasugrel) is a product for which patient labeling could help prevent serious adverse events; that it has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Effient (prasugrel); that the Medication Guide is important to health; and patient adherence to directions for use is crucial to the drug's effectiveness. Under 21 CFR 208, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Effient (prasugrel).

Under 21 CFR 208.24(d), you are responsible for ensuring that the label of each container or package includes a prominent and conspicuous instruction to authorized dispensers to provide a Medication Guide to each patient to whom the drug is dispensed, and states how the Medication Guide is provided. You should submit marked up carton and container labels of all strengths and formulations with the required statement alerting the dispenser to provide the Medication Guide. We recommend the following language dependent upon whether the Medication Guide accompanies the product or is enclosed in the carton (for example, unit of use):

- N23-307 p. 2
  - "Dispense the enclosed Medication Guide to each patient." or
  - "Dispense the accompanying Medication Guide to each patient."

The communication plan must include, at minimum, the following:

- 1. A Dear Health Care Provider letter and a Prescriber's Brochure.
- 2. An Introductory Letter that describes the patient populations identified as having the highest risk of bleeding associated with Effient (prasugrel).
- 3. A description of the audience for the communication plan, stating specifically the types and specialties of healthcare providers to which the communication plan will be directed as well as any professional medical associations and societies that will be sent the communications. The health care providers may include interventional cardiologists, clinical cardiologists, emergency medicine physicians, internal medicine and primary care physicians, and other physician specialties involved in the care of Acute Coronary Syndrome (ACS) patients managed with percutaneous coronary intervention (PCI) (e.g., surgeons, gastroenterologists).
- 4. A schedule for when and how the plan's materials are to be distributed to healthcare providers and medical associations.

Append all educational materials to the proposed REMS.

**Timetable for Submission of Assessments:** The proposed REMS must include a timetable for submission of assessment that shall be no less frequent than by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July  $31^{st}$  should conclude no earlier than June  $1^{st}$ .

Your proposed REMS submission should include two parts: a "proposed REMS" and a "REMS supporting document." Attached is a template for the proposed REMS that you should complete with concise, specific information (see Appendix A). Include information in the template that is specific to your proposed REMS for Effient (prasugrel). Additionally, all relevant proposed REMS materials, including educational and communication materials, should be appended to the proposed REMS. Once FDA finds the content acceptable and determines that the application can be approved, we will include these documents as an attachment to the approval letter that includes the REMS. The REMS, once approved, will create enforceable obligations.

b(4)

N23-307 p. 3

The REMS Supporting Document should be a document explaining the rationale for each of the elements included in the proposed REMS (see Appendix B).

The REMS assessment plan should include but may not be limited to:

a. An evaluation of patients' understanding of the serious risks of Effient (prasugrel)

b. Periodic assessments of the distribution and dispensing of the Introductory Letter and Prescriber Brochure, and the Medication Guide in accordance with 21 CFR 208.24.

c. Any information regarding failures to adhere to distribution and dispensing requirements of the Medication Guide, and corrective actions taken to address noncompliance.

d. A determination as to whether modifications to the REMS are needed (e.g., as a result of new safety information).

Before we can continue with our evaluation of this NDA, you will need to submit the proposed REMS.

Prominently identify the proposed REMS submission with the following wording in bold capital letters at the top of the first page of the submission.

#### NDA 22-307 PROPOSED REMS

Prominently identify subsequent submissions related to the proposed REMS with the following wording in bold capital letters at the top of the first page of the submission:

#### NDA 22-307 PROPOSED REMS-AMENDMENT

If you do not submit electronically, please send 5 copies of REMS-related submissions.

If you have any questions, please call:

Ms. Meg Pease-Fye, M.S., R.A.C. Regulatory Health Project Manager (301) 796-1130

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D. Director Division of Cardiovascular and Renal Products Office of Drug Evaluation I Center for Drug Evaluation and Research N23-307 p. 4

#### APPENDIX A

#### APPENDIX A- REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number Trade Name (DRUG NAME) Class of Product as per label

> Applicant name Address Contact Information

#### PROPOSED RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S): List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document

C. Elements To Assure Safe Use

### If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B),(C), and (D), listed above.

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7<sup>th</sup> year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

N23-307 p. 6

### APPENDIX B: SUPPORTING DOCUMENT

The REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section four the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks

- 1. Table of Contents
- 2. Background
- 3. Goals
- 4. Supporting Information on Proposed REMS Elements
  - a. Additional Potential Elements
    - i. Medication Guide
    - ii. Patient Package Insert
    - iii. Communication Plan
  - b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
  - c. Implementation System
  - d. Timetable for Submission of Assessments of the REMS (for products approved under an NDA or BLA)
- 5. REMS Assessment Plan (for products approved under a NDA or BLA)
- 6. Other Relevant Information

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/ Norman Stockbridge 6/4/2009 05:12:26 PM