SUPPLEMENT TO BACKGROUND INFORMATION

FOR THE

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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Safety of Erythropoiesis-Stimulating Agents (ESAs) in Oncology

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List of Abbreviations

BMI	body mass index
BEST	Breast Cancer Erythropoietin Survival Trial (Study EPO-INT-76)
DAHANCA	Danish Head and Neck Cancer Group
ESA	erythropoiesis-stimulating agent
FDA	Food and Drug Administration
J&JPRD	Johnson & Johnson Pharmaceutical Research and Development, LLC
ODAC	Oncologic Drugs Advisory Committee
PMC	post-marketing commitment
PV	pharmacovigilance
Q3W	once every 3 weeks
SCLC	small-cell lung cancer
TVE	thrombotic vascular event
US	United States

This document provides supplemental information to the briefing material provided by Amgen, Inc. for the United States Food and Drug Administration (FDA) Oncologic Drugs Advisory Committee (ODAC) meeting to be held on 10 May 2007. This amendment to the Background Information document previously submitted provides valuable additional information and data that will contribute to the Advisory committee member discussion at the forthcoming ODAC. Sections 1 to 3 of this document provide supplementary information to the following sections of the ODAC Meeting Briefing Document:

- Section 2.4, Prior FDA and ODAC Assessments of Risks of ESAs in the Oncology Indication
- Section 5.1, Safety of Epoetin Alfa in the Treatment of Chemotherapy-induced Anemia
- Section 7.5, Re-evaluation of Ongoing Risk Management Plan and Need for Further Actions.

1. Regulatory History

The following text is provided as a supplement to the ODAC Meeting Briefing Document, Section 2.4, Prior FDA and ODAC Assessments of Risk of ESAs in the Oncology Indication, including the subsection Conclusions of the 2004 ODAC Committee and Subsequent Risk Management Activities.

Johnson Pharmaceutical Research & Development Regulatory History

Study EPO-INT-76, also referred to as the Breast Cancer Erythropoietin Survival Trial (or BEST), was a Phase 3, double-blind, randomized, placebo-controlled, multicenter study designed to evaluate the effects of maintaining hemoglobin concentration between 12.0 g/dL and 14.0 g/dL using epoetin alfa on survival and health-related, patient-reported outcomes in women with metastatic breast cancer receiving first-line chemotherapy. The first subject was enrolled in the study in June 2000.

After an Independent Data Monitoring Committee recommended discontinuation of the study because of an unexpected increase in mortality among subjects in the epoetin alfa-treated group compared with the placebo-treated group (April 2002), Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) immediately notified investigators, the United States (US) Food and Drug Administration (FDA), and other health authorities. J&JPRD subsequently undertook an extensive investigation of mortality in BEST, which included a blinded chart review, expert panel, and investigators' meetings, and provided an expert report integrating all of this information to the FDA in April 2003, supplemented by a review of all previously conducted oncology studies using epoetin alfa.

When J&JPRD was informed of a potential safety signal in another study (PR00-03-006), the Company informed the FDA (September 2003) and initiated a global re-evaluation of all ongoing epoetin alfa oncology clinical studies in non-anemic patient populations. Study PR00-03-006 was a double-blind, multicenter study in subjects with gastric or rectal cancer receiving fluoropyrimidine- (5-FU or capecitabine)-based therapy concurrent with radiation. Subjects were randomly assigned to receive epoetin alfa or a placebo control, and the hemoglobin target was 14 to 15 g/dL.

J&JPRD also requested cooperative groups and outside investigators conducting oncology studies to conduct their own safety reviews. Subsequently the Company informed FDA that 2 additional studies had been discontinued following review of

preliminary data (September 2003), due to an apparent increase in the frequency of thrombotic vascular events (TVEs) in the epoetin alfa group (PR01-04-005/GOG-0191 [cervical cancer] and EPO-CAN-15 [limited disease small cell lung cancer]). Both studies had hemoglobin targets beyond the correction of anemia.

J&JPRD then discontinued all investigation of hemoglobin correction with epoetin alfa beyond the treatment of anemia in the oncology setting and revised ongoing study protocols to reduce hemoglobin entry criteria and target ranges to more closely reflect correction of anemia. The epoetin alfa investigator's brochure was also revised and provided to all PROCRIT and EPREX investigators. The Company also met with the FDA to review ongoing or completed studies, which could potentially address questions surrounding TVEs or tumor proliferation.

J&JPRD then informed the FDA (December 2003) of 2 additional studies that had been terminated (Study RTOG 99-03 [head and neck cancer] and Study EPO-CAN-20 [non-small cell lung cancer]). Study RTOG 99-03, which was investigating the use of epoetin alfa beyond anemia correction, was suspended following Data Monitoring Committee consideration of adverse results from the ENHANCE study (published in October 2003; Henke et al, 2003). A non-significant trend toward lower locoregional control and an imbalance in survival favoring the control group were observed in the unplanned interim analysis of Study RTOG 99-03. Study EPO-CAN-20 was suspended based on an apparent imbalance in survival favoring the control group, also observed in an unplanned interim analysis. Another study, Study EPO-GBR-7, similar in design to ENHANCE, was previously terminated early for poor accrual (301 of a projected 800 subjects), though no safety signal was observed.

In May 2004, J&JPRD participated in an ODAC meeting, convened to address the safety of erythropoiesis-stimulating agents (ESAs) in patients with cancer. For that ODAC meeting, J&JPRD conducted extensive analyses of its clinical studies database, which showed that, when used for approved indications and within established guidelines for baseline and target hemoglobin concentrations, the safety profile of epoetin alfa therapy was well defined and acceptable. Specifically, mortality, tumor response, and rate of disease progression were all similar between epoetin alfa-treated and placebo-treated subjects with cancer (FDA ODAC Briefing Information, 2004).

J&JPRD has taken several actions since the 2004 ODAC meeting with the goal of ensuring appropriate use of its ESA products, including the following:

- revision of the U.S. Package Insert, the Company Core Data Sheet, and the Summary of Product Characteristics to describe information regarding the potential risk for disease progression and mortality
- dissemination of this information via a "Dear Health Care Professional" letter and the revised and approved package insert (dated 30 June 2004) to the oncology and hematology medical communities, hospital directors of oncology, and pharmacies
- completed studies and revised labels to provide guidance for epoetin alfa treatment of chemotherapy-induced anemia in pediatric patients
- development and implementation of a standardized data collection instrument for prospective data collection of TVEs in epoetin alfa clinical studies
- initiation of a Phase 4 commitment study (Study EPO-ANE-3010) in subjects with metastatic breast cancer to address the question of whether ESAs adversely affect breast cancer outcomes in patients who are receiving treatment according to the product label (Section 7.3.2, Study EPO-ANE-3010: Study in Metastatic Breast Cancer, of the Amgen Briefing Document). A status update for this study has recently been provided to the FDA (March 2007).
- further review of all relevant J&JPRD-sponsored studies in the labeled cancer indications and non-J&JPRD-sponsored studies on the use of ESAs as an adjunct to head and neck radiation upon additional emerging safety data (Studies DAHANCA-10 and Amgen 20010103)
- revision of the Company Core Data Sheet (March 2007) to limit the oncology indication to patients who are receiving myelosuppressive chemotherapy.

Amgen Regulatory History

Amgen has acknowledged the theoretical concerns regarding the potential for tumor promotion with growth factors since the original epoetin alfa approval in 1993 for chemotherapy-induced anemia, as well as at the time of the approval of the CIA indication for darbepoetin alfa in July 2002. Amgen has performed extensive preclinical safety evaluations both pre and post approval (see Preclinical White Paper presented in Appendix 2 of the ODAC Meeting Briefing Document).

With the publication of the controlled trials by Leyland-Jones et al (INT-76; Leyland-Jones, 2003) and Henke et al (2003), performed with epoetin alfa (Eprex®) and epoetin beta (NeoRecormon®) respectively, which raised concerns that erythropoietic agents may worsen survival in patients with cancer, Amgen initiated a thorough investigation of all information in its possession including data available in the public domain at that time.

Although no signal suggesting tumor progression or survival impairment has been observed in preclinical studies of darbepoetin alfa, nor had clinical experience with

darbepoetin alfa from long-term follow-up in oncology clinical trials (Vansteenkiste et al, 2002; Hedenus et al, 2003) revealed a tumor-promoting effect or detrimental effect on survival in subjects with cancer, Amgen took a proactive approach in addressing the recent safety concerns.

Amgen proactively sought a meeting with the FDA (meeting request submitted 19 November 2003) to review the recently published information and Amgen's data pertaining to survival and tumor progression in oncology patients receiving ESAs. FDA granted a Type C meeting which was held on 24 February 2004. The goal of the meeting was to share the above-mentioned information, seek discussion with FDA regarding these recent safety concerns and reach agreement on future appropriate steps in Amgen's ongoing darbepoetin alfa oncology clinical development and pharmacovigilance programs.

As part of the documentation supplied for this meeting, Amgen highlighted to FDA:

- The darbepoetin alfa label already represents the low but real potential for thrombotic events in conjunction with therapy. It also described heightened mortality experience from epoetin alfa nephrology studies (Besarab et al, 1998) that employed high target hemoglobin levels and higher-than-currently-approved dosing regimens.

- Amgen outlined the ongoing, large, randomized, controlled study (20010145) in subjects with small-cell lung cancer (SCLC) receiving placebo versus a front-loading dose of darbepoetin alfa (300 μg once weekly followed by 300 μg Q3W), in which survival was the primary endpoint (described in Section 7.2.1 of the ODAC Meeting Briefing Document). An earlier interim analysis had been added to this study to further strengthen patient safety monitoring. Amgen advised that this study should permit further exploration of the benefit/risk profile of darbepoetin alfa in the oncology population.

- Finally, Amgen advised FDA that it had proactively contacted all investigators conducting investigator-sponsored oncology trials using darbepoetin alfa to request that dosing schedules be revised in accordance with regional labeling, to review study protocols to strengthen support for patient safety, and in some cases, to propose interim analyses.

As part of the outcome of this meeting, Amgen committed to provide details of the five studies now known as those comprising Amgen's pharmacovigilance (PV) program (see section 7 of the ODAC Meeting Briefing Document), and would, where necessary, provide support to investigators to insure that the data is appropriate and of high quality. Amgen has remained committed to this agreement. These studies were presented at the 2004 ODAC (see below) and later, in the context of label discussions addressing inclusion of the Leyland-Jones and Henke study information (corresponding label

changes were approved by FDA December 2004), information was formally requested by the FDA for all five of the PV studies (see Section 7 of the ODAC Meeting Briefing Document for study description/status), to include protocols, statistical analysis plans, data monitoring committee charters, and case report forms (submitted to the FDA in December 2004). These five studies became formal Post Marketing Study Commitments (PMCs) following approval of the BLS for the dosing regimen extension (Q3W) in 2006. It should also be noted that as part of the Q3W BLS submission provided to the FDA in 2005, the corresponding Risk Management Plan included in that filing encompassed the five PV studies as part of Amgen's overall Risk Management Plan.

As noted previously, on 30 March 2004, FDA issued notice of the forthcoming ODAC to be held on 03 and 04 May 2004 [Federal register Vol 69, Number 61]. Amgen participated at this meeting and conducted and presented extensive analysis of studies on darbepoetin alfa performed by the company. Conclusions reached were similar to those reached by J&JPRD in their analysis for epoetin alfa. In addition, Amgen presented the Aranesp Pharmacovigilance Program which includes 5 randomized, prospective clinical trials designed to evaluate specific cancer endpoints in a variety of malignancies, the status of which are addressed in the ODAC Meeting Briefing Document (Section 7). These clinical trials include both investigator-sponsored trials (FR-2003-3005, DE-2001-0033, DE-2002-0015, and SE-2002-9001) and an Amgen-sponsored study (20010145).

Consistent with J&JPRD and in line with its Sponsor responsibilities as BLA Holder, Amgen has also taken various actions since the 2004 ODAC meeting to ensure appropriate use of its ESA products, including the following:

- Ensured appropriate risk communications through the expansion of Warnings and Precautions both in the US labeling as well as the Company Core Data sheet and subsequent label implementation in international markets, to highlight risk of tumor progression and potential impact on survival. These label changes have been accompanied by appropriate communications to health care professionals (Dear Health Care Professional letters) (see Section 7 of the ODAC Meeting Briefing Document for a detailed discussion of Amgen's recent risk minimization and communication actions).

- Promptly advised FDA and other international regulatory agencies of key information received from studies that contribute to the safety questions surrounding survival and tumor progression.

- For the DAHANCA-10 study, Amgen notified the FDA in December 2006 of its receipt of written notification from the principal investigator that indicated that the DAHANCA study group had decided to halt the study for futility in terms of achieving the superiority endpoint. Amgen continues to work with the DAHANCA-10 study team to facilitate obtaining the final results from this study.

- With respect to Amgen's Study 20010103, which evaluated the treatment of anemia in patients with active malignant disease receiving neither chemotherapy nor radiation therapy, results were communicated to the FDA in January 2007 followed by a corresponding Dear Health Care Professional letter that same month.

  In light of the above-mentioned findings from DAHANCA-10 and Study 20010103 appropriate ESA label changes were agreed upon between the companies and the FDA. Such changes provide a warning to health care professionals regarding the risk of a shortened time to tumor progression in patients with advanced head and neck cancer receiving radiation therapy when administered to a target hemoglobin of >12 g/dL.

- Provided consistent support to investigator-sponsored trials defined in the Amgen Pharmacovigilance Program, both prior to and after these studies becoming formal PMCs, in order to facilitate the availability of data from these studies. Amgen has been diligent in maintaining open communication with the principal investigators of these studies. This communication has been in the form of face-to-face meetings, teleconferences and email correspondence with individual investigators. In addition, meetings attended by Amgen representatives and all the principal investigators were held to review clinical trial progress and facilitate sharing of information across the four studies. These studies are ongoing with the timelines for completion still consistent with those PMC timelines agreed with FDA.

- Completed and issued results of the Study 20010145 defined in the Amgen Pharmacovigilance Program in April 2007. This communication was provided to the FDA in the context of a preliminary statistical report, accompanied by the corresponding electronic datasets from the study. Timing of the final clinical study report remains consistent with the PMC timeline agreed with FDA.

- Performed extensive data analysis of all Amgen studies in the oncology population both at a patient level analysis as well as in a meta-analysis approach. A similar approach has been taken with all studies available in the public domain. These analyses are presented in this ODAC Meeting Background Information Document for 10 May 2007.

2. BEST Study Survival Difference: Relationship to Tumor Progression and Thrombotic Vascular Events

The following text is provided as a supplement to the ODAC Meeting Briefing Document, Section 5.1, Safety of Epoetin Alfa in the Treatment of Chemotherapy-induced Anemia.

As the specific cause of death in advanced cancer patients can be very difficult to ascertain, the cause of the survival difference observed in BEST is uncertain. The cause of death most commonly checked off by BEST investigators on the case report form was disease progression, even though time to tumor progression based on investigator assessment did not differ between groups (see Section 5.1.4.1, Clinical Studies, of the ODAC Meeting Briefing Document).

ESAs are associated with an increased risk of TVEs and this information is appropriately reflected in the product labeling. Several recent studies have indicated that this risk may be greater when ESAs are used in non-anemic patients and when patients are treated to high hemoglobin targets, as was the case in BEST. TVEs as a cause of death in patients with cancer may be difficult to diagnose and could account for a substantial proportion of the excess mortality in BEST, rather than tumor progression as attributed by the investigators.

Several lines of evidence support this hypothesis, as follows:

- Time to progression based on investigator assessment showed no suggestion of a difference between the epoetin alfa group and control (Leyland-Jones, 2003). The hazard ratio for this analysis was 0.97 (95% CI: 0.82-1.14).

- In contrast, the incidence of clinically relevant TVEs in BEST was higher in the epoetin alfa group than in the control group.

- The difference in survival rates between the 2 groups was near maximal by 4 months on study. Acceleration of tumor progression might be expected to result in both later separation and continued divergence of the survival curves beyond this time. In contrast, increased TVE hazard would be expected to be greatest early on while most patients are still receiving chemotherapy and (in the treatment arm) epoetin alfa.

- Excess mortality associated with epoetin alfa was almost entirely limited to the population with a body mass index (BMI) greater than 25 and predominantly to the obese population with BMI greater than 30 (Table 1a). The epoetin alfa-associated difference in TVE risk associated with epoetin alfa treatment, like the difference in mortality risk, was greatest in obese patients (Table 1a).

- Although patients with baseline hemoglobin concentration greater than 12 g/dL had better survival than more anemic patients, the *excess* mortality associated with epoetin alfa was predominantly observed in the patients with higher baseline

hemoglobin concentrations (Table 1b). Accelerated tumor progression would not be expected to differentially affect less anemic patients. In contrast, although the small numbers of diagnosed, clinically relevant TVEs observed in BEST in patients with hemoglobin below 12 g/dL did not allow determination of whether TVE risk is lower in the presence of anemia, several studies have suggested additional TVE risk when erythropoietin is used in non-anemic patients.

Table 1a. Mortality and Clinically Relevant Thrombotic Vascular Event Rates and Hazard Ratios by Baseline Body Mass Index (BEST Study Data)

	Baseline BMI	Placebo % (n/N)	Epoetin Alfa % (n/N)	Hazard Ratio 95% CI
Mortality	BMI<18.5	44.4 (4/9)	36.4 (4/11)	1.01 (0.25, 4.03)
	18.5≤BMI<25	30.2 (52/172)	32.4 (56/173)	1.12 (0.76, 1.63)
	25≤BMI<30	22.1 (34/154)	29.3 (44/150)	1.37 (0.88, 2.15)
	BMI≥30	15.7 (19/121)	28.9 (33/114)	2.05 (1.16, 3.60)
Clinically Relevant TVEs				
	BMI<18.5	11.1 (1/9)	18.2 (2/11)	1.64 (0.15, 18.06)
	18.5≤BMI<25	5.8 (10/172)	5.8 (10/173)	1.01 (0.42, 2.42)
	25≤BMI<30	5.8 (9/154)	8.0 (12/150)	1.39 (0.59, 3.31)
	BMI≥30	4.1 (5/121)	10.5 (12/114)	2.74 (0.96, 7.77)

BMI=body mass index; n=number of deaths; N=total number of subjects; TVE = thrombotic vascular events; CI = confidence interval

Table 1b. Mortality and Clinically Relevant Thrombotic Vascular Event Rates Hazard Ratios by Baseline Hemoglobin (BEST Study Data)

	Baseline Hb (g/dL)	Placebo % (n/N)	Epoetin Alfa % (n/N)	Hazard Ratio 95% CI
Mortality	Hb≤10	35.1 (13/37)	44.0 (22/50)	1.44 (0.73, 2.87)
	10<Hb≤11	33.3 (11/33)	37.9 (11/29)	1.18 (0.51, 2.72)
	11<Hb≤12	33.7 (29/86)	31.0 (22/71)	0.91 (0.52, 1.58)
	Hb>12	18.7 (56/300)	27.5 (82/298)	1.58 (1.12, 2.21)
Clinically Relevant TVEs				
	Hb≤10	(0/37)	8.0 (4/50)	(0.00,)
	10<Hb≤11	3.0 (1/33)	6.9 (2/29)	2.45 (0.22, 27.07)
	11<Hb≤12	3.5 (3/86)	5.6 (4/71)	1.60 (0.36, 7.14)
	Hb>12	7.0 (21/300)	8.7 (26/298)	1.29 (0.73, 2.30)

Hb=hemoglobin; n=number of deaths; N=total number of subjects; TVE = thrombotic vascular events

These observations suggest that, assuming the excess mortality in BEST did not arise by chance, an increase in fatal TVEs may have been more of a contributing factor than tumor progression. Given the higher risks for TVEs observed with ESA use in several studies with non-anemic patients and/or high target hemoglobin concentrations (such as BEST), J&JPRD discontinued all such trials in 2003 (see Section 1, Regulatory History, of this document).

3. Future Considerations

In May 2004, J&JPRD initiated a study to investigate the benefit-risk profile of epoetin alfa. Details of Study EPO-ANE-3010 are included in Section 7.3.2, Study EPO-ANE-3010: Study in Metastatic Breast Cancer, of the Amgen Briefing Document. In the conduct of this study, numerous challenges to timely accrual have been encountered.

In recent months, data from several other studies utilizing ESAs in the oncology setting have become available and shed additional light on the safety of ESAs. Amgen and J&JPRD look forward to participating in the deliberations at the 10 May 2007 ODAC meeting regarding the available data from studies of ESAs for patients with cancer. A thorough review of the pertinent data, including meta-analyses, and the advice from the ODAC meeting will help inform the direction that the FDA and the Companies might take in determining appropriate steps to further refine the benefits and safety of ESA therapy in the oncology setting.

As the ODAC deliberates on these matters, we respectfully suggest that several issues regarding the feasibility and interpretation of additional ESA studies merit consideration.

Considerations for Further Pharmacovigilance Studies

- As studies to date have failed to demonstrate that ESAs improve survival in the oncology setting, studies of survival effects will be more difficult to enroll than in the past and may not accrue well in competition with other ongoing therapeutic studies.

- Tumor outcomes are more dependent on the effect of anti-cancer therapy than on any potential effect of ESAs, as existing studies suggest that ESA effects on survival or tumor proliferation within the labeled hemoglobin range must be extremely small, if present at all. Thus, any impact of an ESA would be potentially obscured by the response to chemotherapy. The most efficient way to evaluate the safety of ESAs is in a population of patients with cancer who are not receiving chemotherapy. However, such studies may be difficult to implement, based on prior study results.

- Variability due to tumor type, stage, and chemotherapy can be partially addressed by studying a population with “homogeneous tumors with homogeneous chemotherapy.” These criteria, however, do not define a patient population with a uniform prognosis. Patients enter chemotherapy-induced anemia ESA studies only after becoming anemic. The “time to develop anemia” is variable and in itself a potential predictor of risk. Thus, stratifying on “time to develop anemia” would be advisable from a scientific standpoint, but may require sacrificing other stratification factors to implement.

- Patients who respond well to initial chemotherapy before becoming anemic will not have measurable disease. This further challenges the feasibility of identifying a large, relatively homogeneous, population.

- Can safety be extrapolated from studies showing consistent results in a few common tumor types? What would be an acceptable degree of risk to exclude by such studies?

- Given the difficulties in recruiting large studies with homogenous populations in terms of tumor type, stage, therapy, and other key variables, can studies in mixed-tumor populations provide useful data on important outcomes other than tumor proliferation, for example, transfusion reduction, patient-reported outcomes, and TVEs?
- Would additional patient-level pooled analyses conducted by independent experts (eg, the Cochrane group) provide meaningful data to inform the risk/benefit assessment of ESAs as well as potentially help inform the design of additional studies?

Considerations in the Evaluation of Different Hemoglobin Targets

- Studies comparing labeled hemoglobin targets to lower targets must enroll patients with lower baseline hemoglobin concentrations. This limits the pool of eligible patients and further challenges feasibility. Lower baseline hemoglobin concentrations may also define a higher-risk subset of the oncology patient population and, therefore, results may not be generalizable.

- Studies comparing different ESA hemoglobin targets within the correction of anemia will have limited sensitivity to detect clinically meaningful differences in ESA effects on survival. These studies would be particularly limited in their capability to detect any possible survival effect given that studies of anemia correction to date and results of meta-analyses indicate that if any effects on survival exist in that setting, they must be extremely small.

- The extent to which investigators and patients will be interested in conducting and participating in studies comparing different hemoglobin targets is not clear.

4. References

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