CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-291

OTHER REVIEWS

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Pediatric and Maternal Health Staff
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MATERNAL HEALTH TEAM REVIEW

Date: May 15, 2008 **Date Consulted:** March 26, 2008

From: Richardae Araojo, Pharm.D.
Regulatory Reviewer, Pediatric and Maternal Health Staff

Through: Karen Feibus, MD
Medical Team Leader, Pediatric and Maternal Health Staff

Lisa Mathis, MD
Associate Director, Pediatric and Maternal Health Staff

To: Division of Medical Imaging and Hematology Products (DMIHP)

Drug: NDA 22-291; Promacta (eltrombopag olamine)

Subject: New Molecular Entity/Orphan Product for the short-term treatment of chronic idiopathic thrombocytopenia purpura (ITP)

Materials Reviewed: Relevant data submitted in NDA 22-291, FDA and GlaxoSmithKline Advisory Committee Meeting Background Packages, Interim Clinical Review, Office of Surveillance and Epidemiology (OSE) Review, and Draft Pharmacology/Toxicology Review

Consult Question: Please review the Pregnancy and Nursing Mothers sub-sections of labeling.

EXECUTIVE SUMMARY

DMIHP requested that the Maternal Health Team (MHT) recommend language for the Pregnancy and Nursing Mothers subsections of eltrombopag proposed labeling and address proposed post-marketing studies designed to gather data on the use of eltrombopag by pregnant and breastfeeding women.

On December 19, 2007, GlaxoSmithKline (GSK) submitted a new orphan drug application (NDA 22-291) to the Division of Medical Imaging and Hematology Products (DMIHP) for Promacta (eltrombopag olamine) tablets. Eltrombopag is a thrombopoietin receptor agonist that interacts with the transmembrane domain of the human thrombopoietin receptor. This interaction initiates signaling cascades similar, but not identical, to that of endogenous thrombopoietin, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

The sponsor's proposed indication for eltrombopag is short-term (six week) treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding. Eltrombopag is a small molecular weight compound administered orally with a proposed dose of 50 mg daily (25 mg for East Asians), which may be increased to 75 mg daily if the platelet count remains below 50,000/mcL after three weeks of therapy. b(4)

GSK submitted two randomized, double-blind, placebo-controlled studies of similar design that demonstrated efficacy based on a primary efficacy endpoint of platelet count ≥ 50,000/mcL by the end of treatment. The sponsor and FDA clinical reviewers identified nine major safety concerns during the clinical development program for eltrombopag: (1) hepatobiliary toxicity, (2) worsening thrombocytopenia following discontinuation of eltrombopag, (3) bone marrow reticulin formation/marrow fibrosis, (4) thromboembolic events, (5) cataract formation, (6) renal tubular toxicity, (7) phototoxicity, (8) malignancy progression, and (9) potential off label use.

ITP is predominantly a disease of young adults, particularly females. Estimates of ITP incidence during pregnancy vary widely and has been reported to range from 1/1,000 to 1/10,000.[1] Current treatment of ITP in pregnancy includes IVIG, corticosteroids, and/or splenectomy. Eltrombopag, an oral product under review for the short-term treatment of previously-treated patients with chronic ITP, may be considered an option for pregnant woman who fail current available therapies. Pregnant women may uniquely benefit from short-term eltrombopag therapy to increase their platelet count above 50,000 at time of delivery (women in labor with platelets less than 50,000 require platelet transfusion).

If approved, eltrombopag will be a new, novel, once daily, oral therapy for short-term use. However, ITP is a chronic disease and GSK has only submitted data to support six week use of eltrombopag. Even with limited data, the possibility exists that women with ITP, who are of childbearing potential, may conceive while on eltrombopag therapy, resulting in inadvertent exposure to the drug. During pregnancy, women with ITP may fail currently available therapies, and a clinician may choose to prescribe eltrombopag after considering the serious risks associated with treatment and the benefits of the drug to the mother. Other considerations include the need to collect pharmacokinetic data in pregnant women to determine the dose that b(4)

optimizes efficacy and safety in this population and the need for information about the levels of eltrombopag in breast milk and potential adverse effects in breastfeeding infants.

RECOMMENDATIONS

1. The MHT recommends that the sponsor develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to eltrombopag during pregnancy to an unexposed control population. The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, thrombotic events, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at http://www.fda.gov/cder/guidance/3626fnl.htm.

2. The MHT recommends that — conduct a milk only lactation study in a subset of women enrolled in the pregnancy registry, who choose to breastfeed their infants. This study should be designed to detect the presence and concentration of eltrombopag in breast milk and any effects on milk production and composition. The study should include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. This study should be conducted as a post marketing requirement for this application. Changes are currently being made to the Draft Guidance for Industry on Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, http://www.fda.gov/cder/guidance/5918dft.pdf. The Maternal Health Team can answer questions surrounding current thinking on protocol design.

b(5)

4. The MHT recommended revisions to the sponsors proposed labeling are provided on pages 13-14 of this review.

INTRODUCTION

On December 19, 2007, GlaxoSmithKline (GSK) submitted a new orphan drug application (NDA 22-291) to the Division of Medical Imaging and Hematology Products (DMIHP) for Promacta (eltrombopag olamine) tablets. Eltrombopag is a thrombopoietin receptor agonist that interacts with the transmembrane domain of the human thrombopoietin receptor. This interaction initiates signaling cascades similar, but not identical, to that of endogenous thrombopoietin, inducing proliferation and differentiation of megakaryocytes from bone marrow progenitor cells.

The sponsor's proposed indication for eltrombopag is short-term (six week) treatment of previously-treated patients with chronic idiopathic thrombocytopenic purpura (ITP) to increase platelet counts and reduce or prevent bleeding. Eltrombopag is a small molecular weight compound administered orally with a proposed dose of 50 mg daily, which may be increased to 75 mg daily if the platelet count remains below 50,000/mcL after three weeks of therapy. However, eltrombopag pharmacokinetic data suggests that patients of East Asian ethnicity may have greater exposure to eltrombopag compared to non East Asians. Therefore, GSK proposes a lower initial dose of 25 mg daily for these patients.

Based on data submitted in NDA 22-291, this review responds to DMIHP's consult to the Maternal Health Team (MHT) and recommends language for the Pregnancy and Nursing Mothers subsections of eltrombopag proposed labeling and address proposed post-marketing studies designed to gather data on the use of eltrombopag by pregnant and breastfeeding women.

BACKGROUND

Overview of ITP in Pregnancy

Chronic ITP is a serious and life threatening autoimmune disease characterized by a low platelet count and mucocutaneous bleeding.[1] ITP often occurs in the second or third decade of life and has a female to male ratio of about 3:1.[2] Because ITP is predominantly a disease of young adults, particularly females, it may be encountered in pregnancy. Estimates of ITP incidence during pregnancy vary widely and has been reported to range from 1/1,000 to 1/10,000.[1]

The diagnosis of ITP during pregnancy is one of exclusion and is more difficult because the presentation may resemble that of gestational thrombocytopenia (GT) or incidental thrombocytopenia of pregnancy.[3] GT is the most common cause of thrombocytopenia during pregnancy and accounts for at least 75% of all cases of pregnancy-associated thrombocytopenia.[4]

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[1] Halevy R, Ellis MH, Fejgin MD. Management of Immune Thrombocytopenic Purpura in Pregnancy. Obstet Gynecol Surv. 2008 Mar; 63(3):182-188.
[2] American College of Obstetricians and Gynecologists Practice Bulletin. Thrombocytopenia in Pregnancy. Clinical Management Guidelines for Obstetrician Gynecologists. 1999. Sept;6: 1-12.
[3] George JN, Woolf SH, Raskob GE, Wasser JS, Aledort LM, Ballem PJ, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. Blood. 1996; 88:3-40.
[4] Gernsheimer T, McCrae KR. Immune thrombocytopenia purpura in pregnancy. Current Opinion in Hematology. 2007;14:574-580.

GT occurs late in gestation and is characterized by asymptomatic, mild thrombocytopenia with a platelet count $\geq$ 70,000 x 10^9/L. GT is not associated with fetal thrombocytopenia and resolves spontaneously after delivery. In contrast, according to the American Society of Hematology, ITP is a relatively uncommon cause of thrombocytopenia in pregnancy.[3] When ITP is first diagnosed during pregnancy, thrombocytopenia occurs early in gestation and platelet counts are usually below 50,000 x 10^9/L.[1] Other causes of thrombocytopenia during pregnancy include HELLP syndrome (hemolysis, elevated liver function tests, and low platelet count), which accounts for about 25% of cases, and preeclampsia.[1,3]

The American Society of Hematology (ASH) and the British Committee for Standards in Hematology (BCSH) have guidelines on the medical management of ITP during pregnancy. A summary of these guidelines is provided in Tables 1 and 2 below.[4]

Table 1 Medical management of immune thrombocytopenic purpura in pregnancy: American Society of Hematology guidelines

Treatment indications	Platelets < 10 000/μl Platelets 10–30 000/μl in second or third trimester Bleeding
Intravenous immunoglobulin	Initial treatment: third trimester, platelets <10 000/μl Initial treatment: platelets 10–30 000/μl and bleeding After steroid failure: platelets <10 000/μl After steroid failure: platelets 10–30 000/μl and bleeding After steroid failure: third trimester, platelets 10–30 000/μl, asymptomatic
Splenectomy	Second trimester, platelets <10 000/μl, bleeding
Safe platelet count for delivery	50 000/μl

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ON ORIGINAL

Table 2 Maternal management of immune thrombocytopenic purpura in pregnancy: British Committee for Standards in Haematology guidelines

Treatment indications	Platelets <20 000/μl, unless delivery imminent
Intravenous immunoglobulin (IVIg)	Oral corticosteroids and IVIg have similar responses as in nonpregnant state
Splenectomy	If essential, in the second trimester, laparoscopic advantageous
Safe platelet count for delivery	50 000/μl vaginal 80 000/μl cesarean section or epidural

As described in Tables 1 and 2 above, the medical management of ITP in pregnancy includes the use of IVIG, corticosteroids, and/or splenectomy. According to the ASH, pregnant women with ITP and platelet counts >50,000 do not routinely require treatment and should not receive corticosteroids or IVIG as routine initial therapy. In addition, ASH recommends that pregnant women in the first or second trimester with platelet counts of 30,000 to 50,000 not receive routine initial treatment. However, treatment is recommended for women with platelet counts <10,000 and for those with platelet counts of 10,000 to 30,000 who are in their second or third trimester or are bleeding. ASH and the American College of Obstetrics and Gynecology (ACOG) consider IVIG appropriate initial treatment for women in the third trimester when:

- Platelet counts are less than 10,000,
- Platelet counts are 10,000 to 30,000 and there is clinical evidence of bleeding
- When delivery is planned and platelets are less than 50,000.[2]

In pregnant women who fail corticosteroid and IVIG therapy, splenectomy is considered appropriate in the second trimester when platelet counts are <10,000 and bleeding is occurring. ASH recommends that splenectomy not be performed in asymptomatic pregnant women with platelet counts >10,000.[3]

The course of ITP is usually not affected by pregnancy, although there have been anecdotal reports of patients' conditions worsening during pregnancy and improving postpartum.[2] However, pregnancy may be adversely affected by severe thrombocytopenia. The primary risk to the mother is hemorrhage during the peripartum period.[2] Although pregnant women with ITP may experience several maternal and fetal complications, in most cases, there is neither maternal nor fetal morbidity or mortality, even with very low maternal platelet counts.[1]

REVIEW OF DATA

This review discusses data submitted in the eltrombopag application, pertinent information from the draft medical officer, draft pharmacology/toxicology, and Office of Surveillance and Epidemiology (OSE) application reviews. In addition, this review provides revisions to the sponsors proposed Pregnancy and Nursing Mothers subsections of labeling and recommendations for postmarketing requirements to monitor maternal and fetal exposures to eltrombopag during pregnancy and associated pregnancy and fetal outcomes.

Studies to support product approval

GSK submitted two randomized, double-blind, placebo-controlled studies of similar design to demonstrate eltrombopag short-term efficacy and safety in ITP patients. Both studies enrolled patients with chronic ITP who either had not responded to one or more prior therapies including splenectomy, or who had relapsed within three months of prior therapy and had a baseline platelet count of < 30,000/mcL.[5] Randomization was stratified based upon use or non-use of ITP medications at baseline, splenectomy status, and baseline platelet count (≤ 15,000/mcL or > 15,000/mcL).[5] Eltrombopag was administered daily for six weeks, followed by a six week off-drug follow-up period. In both studies, the primary endpoint was comparison of "responders" defined as a platelet count ≥ 50,000/mcL by the end of treatment. The secondary endpoints included:

- Platelet count shift from <30Gi/L at baseline to ≥50Gi/L over weeks two through six of treatment
- Platelet count of ≥50Gi/L and at least two times the baseline count
- Pharmacodynamics (median platelet counts)
- Bleeding signs and symptoms (assessed via the World Health Organization (WHO) Bleeding Scale and monitoring of subjects facing a hemostatic challenge while on study medication.

In addition to the two pivotal studies described above, GSK submitted data from three ongoing studies. These studies were designed to further assess the efficacy, tolerability, and long term safety of eltrombopag in the treatment of chronic ITP and are described below.

- REPEAT – multi-center, open-label, single-group, repeat-dose, phase II study to evaluate the efficacy, safety and tolerability of eltrombopag, initially administered as 50 mg oral tablets once daily, over three cycles of repeated, intermittent dosing, in adult subjects with previously treated, chronic ITP.

- EXTEND - extension study to evaluate eltrombopag long-term safety in subjects with ITP and previously enrolled in an eltrombopag study.

- RAISE - randomized, double-blind, placebo-controlled, phase III study to evaluate the efficacy, safety and tolerability of eltrombopag, initially administered as 50 mg

[5] FDA Oncology Drugs Advisory Committee Briefing Package.

oral tablets once daily for six months in adult subjects with previously treated chronic ITP and platelet counts <30Gi/L.

Please see the medical officer review by Dr. Andrew Dmytrijuk, for a detailed analysis of the safety and efficacy data submitted for eltrombopag.

Reviewer comment:
Based on the draft clinical review, eltrombopag demonstrated efficacy by increasing platelet counts in ITP patients; however eltrombopag failed to show efficacy in reducing or preventing bleeding in ITP patients.

Safety concerns
The medical officer and OSE reviews for this application describe the following major safety concerns identified from the clinical development program for eltrombopag:

- Hepatobiliary toxicity
- Worsening thrombocytopenia following discontinuation of eltrombopag
- Bone marrow reticulin formation/marrow fibrosis
- Thromboembolic events
- Cataract formation
- Renal tubular toxicity
- Phototoxicity
- Malignancy progression
- Off label use.

Based on the safety concerns identified above, GSK proposed a risk management plan to:

- Ensure safe and appropriate use of eltrombopag
- Promote informed risk-benefit decisions regarding the use of eltrombopag
- Determine the incidence and risk factors for the identified and potential risks of eltrombopag use
- Further assess the overall safety profile of eltrombopag.[6]

The Sponsor proposes to meet these goals and objectives through labeling, educational efforts, and a restricted distribution program that requires patient and healthcare provider enrollment.[6]

Please see the medical officer and Office of Surveillance and Epidemiology (OSE) reviews for a detailed analysis of the safety data submitted for eltrombopag.
The OSE review provides a detailed evaluation and description of the sponsors proposed risk management plan.

[6] Office of Surveillance and Epidemiology for eltrombopag dated May 1, 2008.

Eltrombopag and Use during Pregnancy

Animal Data
GSK conducted reproductive and developmental toxicity studies in rats and rabbits. Based on these studies, no evidence of teratogenicity or fetal harm was observed. However in rats, at maternally toxic doses of 5.3 times the maximum clinical exposure, eltrombopag treatment was associated with embryolethality (increased pre- and post-implantation loss), a slight increase in the incidence of fetal cervical ribs, and reduced fetal body weight.

Please see the pharmacology/toxicology review by Dr. Yash Chopra for a detailed analysis of the reproductive and developmental toxicity studies submitted in support of this application.

Human Data
Pregnant women were excluded from eltrombopag clinical studies. However, while enrolled in the EXTEND study, one subject became pregnant on or around [redacted], after completing eltrombopag therapy. The subject was a 29 year old female who received eltrombopag 75 mg/day from December 26, 2006 to June 21, 2007. Other concomitant medications included ferrous fumarate. The subject's last menstrual period was September 19, 2007 and her estimated delivery date is [redacted] GSK will provide a follow up report on the outcome of this pregnancy. In addition, based on the lack of human data and adverse effects observed in animals, GSK proposes a pregnancy category C for eltrombopag. b(6)

Pharmacokinetic Considerations during Pregnancy
During pregnancy many physiologic changes occur that can impact the pharmacokinetics and pharmacodynamics of a drug. These physiologic changes include:

- Changes in total body weight and body fat composition
- Delayed gastric emptying and prolonged gastrointestinal transit time
- Increase in extra cellular fluid and total body water
- Increased cardiac output, increased stroke volume, and elevated maternal heart rate
- Decreased albumin concentration with reduced protein binding
- Increased blood flow to the various organs (e.g., kidneys, uterus)
- Increased glomerular filtration rate (GFR)
- Altered hepatic enzyme activity, including phase I CYP450 metabolic pathways (e.g., increased CYP2D6 and CYP3A4/5 activity), xanthine oxidase, and phase II metabolic pathways (e.g., N-acetyltransferase, glucuronidation)
- Increased intravascular volume, and increased volume of distribution.[7]

Hepatic and renal changes may cause alterations in drug metabolism and clearance that require maternal dose adjustments to maintain safe and efficacious drug use.

b(5)

[7] Draft Guidance for Industry, Pharmacokinetics in Pregnancy - Study Design, Data Analysis, and Impact on Dosing and Labeling. Published October 2004.

GSK's clinical development program for eltrombopag identified the following PK parameters that may contribute to altered drug metabolism during pregnancy:

- Eltrombopag is highly bound (>99%) to plasma proteins
- Eltrombopag is extensively metabolized in the liver. In addition, about 60% of eltrombopag is eliminated in feces and the remainder is eliminated in urine.

b(5)

In addition, clinicians caring for pregnant women should be advised of the serious adverse events associated with eltrombopag use in clinical trials as well as the lack of data on eltrombopag use during human pregnancy.

Eltrombopag Effects during Lactation
Breastfeeding women were excluded from participating in eltrombopag clinical trials; therefore, there are no data on levels of eltrombopag in breastmilk, effects of the drug on milk production, or potential adverse effects in infants exposed to eltrombopag through breast milk. GSK recommends that caution be exercised when eltrombopag is administered to breastfeeding women.

Sponsors Proposed Pregnancy and Nursing Mothers Labeling
The sponsors proposed Pregnancy and Nursing Mothers subsections of labeling are provided below. The MHT recommended revisions to this labeling are provided on pages 13-14 of this review.

Highlights
Sponsors proposed language – None

8.1 Pregnancy

b(4)

DISCUSSION/CONCLUSIONS

b(4)

Chronic ITP is a serious and life threatening autoimmune disease that may be encountered in pregnancy. Current drug therapy for pregnant women with ITP includes IVIG and corticosteroids. Prednisone and other glucocorticoids are associated with fetal growth impairment and may be associated with an increased risk of oral clefts in humans.[8] Corticosteroid use during pregnancy can be associated with serious adverse events including hypertension, hyperglycemia, osteoporosis, excessive weight gain, and psychosis, and patients should be monitored for these potential complications.[9]

Eltrombopag, an oral product under review for the short-term treatment of previously-treated patients with chronic ITP, may be considered an option for pregnant woman who fail current available therapies. Pregnant women may uniquely benefit from short-term perinatal eltrombopag therapy to increase their platelet count above 50,000 at time of delivery (women in labor with platelets less than 50,000 require platelet transfusion). However, there are no data on the effects of eltrombopag during human pregnancy. In addition, safety concerns were identified in the clinical development program for eltrombopag including:

- Hepatobiliary toxicity
- Worsening thrombocytopenia following discontinuation of eltrombopag
- Bone marrow reticulin formation/marrow fibrosis
- Thromboembolic events
- Cataract formation
- Renal tubular toxicity
- Phototoxicity
- Malignancy progression
- Off label use.

If approved, eltrombopag will be a new, novel, once daily, oral therapy for short-term use. However, ITP is a chronic disease and GSK has only submitted data to support six week use of eltrombopag. Even with limited data, the possibility exists that women with ITP, who are of childbearing potential, may conceive while on eltrombopag therapy, resulting in inadvertent exposure to the drug. During pregnancy, women with ITP may fail currently available therapies, and a clinician may choose to prescribe eltrombopag after considering the serious risks associated with treatment and the benefits of the drug to the mother.

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[8] REPROTOX information for Prednisone: http://csi.micromedex.com/DATA/RX/RX1169.HTM?Top=Yes
[9] British Society for Haematology. Guidelines for the investigation and management of idiopathic thrombocytopenic purpura in adults, children, and in pregnancy. British Journal of Haematology. 2003;120: 574-596.

Physiologic changes that occur in pregnancy and eltrombopag PK characteristics may influence metabolism and excretion of eltrombopag during pregnancy. b(5)

There is no data on the excretion of eltrombopag into human milk. Eltrombopag is highly protein bound, has a molecular weight of 542, and has lipophilic properties. However, it is not known whether eltrombopag will be readily passed into human milk.

DMIHP consulted the MHT and requested review of the Pregnancy and Nursing Mothers sub-sections of labeling. The MHT's recommendations and revisions to the sponsors proposed labeling are provided below.

RECOMMENDATIONS

1. The MHT recommends that the sponsor develop and maintain a prospective, observational pregnancy exposure registry conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to eltrombopag during pregnancy to an unexposed control population. The registry should be conducted as a post-marketing requirement for this application. The outcomes of the registry should include major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, thrombotic events, and other serious adverse pregnancy outcomes. These outcomes should be assessed throughout pregnancy. Infant outcomes should be assessed through at least the first year of life. For guidance on how to establish a pregnancy exposure registry, the sponsor should review the Guidance for Industry on Establishing Pregnancy Exposure Registries available at http://www.fda.gov/cder/guidance/3626fnl.htm.

2. The MHT recommends that Amgen conduct a milk only lactation study in a subset of women enrolled in the pregnancy registry, who choose to breastfeed their infants. This study should be designed to detect the presence and concentration of eltrombopag in breast milk and any effects on milk production and composition. The study should include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. This study should be conducted as a post marketing requirement for this application. Changes are currently being made to the Draft Guidance for Industry on Clinical Lactation Studies – Study Design, Data Analysis, and Recommendations for Labeling, http://www.fda.gov/cder/guidance/5918dft.pdf. The Maternal Health Team can answer questions surrounding current thinking on protocol design.

3. b(5)

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Chardae Araojo
6/9/2008 02:58:55 PM
CSO

Karen Feibus
6/9/2008 10:46:47 PM
MEDICAL OFFICER

Lisa Mathis
6/10/2008 12:10:40 PM
MEDICAL OFFICER

REGULATORY PROJECT MANAGER LABELING REVIEW (PHYSICIAN LABELING RULE)

Division of Medical Imaging and Hematology Products

Application Number: NDA 22-291

Name of Drug: Promacta® (eltrombopag) Tablets

Indication: For the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

Applicant: GlaxoSmithKline

Material Reviewed:

Submission Date: December 18, 2007

Receipt Date: December 19, 2007

Submission Date of Structure Product Labeling (SPL): December 18, 2007

Type of Labeling Reviewed: WORD

Background and Summary:

This provides a list of revisions for the proposed labeling that should be conveyed to the applicant. These comments are based on Title 21 of the Code of Federal Regulations (201.56 and 201.57), the preamble to the Final Rule, Guidance(s), and FDA recommendations to provide for labeling quality and consistency across review divisions. When a reference is not cited, consider these comments as recommendations only.

Recommendations:

b(4)

1 Page(s) Withheld

1 Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager

Supervisory Comment/Concurrence:

Florence Moore, M.S.
Acting RPM Team Leader, Hematology

Drafted: H.Lee/September 8, 2008
Revised/Initialed: F.Moore/September 9, 2008
Finalized: September 9, 2008
Filename: CSO Labeling Review Template (updated 1-16-07).doc
CSO LABELING REVIEW OF PLR FORMAT

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

/s/

Hyon Z Lee
9/10/2008 10:54:53 AM
CSO

Florence Moore
9/10/2008 11:35:17 AM
CSO

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-291 Supplement # N/A Efficacy Supplement Type SE- N/A

Proprietary Name: Promacta
Established Name: eltrombopag olamine
Strengths: 25mg, 50mg tablets

Applicant: GlaxoSmithKline
Agent for Applicant (if applicable): N/A

Date of Application: December 19, 2007
Date of Receipt: December 19, 2007
Date clock started after UN: N/A
Date of Filing Meeting: February 12, 2008
Filing Date: February 17, 2008
Action Goal Date (optional): User Fee Goal Date: June 19, 2008

Indication(s) requested: Short-term treatment of Idiopathic Thrombocytopenic Purpura (ITP)

Type of Original NDA: (b)(1) X (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:
(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S ☐ P X
Resubmission after withdrawal? No Resubmission after refuse to file? No
Chemical Classification: (1,2,3 etc.) 1P
Other (orphan, OTC, etc.) Orphan Designation-May 5, 2008

Form 3397 (User Fee Cover Sheet) submitted: YES X NO ☐

User Fee Status: Paid X Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES ☐ NO X
  If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES X NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
  YES ☐ NO X

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO X
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES X NO ☐
  If no, explain:

- Was form 356h included with an authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO ☐
  If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES ☐

2. This application is an eNDA or combined paper + eNDA YES ☐
   This application is: All electronic X Combined paper + eNDA ☐
   This application is in: NDA format ☐ CTD format X
   Combined NDA and CTD formats ☐

   Does the eNDA, follow the guidance?
   (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES X NO ☐

   If an eNDA, all forms and certifications must be in paper and require a signature.

   If combined paper + eNDA, which parts of the application were submitted in electronic format?

   Additional comments:

3. This application is an eCTD NDA. YES X
   If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

   Additional comments:

- Patent information submitted on form FDA 3542a? YES X NO ☐

- Exclusivity requested? YES, 5 Years NO ☐
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES X NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
  YES X NO ☐

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES ☐ NO X

  --- The application received Orphan Drug designation on May 5, 2008.

- Is this submission a partial or complete response to a pediatric Written Request? YES ☐ NO X

  If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO ☐
  (Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section) YES X NO ☐

- PDUFA and Action Goal dates correct in tracking system? YES X NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? Yes.
  If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: 63,293

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO ☐
  If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date January 24, 2006 NO ☐
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date August 2, 2007 NO ☐

If yes, distribute minutes before filing meeting.

- Any SPA agreements? Dates Clinical: May 19, 2006 NO ☐
  Carcinogenicity: November 4, 2004
  If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO ☐
  If no, request in 74-day letter.

- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
  Was the PI submitted in PLR format? YES X NO ☐

  If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:

- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES X NO ☐

- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO ☐

- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
  N/A ☐ YES X NO ☐

- Risk Management Plan consulted to OSE/IO? N/A ☐ YES X NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA X YES ☐ NO ☐

If Rx-to-OTC Switch or OTC application: N/A

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES ☐ NO ☐

- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES ☐ NO ☐

Clinical: N/A

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
  YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO ☐
  If no, did applicant submit a complete environmental assessment? YES ☐ NO ☐
  If EA submitted, consulted to EA officer, OPS? YES ☐ NO X
  EA consult is not needed.

- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO ☐
- If a parenteral product, consulted to Microbiology Team? N/A YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 12, 2008

NDA #: 22-291

DRUG NAMES: Promacta™ (eltrombopag olamine)

APPLICANT: GlaxoSmithKline

BACKGROUND: This is a new molecular entity. The proposed indication is for the short-term treatment of Idiopathic Thrombocytopenic Purpura (ITP).

ATTENDEES:

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
Andrew Dmytrijuk, M.D., Medical Reviewer
Eldon Leutzinger, Ph.D., Chemistry Pool Reviewer
Young-Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Joseph Grillo, Pharm.D., Clinical Pharmacology Reviewer
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Richard Chen, Ph.D., Statistics Reviewer
Qing Xu, Ph.D., Statistics Reviewer
Yash Chopra, Ph.D., Pharmacology/Toxicology Reviewer
Alice Kacuba, Acting Team Leader, Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline/Organization	Reviewer
Medical:	Andrew Dmytrijuk
Secondary Medical:	Kathy Robie-Suh
Statistical:	Qing Xu (2nd: Richard Chen)
Pharmacology:	Yash Chopra
Statistical Pharmacology:	Karl Lin
Chemistry:	Sue Ching Lin
Biopharmaceutical:	Joseph Grillo
DSI:	Jong-Hoon Lee
Regulatory Project Management:	Hyon-Zu Lee
Other Consults:	DDMAC (Sean Bradley)
	DMETS (Walter Fava)
	Risk Management (Suzanne Berkman)
	Pediatric & Maternal Health (Karen Feibus)

Per reviewers, are all parts in English or English translation? YES X NO ☐
If no, explain:

CLINICAL FILE X REFUSE TO FILE ☐

- Clinical site audit(s) needed? YES X NO ☐
  If no, explain:
- Advisory Committee Meeting needed? YES, date if known May 30,2008
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
  N/A X YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A X FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE X REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE X REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed? YES ☐ NO X

PHARMACOLOGY/TOX N/A ☐ FILE X REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO X

CHEMISTRY FILE X REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES X NO ☐
- Sterile product? YES ☐ NO X
  If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. X Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. X If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)

3. X Convey document filing issues/no filing issues to applicant by Day 74.

Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

1. Does the application reference a listed drug (approved drug)? YES ☐ NO ☐

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES ☐ NO ☐

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES ☐ NO ☐

If "Yes "contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

   (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

   YES ☐ NO ☐

   (***Phqrmaceutical equivalents*** are drug products in identical dosage forms that: **(1)** contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; **(2)** do not necessarily contain the same inactive ingredients; **and** **(3)** meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

   (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

   (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES ☐ NO ☐

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.
Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES ☐ NO ☐

(***Pharmaceutical alternatives*** are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

*If "**No,**" to (a) skip to question 7. Otherwise, answer part (b and (c)).*

(b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES ☐ NO ☐

(c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ NO ☐

*If "**Yes,**" to (c), proceed to question 7.*

NOTE: *If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.*

*If "**No,**" to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.*

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)?

YES ☐ NO ☐

*If "**No,**" skip to question 8. Otherwise, answer part (b).*

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES ☐ NO ☐

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES ☐ NO ☐

11. Is the application for a duplicate of a listed drug whose only difference is YES ☐ NO ☐

that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9).

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES ☐ NO ☐

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

☐ Not applicable (e.g., solely based on published literature. See question # 7

☐ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

☐ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must* ***subsequently*** *submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.*

☐ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

☐ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

☐ 21 CFR 314.50(i)(1)(ii): No relevant patents.

☐ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

  YES ☐ NO ☐

  If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

  Was this listed drug product(s) referenced by the applicant? (see question # 2)

  YES ☐ NO ☐

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

  N/A ☐ YES ☐ NO ☐

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES ☐ NO ☐

If "**Yes**," please list:

Application No.	Product No.	Exclusivity Code	Exclusivity Expiration

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

/s/

Hyon Z Lee
6/2/2008 10:32:04 AM
CSO

Florence Moore
6/2/2008 04:57:54 PM
CSO