

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125164

OFFICE DIRECTOR MEMO

**DIVISION DIRECTOR AND OFFICE DIRECTOR
REVIEW MEMORANDUM
SECOND REVIEW CYCLE**

BLA: 125164
DRUG: methoxy polyethylene glycol-epoetin beta
TRADENAME: Mircera™
FORMULATION: Single use vials of Mircera (50 to 1000 mcg) in 1 mL phosphate buffer with defined excipients; also single use, prefilled syringes of Mircera (50 to 250 mcg) in 0.3 mL or 0.6 mL phosphate buffer with defined excipients
ROUTE: Intravenous (IV) or subcutaneous (SC)
DOSE: 0.6 mcg/kg IV or SC once every two weeks for patients who are not currently receiving an erythropoiesis stimulating agent (ESA); Defined conversion factor in the label for patients receiving an ESA; label describes the same ESA class dosing guidelines
SPONSOR: Hoffmann La Roche
SUBMITTED: Originally on April 18, 2006
FIRST CYCLE: CR letter issued on May 18, 2007
SECOND CYCLE: Submitted on September 13, 2007
PDUFA DUE DATE: November 14, 2007
DD MEMO COMPLETED: November 9, 2007
DD MEMO PREPARERS: Dwaine Rieves, MD, Acting Division Director *Dwaine Rieves* 11-9-07
Division of Medical Imaging and Hematology Products
Richard Pazdur, MD *R Pazdur*
Director, Office of Oncology Drug Products

SPONSOR'S PROPOSED INDICATION:

"Mircera is indicated for the treatment of anemia associated with chronic renal failure including patients on dialysis and patients not on dialysis.

Mircera is not indicated for the treatment of anemia due to cancer chemotherapy."

RELATED DRUGS:

Mircera is a member of the class of ESA that includes the FDA-licensed products, Epoetin alfa (Procrit/Epogen) and Aranesp (Darbepoietin alfa).

RELATED REVIEWS:

Clinical: John Lee, M.D.
Statistics: Yuan Richard Chen, Ph.D, Jyoti Zalkikar, Ph.D.
Chemistry: Ingrid Markovic, Ph.D., Dov Pluznik, Ph.D., Lai Xu, Ph.D., Serge Beaucage, Ph. D., Susan Kirshner, Ph.D., Barry Cherney, Ph.D.
Microbiology: Patricia Hughes, Ph.D., Michelle Clark Stuart, M.S.
Pharm-toxicology: Yanli Ouyhang, Ph.D., Adebayo Lanionu, Ph.D.
Clin Pharmacology: Ike Lee, Ph.D, Hong Zhao, Ph.D.
Pharmacometrics: Pravin Jadhve, Ph.D., Jogarao Gobburu, Ph.D.
Project Manager: Florence Moore, RN, MSN, RAC

Advisory Committee: None

RECOMMENDED REGULATORY ACTIONS:

a. Licensure for proposed indication:

Mircera is a form of epoietin beta (a product marketed in Europe) that has been modified by pegylation to produce a molecule that has a longer serum half-life than the currently marketed ESAs. This longer half-life allows more convenient (biweekly or monthly) dosing compared to the currently marketed ESAs. Roche submitted this application to support solely an indication for Mircera use in the treatment of the anemia of chronic renal failure and the proposed text for this indication is identical to the currently marketed ESAs (however, these marketed ESAs also have other indications, including use in the treatment of chemotherapy-induced anemia in some patients with cancer). The Mircera indication statement specifically states that Mircera is not indicated to treat anemia due to cancer chemotherapy.

Overall, the sponsor has supplied clinical data that sufficiently supports licensure of Mircera for the treatment of the anemia due to chronic renal failure (CRF), including patients on dialysis and not on dialysis. The product labeling includes the ESA "class" labeling components, a medication guide and two "Instructions for Use" that describe proper Mircera administration procedures.

b. Requirement of the sponsor to conduct post-marketing studies and to submit additional information:

During the review the following findings were of special note and are applicable to the agreed-upon post-marketing clinical studies:

-A need for a randomized, controlled, post-marketing clinical study assessing safety outcomes in patients with serum C-reactive protein concentrations in excess of 30 mg/L. This will be addressed by a clinical study that compares Mircera to another ESA among patients with a broad variety of serum C-reactive protein levels.

Roche actively screened and eliminated subjects with C-reactive protein levels in excess of 30 mg/L. This exclusion process eliminated approximately 3% of subjects who, in clinical practice, would be eligible for treatment with an ESA. Analyses of adverse outcomes categorized by C-reactive protein support the sponsor's conclusion that the active screening program did not adversely impact the safety database. Nevertheless, the soundness of this conclusion will be verified by obtaining additional clinical data from patients with elevated C-reactive protein concentrations. In general, the study would compare Mircera to other ESAs.

-Completion of deferred pediatric clinical studies, including an initial dose finding clinical study and a subsequent clinical study that is designed to establish a Mircera pediatric dosage regimen. These studies will enroll pediatric subjects 5 to 17 years. The sponsor has been granted a waiver for pediatric studies in subjects under 5 years of age.

It is important to note that, on November 9, 2007, we had a telephone conversation with Roche where we ardently tried to persuade the company to agree to conducting a clinical study as a post-marketing commitment in order to help determine whether the —

"dose or dose regimen" of an ESA is more important than a "target" hemoglobin. Roche would not commit or agree to conducting this type of study. Failure to reach agreement on this study does not preclude licensure but illustrates the difficulty of obtaining these types of data.

c. Approval of the trade name, Mircera

This recommendation is consistent with that of the FDA Office of Drug Safety/Division of Medication Errors and Technical Support finding of July 19, 2006.

d. Pediatric Research Equity Act (PREA) of 2003 expectations:

In a February 21, 2006 letter, FDA informed Roche that clinical studies of Mircera usage among pediatric patients aged 5 through 17 years were deferred and that clinical studies were waived for pediatric patients aged 0 to 5 years. Within the original BLA application, Roche noted, "Based on the FDA recommendations, Roche intends to revise the pediatric development plan and submit protocols for FDA review to IND 10158 by November, 2006. In accordance with the PREA of 2003, Roche commits that the pediatric development plan and any agreed pediatric study will be developed and conducted with due diligence at the earliest time possible." Roche submitted final study protocols for the two pediatric clinical studies on December 20, 2006. FDA regarded these protocols as reasonable.

REVIEW COMPONENTS:

Background

The original/first BLA review cycle was extended by a December 4, 2006 submission of additional clinical safety data that was recorded as a major amendment. During this extended first review cycle new published data and submitted license application study data raised important questions regarding the safety of ESAs, especially with respect to the "targeting" of hemoglobin values in excess of 12 g/dL (specifically, the "CHOIR" study, a study which examined patients with CRF, and several studies of ESA use in cancer patients). Together these publications and new study data necessitated the development of a boxed warning and additional safety text for the currently marketed ESAs and this labeling was approved in March, 2007. These March, 2007 label revisions and supportive data were subsequently discussed at advisory committees.

Safety issues regarding the use of ESAs were discussed at a May 10, 2007 meeting of the Oncologic Drugs Advisory Committee. Safety issues regarding the use of ESAs in the treatment of the anemia of CRF were discussed at a September 11, 2007 joint meeting of the Cardiovascular Drugs and Drug Safety and Risk Management Advisory Committees. Both committees advised revision of the ESA labels and revised ESA labeling was approved on November 8, 2007. This revised labeling for the marketed ESAs is important because Mircera is a member of the ESA class, and most of the "class" labeling approved for the marketed ESAs has been incorporated into the Mircera label, including the labeling pertaining to oncologic use of ESAs (even though Mircera is not proposed for use in the oncology setting).

The original/first Mircera review cycle resulted in the identification of several items for the sponsor to address, including clinical, manufacturing and immunogenicity concerns. No

new clinical data were requested. However, the sponsor was informed that final labeling and final product labeling were contingent upon the sponsor justifying the appropriateness of all components of "class labeling" for Mircera with respect to dosing and usage (including the extensive class labeling regarding use of ESAs in the treatment of cancer chemotherapy anemia). This was regarded as especially important since Mircera has different pharmacokinetics from the currently marketed ESAs and certain clinical data indicate that the hemoglobin response to Mircera may be delayed, compared to other ESAs.

Roche targeted usage of Mircera in the treatment of anemia of CRF for the first clinical indication under FDA consideration for licensure. Indeed, the clinical development program was strikingly similar to that for darbepoetin alfa and differed predominantly in that Roche provides more long term (one year or more) clinical exposure data.

Roche has also performed clinical studies of Mircera usage in the treatment of anemia due to cancer chemotherapy. However, that indication (common to all marketed ESAs) is not sought by Roche. Importantly, a clinical study of Mircera usage among approximately 150 patients with non-small cell lung cancer showed an excess in the number of deaths among patients receiving Mircera, compared to patients receiving another ESA. The sponsor's exploratory analyses of this study do not suggest that apparent mortality disadvantage was due to imbalances in baseline characteristics and no other analyses (outside of a drug effect) convincingly account for the mortality finding. Instead, the study provides an important safety signal for Mircera usage among cancer patients.

Brief Regulatory Timeline

- April 18, 2006 - submission of BLA
- June 1, 2006 Filing action, BLA was assigned a standard review
- October 16, 2006 Mid-cycle meeting
- December 4, 2006 Submission of major amendment
- March 16, 2007 Regulatory briefing regarding C-reactive protein issues and safety
- May 18, 2007 First cycle CR letter issued
- September 13, 2007 Submission of second cycle information/response to CR
- November 14, 2007 PDUFA due date

Major Findings from Second Cycle Review:

The second cycle clinical review findings mainly involved consideration of the sponsor's responses to multiple discussion items and justification requests. These responses were regarded as reasonable and concerns generally related to the deficits in the understanding of ESA activity, in general (not specifically Mircera). The second cycle response also included certain manufacturing data and these data were assessed as sufficiently resolving issues, according to the FDA manufacturing reviewers.

The major clinical findings from the second cycle review related to:

- information for all ESAs are insufficient to establish any specific "threshold" for initiation of ESA therapy;

- the highest Mircera dose administered in the clinical development program was approximately 5,000 mcg (for a patients who achieved/maintained desired hemoglobin levels); the total data are insufficient to establish any "maximum" Mircera dose;
- hemoglobin goal considerations for Mircera are similar to those for other ESAs;
- clarification of platelet count alterations for patients in the study database;
- observation that the imbalance in gastro-intestinal hemorrhage rates (higher for Mircera than comparator) appears related to baseline characteristic imbalances (especially considering overall hemorrhage rates were similar between Mircera and comparator ESAs);
- supply of a clinical study protocol proposal to address the C-reactive protein concern;
- submission of the final study report for the cancer study NG19960 (a study in patients with non-small cell lung cancer.

Study NG19960 was the first oncology study in which sufficient Mircera doses were administered to raise hemoglobin levels. In prior exploratory studies, hemoglobin levels were not clearly responsive to the tested doses.

Study NG19960 was an open label, parallel, randomized (1:1:1:1) dose finding study of stage 3 or 4 patients with lung cancer who were undergoing chemotherapy. Overall, 153 patients were randomized among: darbepoetin or one of three Mircera doses. All doses were administered over a 12 week period with a comparison of hemoglobin responses as the main outcome (a hemoglobin target of 11 to 13 g/dL was proposed). The study was terminated prematurely by the safety monitoring board due to excessive deaths in the Mircera group. Overall, 33 patients died (8, 12, 9 in each of the three Mircera arms and 4 in the darbepoetin arm). Analyses of deaths were all post-hoc but the Mircera group had a statistically higher death rate than the darbepoetin group. Progressive lung cancer was assessed as the cause of death in half the cases. Additional study details are described below.

Most of the review findings pertaining to use of Mircera in the treatment of the anemia of CRF were determined during the original/first review cycle and the subsequent portions of this document summarizes these findings/with applicable updates through the second cycle.

Clinical Review

The clinical review was performed by Dr. John Lee. Dr. Ruyi He provided Team Leader expertise to the review and a secondary review during the first review cycle. I have examined this clinical review as well as the second cycle review and I generally concur with the major findings and the important comments regarding recommendation for licensure. Some components of the review are clarified and highlighted below.

Substantial evidence of safety and effectiveness for Mircera was obtained from six confirmatory clinical studies. The primary endpoints in all these studies were

assessments of the extent to which Mircera could elevate or maintain blood hemoglobin concentrations, a surrogate marker for the actual clinical benefit of "avoidance of blood transfusion."

a. Efficacy:

As summarized below, Roche provides persuasive evidence of Mircera efficacy both in the "initiation" setting and the "maintenance" setting for the treatment of anemia due to chronic renal failure. All primary endpoints were achieved in a statistically and clinically meaningful manner.

The "initiation" setting refers to clinical studies that assess Mircera effects in anemic patients with chronic renal failure who have never previously been treated with an ESA. Studies 16736 (dialysis patients) and 16738 (patients not receiving dialysis). These are probably the most informative clinical studies in the entire clinical development program since the study databases include patients who are potentially intolerant of ESAs. The primary endpoints in these studies were not comparisons between study groups but statistical tests that the proportion of "responders" to Mircera exceeded 60%. "Responders" were assessed as patients who achieved a 1 g/dL increase in hemoglobin concentration with the achieved hemoglobin > 11 g/dL and avoidance of blood transfusion. Multiple secondary endpoints explored various permutations of changes in blood hemoglobin concentration.

The "maintenance" setting refers to clinical studies that assess Mircera effects in anemic patients with chronic renal failure who are currently receiving an ESA. Hence, the database from these studies is limited to patients who, at study enrollment, are known to be tolerant of ESAs. Since ESAs are so widely used in clinical practice and often initiated early in the development of anemia, recruitment of subjects for maintenance studies is much easier than the recruitment for initiation studies. Hence, maintenance studies account for the vast majority of clinical data in the Mircera database. As summarized below, four studies assessed Mircera efficacy in the hemoglobin maintenance setting. The primary endpoints in these studies was a comparison of the changes (various end of study periods - baseline) in hemoglobin concentration between the study groups using a non-inferiority margin of - 0.75 g/dL for the lower limit of the two-sided 95% confidence interval (this is a reasonable margin since clinical data show that a 0.5 g/dL change in hemoglobin concentration may result from diurnal variation alone).

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Table 1. Confirmatory Studies of Mircera Safety and Efficacy

Study	Design Features	Results
"Initiation"		
16736	Mircera vs Epoetin alfa or beta in 181 dialysis patients over 24 week period, IV	Mircera responders: 93% Epoetin responders: 91%
16738	Mircera vs Darbepoetin alfa in 324 non-dialysis patients over 28 week period, SC	Mircera responders: 98% Darbepoetin responders: 96%
"Maintenance"		
16739	Mircera vs Epoetin alfa or beta in 540 dialysis patients over 1 year; IV	Average change in hemoglobin values for Mircera were all < 0.1 g/dL; all comparator p values < 0.001
16740	Mircera vs Epoetin alfa or beta in 474 dialysis patients over 1 year; SC	
17283	Mircera vs Darbepoetin alfa in 249 dialysis patients over 1 year; IV	
17284	Mircera prefilled syringes vs Epoetin alfa or beta in 256 dialysis patients over 36 weeks	

Of special note from the efficacy analyses was that, in the correction studies, the increase in hemoglobin concentration was delayed for Mircera patients, compared to patients receiving other ESAs (median time to response was 57 and 43 days in the Mircera groups and 31 days in the Epoetin group and 29 days in the Darbepoetin group).

b. Safety:

Overall, 1789 patients received Mircera in phase 2 or 3 clinical studies, including 1144 patients who received Mircera for at least one year and 95 patients who received Mircera for at least two years. This safety database is consistent with prior expectations for ESAs. For example, the safety database for Darbepoetin included 1598 patients with 185 exposed for at least one year.

Comparisons between Mircera and other ESAs are based upon a database of 1789 Mircera patients (84% on hemodialysis) and 948 reference ESA patients (80% on hemodialysis). Since hemodialysis patients are generally regarded as clinically more vulnerable to medical problems, the slight imbalance in hemodialysis representation (more hemodialysis patients receiving Mircera) may have impacted some of the imbalances detected in safety analyses.

The most notable findings from the Mircera safety database review were the following:

-Sudden deaths:

Overall, mortality rates were similar between patients receiving Mircera (10%) and other ESAs (11%), based upon cumulative safety information supplied in the major amendment. However, the sponsor reported in the original submission that deaths recorded as "sudden death" were different between study group with 9 sudden deaths in the Mircera group but none in the comparator ESA groups. Information supplied in the major amendment included "extended follow-up" from extension studies (in which subjects were continued on randomized/assigned treatment regimens). In this

"extended follow-up, the cumulative total number of sudden deaths was 14 (Mircera) vs 5 (reference ESA).

As Dr. Lee noted in his review, no unique features appear to implicate Mircera in the occurrence of sudden deaths and it is notable that no sudden deaths were reported in the two "initiation" studies (the studies perhaps most important to assessing safety).

Notably, preclinical studies did not suggest QT abnormalities in animals and the sponsor's clinical QT study also did not disclose abnormalities although the study lacked the "positive control" and was regarded as not fulfilling the expectation of a "thorough" QT clinical study. However, it is important to note that a "thorough" QT clinical study performed among healthy subjects is generally intended to assess the effects of small molecular weight products (not biologic products like Mircera) and may have very little applicability to subjects in renal failure.

Together, the long term follow-up data, nonclinical data and overall mortality findings sufficiently resolve the initial concerns regarding an possible increase in sudden deaths among Mircera patients, compared to patients receiving other ESAs.

-C-reactive protein concern:

As previously noted, Roche excluded approximately 3% of potentially eligible subjects solely because of elevated C-reactive protein (CRP) concentrations. This is an important consideration since patients with elevated CRP (> 10 mg/L) have been identified as especially vulnerable to toxicity from ESAs. This concern was discussed at an internal FDA regulatory briefing where the consensus was that active CRP screening did not importantly compromise the Mircera safety database since:

- the upper limit (30 mg/L) was relatively high
- a small number of subjects were excluded (~ 3%)

The sponsor also supplied additional exploratory analyses that showed that, when the entire database is subdivided into quartiles according to baseline CRP values, all risk ratios (Mircera compared to ESA) for important safety outcomes within all quartiles either favored Mircera or included 1 (showing similar risks for Mircera to ESA).

Together, the exploratory analyses and supportive data support the reasonableness of the submitted safety database. Nevertheless, a post-marketing commitment is proposed to address this subject.

-Hemorrhage:

Overall, the rate of serious adverse events was numerically lower for Mircera patients (37%) compared to reference ESAs (40%). However, serious gastrointestinal hemorrhage rates were higher for Mircera patients (1.2% versus 0.2%). Overall serious bleeding events were also slightly higher for Mircera patients (5.2% versus 4%). As Dr. He notes in his review, co-medications did not appear to account for the slightly higher hemorrhage rate among Mircera patients.

The hemorrhage findings will be noted in the product label to suggest a possible risk for Mircera but given the multiplicity of safety endpoint assessments and the slight

imbalance in the proportion of hemodialysis patients as well as no preclinical data to support a hemorrhage risk for Mircerā, the actual risk for hemorrhage with Mircerā appears only slightly increased or similar to that for other ESAs.

-Thrombocytopenia

The laboratory data show that most patients exposed to Mircerā experience a small decrease in platelet counts, with the lowered count still within the range of "normal." Additionally, 7.5% of Mircerā patients but only 4.4% of reference ESA patients have a platelet count at any time of less than 100 x 10⁹/L. It is notable that this imbalance also mirrors the imbalance in the baseline distribution of hemodialysis patients between the two study groups (Mircerā versus ESA). Of note also is that, with respect to the two "initiation" clinical studies and comparisons between Mircerā and another ESA, decreases in platelet counts following Mircerā exposure were seen only in the patients on hemodialysis (Study 16738), not in the non-hemodialysis clinical study (study 16736). In the non-hemodialysis study, both Mircerā and the comparator ESA slightly decreased platelet counts.

Together, the clinical data suggest that Mircerā may lower platelet counts modestly more than other ESAs and the product label will indicate this lowering although the clinical data do not indicate clinically important risks related to the platelet alteration.

c. Cancer study:

Roche performed Study NH19960 study in Europe to provide exploratory clinical data for Mircera use in treatment of chemotherapy-induced anemia. In this study, 153 anemic patients with non-small cell lung cancer were randomized 1:1:1:1 to 1 of 3 Mircerā dose cohorts or Darbepoietin alfa. The study was suspended by the Data Safety Monitoring Board on March 26, 2007 due to excessive deaths in the Mircerā group. Roche submitted an interim study report (data collection and data clean-up is continuing) to the license application along with interim electronic datasets.

Overall, deaths occurred among 29/114 (25%) Mircerā-exposed subjects and 4/39 (10%) Darbepoietin alfa-exposed subjects. These findings included 2 "sudden deaths" in the Mircerā group but no "sudden deaths" in the Darbepoietin group. A dose-response effect was not evident for mortality in the Mircerā dose cohorts, as follows:

Mircera cohort	deaths
6.3 mcg/kg	7/38
9.0 mcg/kg	13/38
12 mcg/kg	9/38

Roche performed logistical regression modeling to attempt to identify any baseline factors that could contribute to the excessive mortality in the Mircerā group; no covariates could be identified as accounting for the mortality imbalance. The study groups did not differ in rates of thromboembolic events or in the rate of "progressive disease" determination by the site investigators.

Importantly, the clinical development program for treatment of the anemia of chronic renal failure did not reveal evidence of cancer problems. The overall incidence of neoplasm in the safety database (Mircerā n = 1789 and comparator n = 948) showed a

4% incidence of neoplasm in both groups. One death in the entire database was attributed to malignancy and that death was in a patient receiving Mircera (an occurrence likely due to chance since twice as many patients were exposed to Mircera as to a comparator). Hence, the occurrence of malignancy was very low in the entire clinical CRF database.

Together, the phase 2 cancer study provides important evidence that, at least in non-small cell lung cancer patients, Mircera treatment may increase mortality. Hence, the product label will describe this finding. Additionally, the sponsor will be requested to address the potential for misinformation related to extensive "class labeling" of cancer risks in the Mircera label. One concern for labeling was that, given Mircera's dosing convenience, and the clinical perception that all ESAs perform the same as a class, Mircera may mistakenly be assumed as a reasonable alternative for some cancer patients. This concern was addressed by stating specifically that Mircera is not indicated for treatment of the anemia due to cancer chemotherapy, inclusion of the results of the bothersome Mircera phase 2 clinical study that showed mortality problems and inclusion of the important parts of "class labeling" as it applies to potential oncologic use of ESAs.

d. Risk Management Plan:

Roche supplied a document referred to as a "Risk Management Plan" with the original submission of the license application. However, this document supplies only a summary description of the product labeling (warnings, precautions, adverse reactions) and notes that routine pharmacovigilance procedures will be performed along with focused investigation of potential cases of pure red cell aplasia (including performance of anti-erythropoietin antibody assays by Roche). This "Risk Management Plan" is essentially identical to that performed by sponsors of other ESAs and is reasonable.

Statistical Review:

The statistical review was performed by Dr. Richard Chen, lead statistician for the BLA. The findings from her review were secondarily reviewed by Dr. Jyoti Zalkikar, Biometric Team Leader.

I have read Dr. Chen's statistical review report and I concur with his statistical analyses, findings and comments that the sponsor has provided persuasive evidence of Mircera efficacy and his notation that safety considerations are especially important for the labeling of ESAs, including Mircera.

Clinical Pharmacology and Biopharmaceuticals (OCPB) Review

The clinical pharmacology and biopharmaceutical review was performed by Dr. Jang-Ik Lee. The findings from the review were secondarily reviewed by Dr. Hong Zhao, Team Leader. Dr. Pravin Jadhav provided a pharmacometrics review.

I have read the clinical pharmacology and biopharmaceuticals review report and I concur with the observations and comments. Dr. Lee actively participated in labeling discussions regarding Mircera and I concur with his final pharmacology findings (as incorporated into the Mircera label).

Chemistry and Microbiology

The Chemistry review was performed mainly by Drs. Dov Pluznik, Ingrid Markovic, Serge Beaucage and Lai Xu. Multiple components of the manufacturing information were reviewed by component-specific reviewers and I rely upon the "Chemistry Executive Summary" statements that the final conclusion is one of recommendation for approval. This summary noted that all manufacturing issues were resolved during the review.

Facility review and site inspectional findings support Mircera licensure, as documented by Dr. Patricia Hughes.

Pharmacology/Toxicology

The pharmacology/toxicology review was performed by Dr. Yanli Ouyang and was secondarily reviewed by Dr. Adebayo Laniyonu.

I have read the pharmacology/toxicology recommendations and I concur with the observations that the important animal toxicity findings relate to exaggerated hematopoiesis (an expected outcome). The reviewers noted that the submitted pharmacology/toxicology data support the licensure for Mircera with no need for additional nonclinical studies.

Pediatric Safety and Efficacy

As previously noted, the sponsor is to collect pediatric usage information in the post-marketing period from a previously proposed pediatric study of patients over 5 years of age.

Proposed Labeling

During the review cycle, FDA and the sponsor worked to develop the product label. The review of the PLR format was assisted by Ms. Iris Massuci of the SEALD team and Ms. Sharon Mills, BS from the Division of Surveillance, Research and Communications Support Division. The labeling incorporates the ESA "class" labeling.

Office of Drug Safety/Division of Medication Errors and Technical Support (ODS/DMETS/)

Nora Roselle, PharmD, provided a DMETS review of the proposed product label, container label and proprietary name. The team provided recommendations for altered colors on package labeling which will be addressed in the final review of the carton and container labels. The sponsor has been informed of the necessary changes and has supplied a response.

Division of Scientific Investigation (DSI)

Ms. Dianne Tesch provided a report of the FDA inspectional findings at selected clinical sites. The secondary reviewer on his report was Dr. Leslie Ball. The inspectors found the clinical data reliable. Only minor protocol violations were detected. I have read the report and concur with the findings.

Financial Disclosure

As noted in Dr. John Lee's review, the sponsor has submitted required financial disclosure information and the information is acceptable.

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