

MEMORANDUM

Date: May 1, 2004

Subject: Errata for FDA Briefing Document for May 4, 2004 Oncologic Drugs Advisory Committee Meeting on Evolving Safety Issues Associated with Erythropoietin Products

Additions (with the exceptions of the replacement table identified below) are in BOLD type and deletions are in strikeout.

Page 4 Executive Summary

Under a contractual agreement, Ortho Biotech L.P. has rights to development and marketing of Procrit for any indication other than for the treatment of anemia associated with chronic renal failure **in patients undergoing dialysis and diagnostics.**

Page 6 (Section I)

In addition to proliferation and differentiation of erythroid precursors, erythropoietin has also been shown to be an ~~erythrocyte~~ **erythroid** survival factor, by modulating pro- and anti-apoptotic mechanisms, and a pro-angiogenic factor⁵.

Page 6 (Section I)

~~There are two types of~~ **is only one** erythropoietin receptors, **but, possibly due to the presence of different accessory proteins in the membrane and tissue-dependent receptor numbers, two different receptor affinity classes are observed.** ~~High~~ **High** affinity receptors, **are** expressed predominantly on hematopoietic cells, **and have** ~~with~~ **with** ~~kDs~~ **kDs** of approximately 95 pM, **and while** low affinity receptors **are** expressed **primarily** on non-hematopoietic cells, ~~with~~ **and have** binding affinities of approximately **96 pM to 16 nM**. ~~The binding affinity of an erythropoietin ligand for the erythropoietin receptor is not only influenced by the type of receptor alone, but also by tissue dependent receptor numbers and accessory proteins⁸.~~

While the role of.....erythropoietin receptors expressed on **some of** these tissues are functional.

Page 8 (Section II)

Arcacoy, et al³³ examined 26 mammary tumor biopsies **from 10 patients.**

Page 9 (Section II)

A lack of proliferative response on erythropoietin receptor-positive cells was also observed by Takashita, et al⁴² when primary AML and ~~melanoma~~ **ALL** cells were treated with exogenous erythropoietin.

Page 10 (Section III)

References 44, 45, and 45 are incorrect and should read changed from "Ibid" to "Summary for Basis of Approval, Epoetin alfa (EPOGEN), June 1, 1989."

Page 18 (Section V)

6). Slope (m) was classified by group, as follows:

$m \leq 0.1$ g/dL/week (≤ 1 g/dL per 10 weeks)

$m > 0.1$ and ≤ 0.2 g/dL/week (1 g/dL per < 10 to 5 weeks)

$m > 0.2$ and ≤ 0.25 g/dL/week (1 g/dL per < 5 to 4 weeks)

$m > 0.25$ and ≤ 0.333 g/dL/week (1 g/dL per < 4 to 3 weeks)

$m > 0.333$ and ≤ 0.5 g/dL/week (1 g/dL per < 3 to 2 weeks)

$m > 0.5$ and ≤ 1 g/dL/week (1 g/dL per < 2 to 1 week)

$m > 1$ g/dL/week (1 g/dL per < 1 week)

Page 18 (Section V)

For Aranesp-treated subjects, there were trends suggesting possible associations between reported Hgb values >13 and seizures, hypertension (HTN), and arrhythmias, though the latter appeared to be associated with Hgb values $\geq \leq 11$ g/dL, as well. Importantly, Hgb values of $\geq \leq 13$ g/dL did not appear to be associated with increased risks of these events. Of note, for ARANESP-treated subjects, Hgb values $\leq \leq 10$ g/dL appeared to be associated with excess risks of fluid overload, CHF, pulmonary edema, acute MI and TVA, whereas these risks were not apparent at Hgb values $\geq >10$ g/dL.

Page 23 (Section V)

Note that event rates (bottom panel) tend to be similar for all ROR categories ≤ 0.50 g/dL/week, whereas event rates for ROR > 0.50 g/dL/week tend to be higher. The individual Hgb categories are summed in the bottom row ("All Slopes"). The lowest event rates are in the >11 to ≤ 12 g/dL Hgb category.

Page 26 (Section VII.)

Post-Marketing Study to Assess for Tumor Stimulatory effects of EPOGEN/Procrit: Study N93-004

Page 26 (Section VII)

In July 2001, Amgen and Ortho Biotech LP notified FDA of its intention to prematurely terminate the study after accrual of ~~225~~ **224** subjects

Page 27 (Section VII.)

Twenty-two percent of the subjects in the Procrit arm and 23% of the subjects in the placebo arm ~~expired~~ **experienced** at least one thrombotic vascular event.

Page 27 (Section VII, table, column 2, row 3)

Correction of upper bound of the 95% confidence interval around observed response rate in placebo arm (upper bound should read **76%** rather than 67%)

Page 28 (Section VII.)

Correction of incidence of myocardial infarction in table (should read **0%** rather than 2%)

The median duration of survival (based on Kaplan Meier estimates) was 10.5 months among Procrit-treated subjects compared with ~~20.4~~ **10.4** months among placebo-treated subjects.

Page 30 (Section VIII.)

The recommended starting dose of ~~EpoGen~~/Procrit in cancer patients receiving chemotherapy in the package insert is 150 Units/kg t.i.w. However, many community oncologists administer ~~EpoGen~~/Procrit at a dose of 40,000 Units once a week. FDA is currently reviewing the results of a study⁵⁵, in which 344 patients with cancer receiving chemotherapy were randomized to receive either placebo or ~~EpoGen~~/Procrit 40,000 U/week.

Page 34 (Section IX).

INCIDENCE OF AEs ASSOCIATED WITH EPOETIN ALFA

	ISS			Protocol 980297	
	Aranesp	Placebo	Procrit	Aranesp	Placebo
	n=86273	n=2217	n=1153	n=155	159
Hypertension+	3.7%	3.2%	2%	9 (6%)	6 (4%)
Convulsions**	0.6%	0.5%	0.4%	0	1 (1%)
Thrombotic events\$	6.2%	4.1%	5.4%	7 (5%)	5(3%)

Page 35 (Section IX)

There was also a ~~trend toward~~ higher incidences of **deep venous thrombosis (3.3% vs. 2.7% placebo controls)** ~~thrombophlebitis thrombophlebitis deep, and thrombosis-in~~ Aranesp-treated patients.

Incidence of Thrombotic Events By Preferred Term

Preferred term	rHuEPO	Aranesp	Placebo
	N= 115	N=873	N=221
Embolism, pulmonary	0	11	0
Thromboembolism	0	1	0
Thrombophlebitis	0	4	0
Thrombophlebitis , deep	0	2	1
Thrombosis, venous	1	8 9	2
Thrombosis, venous deep	3 5	27 29	6
Thrombosis	0	5	0
Total # Thrombotic AEs	4 (4.7%) 6(5.2%)	58 (7.4%) 61(7.0%)	9 (4.1%)
Total pts with AEs	85	781	221

Delete current table and replace with the following:

Adverse Event	Event Rates as a function of the slope of increase in hemoglobin (g/dL/week) in 873 patients with cancer receiving Aranesp in clinical studies							
	≤ 0.1	>0.1-0.2	>0.2-0.25	>0.25-0.333	>0.333 to 0.5	0.5 to >0.67	>0.67	Unknown
# of slopes	1074	686	635	404	1177	640	1758	2033
Hypertension	1.9	2.9	4.7	7.4	2.5	1.6	5.1	1.0
Seizures	0.9	1.5	0.0	0.0	0.0	0.0	1.1	0.0
Vascular*	1.9	7.3	0.0	2.5	2.5	7.8	4.0	5.9
Fluid overload	27.0	27.7	28.3	27.2	31.4	26.6	31.3	45.3
Cardiac arrest	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Acute MI	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
CVA	0.0	0.0	1.6	0.0	0.0	0.0	0.4	0.0

*thrombosis, ischemia, infarction

The analysis provided **does not suggest an association between more rapid ROR and thrombotic events in patients with cancer receiving Aranesp.** suggests that the incidences of hypertension and vascular events are increased in patients with higher ROR compared to those who had less rapid ROR.

Page 37 (Section IX)

Corrections to Table titled “Assessment of ROR and Maximum Hemoglobin Levels in Relationship to the Development and Time of Onset of Pulmonary Emboli in Aranesp-Treated Patients”

- Rows 9-12, column 2 “OW” should read “**QW**”
- Row 1, columns 7 and 8, units should read **g/dL** rather than µg/dL

Page 38 (Section X)

The trial was not powered for survival, but there was a trend in overall survival favoring the ~~EPREX~~ **placebo** arm (log rank test p=0.13; Cox regression analysis hazards ratio of 1.3069 (p=0.0542)).

Page 39 (Section X)

The study drug was withheld if the hemoglobin rose above 14 g/dl **or if rate of rise in hgb exceeded 2 g/dL/month.**

Page 40 (Section X. 3rd bullet)

Twice as many patients in EPREX arm experienced **death due to** disease progression **within four months of randomization** as in the placebo arm: 28 (6%) versus 13 (3%).

Page 40 (Section X. 4th bullet)

There was also an increased incidence **of death in the first four months of study due** to thrombotic vascular and cardiovascular adverse events: 2.3% in the EPREX arm versus 0.4% in the placebo arm.

Page 42 (Section X)

Correction of lower bound of 95% CI for HR in the ITT population; should read **1.37** and not 1.07

Page 49 (Section XII)

Title of Section XII should read “Procrit **and EPREX** Trials Halted by Johnson & Johnson For Excessive Thrombotic and Cardiovascular Adverse Events”

Page 49 (Section XII)

The objective of this study is to evaluate the impact of maintaining Hgb in the range of 14 to 16 g/dl on disease progression-free survival using EPREX (Epoetin alfa)/~~Procrit~~ or placebo

Page 50 (Section XII)

Of these 106 patients, ~~3 (6%)~~ **2(4%)** placebo and ~~18 (34%)~~ **16 (30%)** epoetin alfa-treated subjects had a thrombotic vascular event reported.

Page 52 (Section XII, table, column 1, row 10)

Correction of Treatment Subject ID from 15 to 1145

Page 55 (Section XII)

Trial suspended effective Sept. 12, 2002~~3~~.

Page 58 (Section XII)

2. A large proportion of patients on the trial had **not** completed the 12 week QoL assessment (the primary outcome measure), due to high rates of mortality.

Page 61

...dosing resumed when Hgb = 13.5 in males and = \leq 12.5 in females, at a dose reduction of 30,000 IU.

Page 62 (Section XIV)

In the EPO-INT-76 trial, in a population of women with metastatic breast cancer, at four months, there was a higher incidence of **death attributed to** cardiovascular/thrombotic vascular events in the group who received EPREX (~~10.4%~~ in the placebo arm versus 2.3% in the EPREX arm).