

Appendix 2: Risk Management Considerations for ESAs



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

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To: FDA Oncology Drugs Advisory Committee

Thru: Gerald Dal Pan, MD, MHS
Office of Surveillance and Epidemiology (OSE)

From: **OSE Review Team**
Lead Author:
Claudia Karwoski, PharmD, Acting Director, Division of Risk Management (DRM)

Janet Anderson, PharmD, Project Manager, OSE-IO
Marcia Britt, PhD, Regulatory Health Specialist, DRM
Mary Dempsey, Risk Management Coordinator, DRM
Jodi Duckhorn, MA, Team Leader, DRM
Laura Governale, PharmD, M.B.A., Team Leader, Division of Epidemiology
Betsy Scroggs, Pharm.D., Safety Evaluator, Division of Adverse Event Analysis

Subject: Risk Management Considerations for the Erythropoiesis Stimulating Agents

Products: Epogen/Procrit (epoetin alfa), BLA 103234
Aranesp (darbopoetin alfa), BLA 103951
Mircera (methoxy polyethylene glycol-epoetin beta), BLA 125164

OSE RCM #: 2008-277

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EXECUTIVE SUMMARY

The erythropoiesis-stimulating agents (ESA) are associated with a number of serious risks including pure red cell aplasia, thromboembolic disease events among patients with chronic renal failure, and promotion of tumor growth and decreased survival in cancer patients treated anemia secondary to chemotherapy. As of February 2008, eight randomized clinical trials have demonstrated decreased survival and/or decreased time to locoregional tumor progression.

A number of communication strategies have been implemented to address the risk of tumor progression and decreased survival including labeling revisions, health advisories, press releases, healthcare professional sheets, MedWatch Safety Alerts, E-mailed burst communications to healthcare professional societies, and Dear Healthcare Professional letters. We recommend the Advisory Committee discuss additional risk minimization strategies to 1) risk communicate to the prescriber and patient about the important risk-benefit information, and 2) to guide appropriate use.

1 BACKGROUND

1.1 PRODUCT INFORMATION AND APPROVAL HISTORY

The erythropoiesis-stimulating agents (ESA) were first licensed in the US in 1989 for the treatment of anemia in patients with chronic renal failure (CRF); the first approval of an ESA, for treatment of chemotherapy-associated anemia, was in 1993.

There are currently three ESA products licensed in the US:

- Epoetin alfa is manufactured by Amgen as Epogen and Procrit. Epogen is distributed by Amgen for the anemia of chronic renal disease indication and Procrit is distributed by Ortho Biotech (a subsidiary of Johnson & Johnson) for all other indications.
- Darbepoetin alfa is manufactured by Amgen as Aranesp
- Methoxy polyethylene glycol-epoetin beta is manufactured by Hoffman-La Roche as Mircera

Epoetin alfa is currently indicated for the treatment of the following conditions:

6/1/89	Treatment of Anemia of Chronic Renal Failure Patients
12/31/90	Treatment of Anemia in Zidovudine-treated HIV-infected patients
4/1/93	Treatment of Anemia in Cancer Patients on Chemotherapy
12/23/96	Reduction of Allogenic Blood Transfusion in Surgery Patients

Darbepoetin alfa is currently indicated for the treatment of the following conditions:

9/17/01	Treatment of Anemia of Chronic Renal Failure Patients
7/19/02	Treatment of Anemia in Cancer Patients on Chemotherapy

Methoxy polyethylene glycol-epoetin was approved on November 14, 2007 for the treatment of anemia associated with chronic renal failure. It is not indicated for the treatment of anemia due to cancer chemotherapy.

1.2 SAFETY CONCERNS IN CANCER

The serious risks associated with the ESAs include pure red cell aplasia, thromboembolic disease events among patients with chronic renal failure, hypertension, seizures, and promotion of tumor growth and decreased survival in cancer patients for treated anemia secondary to chemotherapy.¹

Tumor promotion and decreased survival were observed in several clinical studies most of which used unapproved dosing regimens. The results of two of the studies, ENHANCE and BEST, were presented to the ODAC in May 2004. These studies were specifically designed to test whether the use of an ESA at a dose intended to achieve and maintain a hemoglobin of >12 g/dL would improve tumor outcomes and survival compared with standard transfusion support. The results instead showed evidence of detrimental effects on survival and tumor outcomes.²

Additional studies have accumulated since that time regarding the increased risks of mortality and of possible tumor promotion from the use of ESAs. At the March 2007 ODAC, FDA presented five studies with evidence of increased tumor promotion or decreased survival when hemoglobin was targeted at values >12 g/dL (BEST, ENHANCE, DAHANCA, 161, CAN-20) and one study with evidence of decreased survival with target hemoglobin < 13g/dL (103). Results of these studies led to additional labeling changes in November 2007. Since those labeling changes, FDA has learned of findings from two additional clinical studies (PREPARE and GOG-191 studies) showing an increase in mortality and shorter time to tumor progression in patients with cancer receiving an ESA.³

The biological plausibility of the observed findings is supported by demonstration of the presence of erythropoietin receptors on malignant cells. However a direct relationship between the presence of erythropoietin receptors on tumor and tumor proliferation in response to exogenous erythropoietin has not been established.

1.3 OVERALL ESA DRUG USE PATTERNS

Usage data by dispensed prescriptions, number of patients, prescribing specialty and indications for use was requested for the three currently marketed ESA's, Epogen[®] (epoetin alpha), Procrit[®] (epoetin alpha), Aranesp[®] (darbepoetin alpha), for the last 5 calendar years, 2003 through 2007. The complete review of this data is provided as Appendix A.

¹ Aranesp (darbepoetin alfa) for Injection Prescribing Information (Issue date 11/2007) available at http://wwwext.amgen.com/pdfs/misc/aranesp_pi.pdf

Epogen (epoetin alfa) for Injection Prescribing Information (Issue date 11/2007) available at http://wwwext.amgen.com/pdfs/misc/epogen_pi.pdf

Procrit (epoetin alfa) for Injection Prescribing Information (revised 11/2007) available at <http://www.procrit.com/procrit/shared/OBI/PI/ProcritBooklet.pdf#page=1>

Mircera (Methoxy polyethylene glycol-epoetin beta) Solution for Injection (approved 11/14/07) available at <http://www.fda.gov/cder/foi/label/2007/1251641b1.pdf>

² FDA Briefing Material: Continuing Reassessment of the Risks of Erythropoiesis-Stimulating Agents (ESAs) Administered for the Treatment of Anemia associated with Cancer Chemotherapy available at <http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4301b2-02-FDA.pdf>

³ Information on Erythropoiesis Stimulating Agents (ESA) (marketed as Procrit, Epogen, and Aranesp) available at <http://www.fda.gov/cder/drug/infopage/RHE/default.htm>.

- Wholesale distribution data show that the outpatient clinic setting is the largest setting of use for Epogen[®] and Aranesp[®], each accounting for approximately 97% and 54% sales, respectively. The largest setting of use for Procrit[®] was non-federal hospitals, accounting for approximately 39% of vials sold to that channel.
- Outpatient retail pharmacy distribution accounted for approximately 11%, 5%, and less than 1% of wholesale distribution for Procrit[®], Aranesp[®], and Epogen[®], respectively. Interestingly, the long-term care channel accounted for approximately 10% and 5% of sales distribution for Procrit[®] and Aranesp[®], respectively.
- The most common ESA product dispensed from outpatient retail pharmacies was Procrit[®], accounting for approximately 66% to 70% of the outpatient prescription market during years 2003 through 2007.
- The top two diagnoses or indications associated with the use of Procrit[®] and Aranesp[®] as reported by office-based physician practices were “other and unspecified anemias” (ICD-9 285), and “chronic kidney disease” (ICD-9 585), each accounting for roughly 60% and 12% of use during year 2007. “Chronic kidney disease” (ICD-9 585) and “other and unspecified anemias” (ICD-9 285) accounted for approximately 38% and 37% of use for Epogen[®].
- “Lymphoid leukemia” was the only cancer-related diagnosis reported as the primary reason for treatment for Procrit[®]. “Malignant neoplasm of prostate” (ICD-9 185) also appeared as a concurrent cancer-related diagnosis with “other and unspecified anemias” (ICD-9 285) as the primary diagnosis for Procrit[®].
- No cancer-related diagnoses were reported as the primary reason for treatment visit for Aranesp[®], however, “malignant neoplasm of trachea, bronchus, and lung” (ICD-9 162) and malignant neoplasm of colon” (ICD-9 153) were reported as concurrent diagnoses with “other and unspecified anemias” (ICD-9 285) as the primary diagnosis for Aranesp[®].
- No cancer-related diagnoses were reported as the primary or concurrent diagnosis for Epogen[®].

2 RISK MANAGEMENT STRATEGIES

A variety of tools or strategies are used to minimize risks associated with drugs and therapeutic biologics. Tools minimize risks in a number of ways. Tools communicate specific risk information as well as information regarding optimal product use. Tools provide guidance and/or assure adherence to certain prescribing/dispensing requirements or monitoring, and/or limit use of a product to only the most appropriate situations or patient populations.

Because the risk of tumor progression and decrease in survival are not thought to be risks that are preventable, the goals of risk minimization strategies are limited 1) communicating risk to the prescriber and patient about the important risk-benefit information, and 2) guiding appropriate use.

2.1 ACTIVITIES TO DATE

2.1.1 COMMUNICATION OF RISK INFORMATION

Since the March 2007 ODAC, the labeling for the ESAs was implemented consistent with the AC’s recommendations. The following safety messages have also been conveyed through FDA communications (Public Health Advisories, Press Releases, Healthcare Professional Sheets, MedWatch Safety Alerts, and E-mailed burst communications to healthcare professional societies) and recent revisions to the each of the ESA product labels:³

- ESAs shortened the overall survival and/or time-to-tumor progression in patients with various cancers
- Risks of shortened survival and tumor progression have not been excluded when ESAs are dosed with the intent to achieve hemoglobin levels <12g/dL
- Use ESAs only in the treatment of anemia due to concomitant myelosuppressive chemotherapy
- Use the lowest dose of ESA needed to avoid red blood cell transfusions. Do not exceed the upper safety limit for hemoglobin levels of 12 g/dL
- Reduce the ESA dose by 25% when hemoglobin reaches a level needed to avoid transfusion
- Withhold dosing with an ESA when hemoglobin level exceeds 12 g/dL
- Restart dosing at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required
- Discontinue treatment with an ESA following the completion of a course of chemotherapy

The Sponsor has also issued Dear Healthcare Professional letters to oncologists about study findings and labeling changes.⁴

Patient Package Inserts (PPIs) for the ESAs were approved with the labeling revisions on November 8, 2007. PPIs are part of FDA-approved labeling but the sponsors are not obligated to make these available to patients. FDA has required the ESA sponsors to convert the PPIs to Medication Guides for all ESA products. Dissemination of Medication Guides is required at the point of dispensing. Medication Guides are required for a small number of products that FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information necessary for the product's safe and effective use. FDA requires that Medication Guides be issued with certain prescribed drugs and biological products when the Agency determines that certain information is necessary to prevent serious adverse effects; patient decision-making should be informed by information about a known serious side effect with a product; or patient adherence to directions for the use of a product are essential to its effectiveness.

2.1.2 ENSURING APPROPRIATE USE OF ESAS

Although the FDA to date has not intervened in the way ESAs have been prescribed and used, the labeling revisions and communications appear to have facilitated a revision in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines: Cancer and Treatment-Related Anemia.⁵

In July 2007, the Centers for Medicare and Medicaid Services (CMS) issued a National Coverage Determination that stipulates ESAs would be covered for the treatment of anemia secondary to myelosuppressive anticancer chemotherapy in solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia when the hemoglobin level immediately prior to initiation or maintenance of ESA treatment is <10 g/dL. ESAs would not be covered under the following conditions:⁶

- Any anemia in cancer or cancer treatment patients due to folate deficiency, B-12 deficiency, iron deficiency, hemolysis, bleeding, or bone marrow fibrosis;
- Anemia associated with the treatment of acute and chronic myelogenous leukemias (CML, AML), or erythroid cancers;

⁴ Amgen/Ortho Biotech – Dear Healthcare Professional Letter issued November 8, 2007 available at http://www.amgen.com/pdfs/misc/healthcare_professionals_letter.pdf

⁵ http://www.nccn.org/professionals/physician_gls/PDF/anemia.pdf

⁶ NCD for Erythropoiesis Stimulating Agents(ESAs) in Cancer and Related Neoplastic Conditions (110.21) available at <http://www.procritline.com/lmrp/ncd.cms.2.pdf>

- Anemia of cancer not related to cancer treatment;
- Any anemia associated only with radiotherapy;
- Prophylactic use to prevent chemotherapy-induced anemia;
- Prophylactic use to reduce tumor hypoxia;
- Patients with erythropoietin-type resistance due to neutralizing antibodies; and
- Anemia due to cancer treatment if patients have uncontrolled hypertension

Some private insurers have altered their coverage, required prior authorization, or taken other measures such as monitoring hemoglobin levels to ensure appropriate use.⁷

2.1.3 USE TRENDS FOLLOWING RISK MANAGEMENT ACTIVITIES

Use appears to have declined between year 2006 and 2007 for all three of these agents. As indicated in the table 1 below.

Total number of dispensed prescriptions for Procrit®, Aranesp®, and Epogen® from U.S. outpatient retail pharmacies (mail order excluded) for years 2003 through 2007.

	2003		2004		2005		2006		2007	
	Retail TRxs	Share								
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	504,432	100.0%	492,742	100.0%	491,755	100.0%	534,802	100.0%	454,640	100.0%
Procrit	353,989	70.2%	336,800	68.4%	323,201	65.7%	364,636	68.2%	319,054	70.2%
ARANESP	52,032	10.3%	75,772	15.4%	101,922	20.7%	116,369	21.8%	95,847	21.1%
Epogen	98,411	19.5%	80,170	16.3%	66,632	13.5%	53,797	10.1%	39,739	8.7%

Source: Verispan, LLC. Vector One: National. Years 2003 - 2008. Extracted 2-7-08. File: VONA ESA TRx 2-7-08.qry

The Sponsor’s background package indicates that the number of patients receiving darbepoetin alfa for chemotherapy induced anemia (CIA) has declined by 48% (data not provided). They also indicate that oncologists are initiating ESAs at lower hemoglobin levels than prior to the labeling changes.⁷ What is not clear is the extent to which the ESAs are used off-label (e.g., anemia of cancer not related to cancer treatment, anemia associated only with radiotherapy, or prophylactic use to prevent CIA) or the average length of therapy and whether these parameters have improved following the CMS reimbursement changes, the risk communication activities and labeling revisions.

2.2 ADDITIONAL RISK MANAGEMENT STRATEGIES FOR CONSIDERATION

In this section, we provide an overview of additional possible risk management tools that might be used to manage the risks of ESAs.

- **Informed Consent/Patient Agreement**

The informed consent process could be used to facilitate communication between a patient and physician. The result of this communication is the patient's authorization or agreement to undergo treatment with the ESA. In the process, the physician prescribing the ESA treatment would discuss with the patient:

- The nature and purpose of a proposed ESA treatment

⁷ 13 March 2008 ODAC Meeting Briefing Document-Epoetin alfa (Epogen/Procrit) and darbepoetin alfa (Aranesp); pg 72.

- The risks and benefits of a ESA treatment including the potential increased risk of tumor progression
- Alternative treatment including the risks and benefits of the alternative treatment
- The risks and benefits of not receiving or undergoing a treatment or procedure.

The informed consent process gives the patient the opportunity to ask questions to elicit a better understanding of the treatment, so that he or she can make an informed decision to proceed or to refuse treatment with the ESA. Informed consent (also referred to as Patient Agreements) is required for several products including Lotronex, Accutane, Tysabri,

- **Limits in Advertising and Promotion**

Limits might include self-imposed restrictions on advertising and promotion of ESAs including:

- No direct-to-consumer (DTC) advertising – the Sponsor states that DTC broadcast advertising has been discontinued since 2005⁸
- Restrictions on physician incentives
- Limited professional promotion to specific, defined specialties and journals for very defined populations

- **Restricted Distribution System**

Appropriate use conditions can also be implemented through a program that links product access to compliance with elements to assure safe use. Restricted distribution systems may include:

- Limit ESA prescribing to enrolled prescribers who agree and are willing to the following conditions in order to prescribe an ESA:
 - i. Educate patients on the benefits and risks of treatment with an ESA, including the risk of shortened the overall survival and/or time-to-tumor progression in patients with various cancers, provide patients with a Medication Guide, instruct them to read it, and encourage them to ask questions when considering treatment with an ESA.
 - ii. Use ESAs only in the treatment of anemia due to concomitant myelosuppressive chemotherapy
 - iii. Use the lowest dose of ESA needed to avoid red blood cell transfusions. Do not exceed the upper safety limit for hemoglobin levels of 12 g/dL
 - iv. Reduce the ESA dose by 25% when hemoglobin reaches a level needed to avoid transfusion
 - v. Withhold dosing with an ESA when hemoglobin level exceeds 12 g/dL
 - vi. Restart dosing at 25% below the previous dose when the hemoglobin approaches a level where transfusions may be required
 - vii. Discontinue treatment with an ESA following the completion of a course of chemotherapy
- Limit distribution of ESAs to pharmacies (inpatient and outpatient) who enroll and who certify:
 - i. They will only accept prescriptions from enrolled prescribers

⁸ 13 March 2008 ODAC Meeting Briefing Document-Epoetin alfa (Epoen/Procrit) and darbepoetin alfa (Aranesp); pg 72.

- ii. They will only distribute ESAs to dialysis centers, physicians offices, or infusions that are registered with Company
- Limit distribution of ESAs to clinics, physicians' offices, or dialysis centers who enroll and who certify:
 - i. They will only administer the ESA to enrolled patients
 - ii. They will only accept prescriptions from enrolled prescribers
- Limit dispensing or administration to patients with evidence or other documentation of safe use (e.g., target hemoglobin values)

3 DISCUSSION

A number of communication strategies have been implemented to address the risk of tumor progression and decreased survival including labeling revisions, health advisories, press releases, healthcare professional sheets, MedWatch Safety Alerts, E-mailed burst communications to healthcare professional societies, and Dear Healthcare Professional letters. While communication tools are important to communicate the messages and educate the prescriber and patient, there is limited experience on their effectiveness in ensuring safe use of a product. Traditional risk communication tools such as labeling and Dear Healthcare Professional letters have been shown to have little effect on impacting prescribing behavior or increasing compliance with labeled laboratory monitoring recommendations.^{9,10,11,12} The impact of the communication strategies for the ESAs in communicating risk and in how these products are prescribed is not known and for the more recent communications may be too soon to realize; however overall use of ESAs appears to have declined between 2006 and 2007. The Sponsor also provides some information that suggests more judicious use of ESA following the risk communication activities.¹³

The effectiveness of informed consent as a risk communication tools for marketed products is also largely unknown. We have no information on the effectiveness of the informed consents for Soriatane and Cylert as these were implemented without a plan to evaluate their effectiveness. We are not even sure to what extent the informed consents are being completed because there was no requirement to complete them in order to receive or prescribe these products. We do have some data on the compliance with the patient-physician agreement (e.g., informed consent) for Lotronex. According to summary data of the Lotronex Patient Follow-up Survey, a survey designed to monitor compliance with the Lotronex RiskMAP as well as other aspects (e.g., dosing, cognitive information), 93% of surveyed patients had signed a patient-physician agreement (e.g., informed consent) and 96% of surveyed patients said that their physician discussed benefit-risk of Lotronex.¹⁴

⁹ Willy M, et al. *A study of compliance with FDA recommendations for pemoline (Cylert)*. J Am Acad Child Adolesc Psychiatry. 2002 Jul;41(7):785-90.

¹⁰ Graham D, et al. *Liver enzyme monitoring in patients treated with troglitazone*. JAMA. 2001 Aug 15;286(7):831-3.

¹¹ Smalley W, Shatin D, Wysowski D, Gurwitz J, Andrade S, et al. *Contraindicated Use of Cisapride: Impact of Food and Drug Administration Regulatory Action*. JAMA 2000;284(23):3036-3039.

¹² Weatherby LB, Nordstrom BL, Fife D, Walker AM. *The Impact Of Wording in "Dear Doctor" Letters and In Black Box Labels*. Clin Pharmacol Ther. 2002;72:735-742.

¹³ 13 March 2008 ODAC Meeting Briefing Document-Epoetin alfa (Epoen/Procrit) and darbepoetin alfa (Aranesp); pg 72.

¹⁴ Lotronex (alosetron) Tablets. GlaxoSmithKline, Briefing Document for DSaRM, May 5, 2004, pg 38; available at http://www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4040B1_13_Glaxo-Background.pdf

While the extent to which advertising (including DTC advertising), promotion, and physician incentives may have played in the use of ESAs is unknown to the FDA, given the serious safety issues associated with the class of product, measures to curtail these activities should be strongly considered.

Although the data are limited, risk minimization strategies that link product access to compliance with elements to assure safe use appear effective in minimizing product risks. Examples include the restricted distribution systems implemented for Thalomid (thalidomide) and Clozaril (clozapine). Clozaril, a drug approved for treatment-resistant schizophrenia, is associated with agranulocytosis. It was approved with a restricted distribution system that ensured the weekly monitoring of patients' white blood count (WBC). A WBC that is discovered to be too low prompts certain action such as drug discontinuation on a temporary or permanent basis and more frequent monitoring. Analyses of the data collected in the Clozaril National Registry (CNR) on WBC monitoring indicate that while the rate of leucopenia remained unchanged, the use of the CNR was associated with far lower than expected agranulocytosis-related morbidity and mortality. CNR provides an important mechanism for monitoring and optimizing compliance of WBC monitoring by patients and treatment systems.¹⁵

Thalomid was approved with a RiskMAP entitled the System for Thalidomide Education and Prescribing Safety (STEPS) because of the link between thalidomide use and congenital malformations discovered in Europe over four decades ago. The RiskMAP was put into place to prevent fetal exposure to thalidomide. Female patients who are able to become pregnant are required to undergo routine pregnancy testing and must commit to using appropriate birth control methods. The STEPS program appears to be effective in preventing fetal exposure to thalidomide. A review of the STEPS program, presented to an Advisory Committee in 2004, indicated that there has been one thalidomide-exposed pregnancy reported (ending in miscarriage) and there have been no reports of fetal malformations. There is additionally good compliance with pregnancy testing and patient reported contraceptive use in females of child-bearing potential treated with thalidomide.¹⁶

There are disadvantages to restrictive distribution programs. In general they are difficult to implement and we anticipate that implementing restrictive programs for the three ESAs would present very unique challenges. While the risk-benefit of ESAs for anemia of chemotherapy in cancer patients is being considered today, any restrictive distribution program would need to apply to all patients and for all indications. The program would require participation by all participants, including prescribers, clinics, hospitals, dialysis centers, mail order and retail pharmacies. But there would likely need to be customization for each indication because the risk-benefit considerations are different as are the dosing regimens and length of therapy are vastly different. Such a program would be extremely complex and may have unintended consequences, such as obstructing patient access or driving patients to seek alternative product sources (e.g., internet sales). In order to implement a restricted distribution program for the ESAs, the Sponsors should seek input from stakeholders and develop programs for the ESAs with similar elements to minimize burden on the healthcare delivery system.

4 CONCLUSION

¹⁵ J Clin Psychiatry 1998; 59 (suppl 3);3-7.

¹⁶ Drug Safety 2006; 29(4):321-9.

A number of communication strategies have been implemented to address the risk of tumor progression and decreased survival. We recommend the advisory committee discuss additional risk minimization strategies to 1) risk communicate to the prescriber and patient about the important risk-benefit information, and 2) to guide appropriate use.

APPENDIX A. Utilization patterns of Erythropoetin Stimulating Agents (ESA's)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Date: February 11, 2008

To: Claudia Karwoski, Pharm.D.
Acting Director
Division of Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Thru: Solomon Iyasu, M.D., M.P.H.
Director
Division of Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

From: Laura Governale, Pharm.D., MBA
Drug Use Data Analysis, Team Leader
Division of Epidemiology
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

Subject: Utilization patterns of Erythropoetin Stimulating Agents (ESA's)

Drug Name(s): Epogen[®] (epoetin alpha), Procrit[®] (epoetin alpha), Aranesp[®]
(darbepoetin alpha)

Application Type/Number:

Submission Number: Multiple

Applicant/sponsor: Multiple

OSE RCM #: Unknown

INTRODUCTION

Over the years, clinical trial data have emerged suggesting a possible link between increased tumor progression and decreased survival with the use of erythropoietin stimulating agents (ESA's). The Division of Risk Management is exploring various risk management options to manage the risk of increased tumor progression associated with the use of these agents. In support of that assessment, usage data by dispensed prescriptions, number of patients, prescribing specialty and indications for use was requested for the three currently marketed ESA's, Epogen[®] (epoetin alpha), Procrit[®] (epoetin alpha), Aranesp[®] (darbepoetin alpha), for the last 5 calendar years, 2003 through 2007.

1 METHODS AND MATERIAL

1.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales Perspectives[™] (see Appendix B) was used to determine the various retail and non-retail channels of distribution for the three currently marketed ESA's, Epogen[®] (epoetin alpha), Procrit[®] (epoetin alpha), Aranesp[®] (darbepoetin alpha), by number of vials sold for year 2007. Although the Agency currently lacks resources to examine utilization data in outpatient clinics, we were able to examine a portion of use in the outpatient pharmacy setting (which include chain, independent, and food stores with pharmacies) as well as the office-based physician practice setting. The mail order pharmacy and inpatient use were not examined in this analysis.

Table 1 below shows the wholesale distribution of ESA's by total number of vials sold from the manufacturer to various channels of distribution for year 2007.

Table 1: Wholesale distribution of erythropoietin stimulating agent (ESA) vials (in thousands; add 3 zeros) from manufacturer to various channels of distribution for year 2007.

	Year 2007	
	N (000)	%
48140 ERYTHROPOIETINS	62,064.3	100.0
EPOGEN 0689 AAI	44,208.0	71.2
CLINICS	42,914.2	97.1
NON-FEDERAL HOSPITALS	691.8	1.6
Retail Pharmacies	247.0	0.6
MAIL SERVICE	105.0	0.2
LONG-TERM CARE	48.4	0.1
OTHERS	201.7	0.5
PROCRIT 0291 OBD	11,935.8	19.2
NON-FEDERAL HOSPITALS	4,702.3	39.4
CLINICS	3,393.2	28.4
Retail Pharmacies	1,250.1	10.5
MAIL SERVICE	928.2	7.8
LONG-TERM CARE	1,145.9	9.6
OTHERS	516.0	4.3
ARANESP 1001 AAI	5,920.5	9.5
CLINICS	3,229.6	54.5
NON-FEDERAL HOSPITALS	1,714.2	29.0
Retail Pharmacies	280.1	4.8
MAIL SERVICE	220.1	3.7
LONG-TERM CARE	277.3	4.7
OTHERS	199.1	3.3

Source: IMS Health, IMS National Sales Perspectives. Year 2007. Extracted Feb08. File: 0801ery.dvr

1.2 DATA SOURCES

Proprietary drug use databases licensed by the Agency were used to conduct this analysis.

We examined total dispensed prescriptions for the ESA's using Verispan, LLC: Vector One[®]: National (VONA) for calendar years 2003 through 2007. We also examined number of patients who received a prescription for the ESA's in the outpatient setting using Verispan, LLC: Vector One[®]: Total Patient Tracker (TPT) cumulatively from year 2002 to 2007. Diagnoses associated with the use of the ESA's, concomitant medication use, and length of therapy, as reported by office-based physicians, were measured by Verispan, LLC: Physician Drug and Diagnosis Audit (PDDA) for calendar years 2003 through 2007.

2 DATA

2.1 DISPENSED OUTPATIENT PRESCRIPTIONS FOR ESA'S

Table 2 below shows the total number of dispensed prescriptions for Procrit[®], Aranesp[®] and EPOGEN[®] for years 2003 through 2007.

Table 2: Total number of dispensed prescriptions for Procrit®, Aranesp®, and Epogen® from U.S. outpatient retail pharmacies (mail order excluded) for years 2003 through 2007.

	2003		2004		2005		2006		2007	
	Retail TRxs	Share								
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	504,432	100.0%	492,742	100.0%	491,755	100.0%	534,802	100.0%	454,640	100.0%
Procrit	353,989	70.2%	336,800	68.4%	323,201	65.7%	364,636	68.2%	319,054	70.2%
ARANESP	52,032	10.3%	75,772	15.4%	101,922	20.7%	116,369	21.8%	95,847	21.1%
Epogen	98,411	19.5%	80,170	16.3%	66,632	13.5%	53,797	10.1%	39,739	8.7%

Source: Verispan, LLC. Vector One: National. Years 2003 - 2008. Extracted 2-7-08. File: VONA ESA TRx 2-7-08.qry

2.2 PATIENTS RECEIVING OUTPATIENT PRESCRIPTIONS FOR ESA’S

Table 3 shows the projected number of unique patients receiving a prescription for an ESA in the outpatient retail pharmacy setting for the cumulative period of years 2002 through 2007.

Table 3: Projected number of unique patients receiving a prescription for an ESA product from outpatient retail pharmacies in the U.S. for years 2002 through 2007.

	Projected Patients	
	N	%
Grand Total	643,738	100.00%
PROCRT	460,313	71.51%
EPOGEN	120,209	18.67%
ARANESP	111,550	17.33%

Verispan, Vector One®: Total Patient Tracker. Years 2002 – 2007. Extracted 2-08. File: TPT ESA's 02-07 Aggregate.xls

2.3 DIAGNOSES ASSOCIATED WITH THE USE OF ESA’S

Table 4 shows the diagnoses associated with the use of Epogen® (epoetin alpha), Procrit® (epoetin alpha), Aranesp® (darbepoetin alpha) during years 2003 through 2007.

Table 4: Diagnoses associated with the use of ESA's as reported by office-based physician practices for years 2003 - 2007.

	2003		2004		2005		2006		2007	
	Uses	Share								
	N	%	N	%	N	%	N	%	N	%
TOTAL MARKET	1,826,703	100.0%	1,913,088	100.0%	2,522,749	100.0%	3,250,378	100.0%	2,254,614	100.0%
Procrit	1,190,049	65.1%	1,249,240	65.3%	1,570,049	62.2%	1,775,355	54.6%	1,371,352	60.8%
285 ANEMIA NEC/NOS	773,589	65.0%	827,740	66.3%	924,565	58.9%	998,438	56.2%	836,339	61.0%
185 MALIGN NEOPL PROSTATE	12,236	1.6%	4,669	0.6%	3,667	0.4%	--	--	13,905	1.7%
585 CHRONIC KIDNEY DISEASE	44,997	3.8%	37,327	3.0%	77,377	4.9%	299,904	16.9%	163,870	11.9%
238 UNC BEHAV NEO NEC/NOS	116,929	9.8%	120,439	9.6%	135,293	8.6%	61,107	3.4%	66,091	4.8%
586 RENAL FAILURE NOS	19,056	1.6%	21,252	1.7%	47,077	3.0%	64,634	3.6%	65,489	4.8%
593 OTH RENAL & URETERAL DIS	8,209	0.7%	32,896	2.6%	106,889	6.8%	65,697	3.7%	59,520	4.3%
070 VIRAL HEPATITIS	3,829	0.3%	3,223	0.3%	3,576	0.2%	--	--	19,159	1.4%
204 LYMPHOID LEUKEMIA	13,134	1.1%	9,412	0.8%	27,878	1.8%	23,809	1.3%	18,535	1.4%
359 MUSCULAR DYSTROPHIES	--	--	--	--	--	--	--	--	15,917	1.2%
710 DIFF CONNECTIVE TISS DIS	--	--	--	--	--	--	--	--	14,446	1.1%
782 SKIN/OTH INTEGUMENT SYMP	--	--	--	--	--	--	10,344	0.6%	13,766	1.0%
All Others	210,306	17.7%	196,952	15.8%	247,394	15.8%	251,422	14.2%	98,220	7.2%
Aranesp	225,357	12.3%	375,580	19.6%	774,290	30.7%	1,162,573	35.8%	661,671	29.3%
285 ANEMIA NEC/NOS	113,716	50.5%	235,474	62.7%	412,672	53.3%	617,676	53.1%	415,418	62.8%
162 MAL NEO TRACHEA/LUNG	1,609	1.4%	3,517	1.5%	3,517	0.9%	7,700	1.2%	8,702	2.1%
153 MALIGNANT NEOPLASM COLON	10,993	9.7%	6,637	2.8%	1,135	0.3%	--	--	6,892	1.7%
585 CHRONIC KIDNEY DISEASE	13,486	6.0%	1,363	0.4%	41,819	5.4%	223,229	19.2%	74,077	11.2%
238 UNC BEHAV NEO NEC/NOS	5,934	2.6%	--	--	15,349	2.0%	47,499	4.1%	45,080	6.8%
583 NEPHRITIS NOS	--	--	--	--	20,705	2.7%	--	--	22,598	3.4%
404 HYPERTEN HEART/RENAL DIS	--	--	--	--	--	--	--	--	22,598	3.4%
584 ACUTE RENAL FAILURE	--	--	--	--	--	--	--	--	10,802	1.6%
710 DIFF CONNECTIVE TISS DIS	--	--	--	--	--	--	9,688	0.8%	10,498	1.6%
V42 ORGAN TRANSPLANT STATUS	--	--	--	--	--	--	--	--	9,740	1.5%
706 SEBACEOUS GLAND DISEASE	--	--	--	--	--	--	--	--	8,431	1.3%
586 RENAL FAILURE NOS	29,879	13.3%	15,545	4.1%	31,712	4.1%	70,606	6.1%	7,281	1.1%
All Others	62,341	27.7%	123,199	32.8%	252,033	32.6%	193,876	16.7%	35,148	5.3%
Epogen	411,298	22.5%	288,268	15.1%	178,410	7.1%	312,449	9.6%	221,591	9.8%
585 CHRONIC KIDNEY DISEASE	77,701	18.9%	82,351	28.6%	65,560	36.7%	177,470	56.8%	83,546	37.7%
285 ANEMIA NEC/NOS	196,441	47.8%	127,325	44.2%	90,079	50.5%	67,668	21.7%	81,448	36.8%
593 OTH RENAL & URETERAL DIS	11,990	2.9%	15,140	5.3%	--	--	11,148	3.6%	25,866	11.7%
252 PARATHYROID DISORDER	--	--	--	--	--	--	--	--	10,370	4.7%
820 FRACTURE NECK OF FEMUR	--	--	--	--	--	--	--	--	9,721	4.4%
070 VIRAL HEPATITIS	11,729	2.9%	--	--	--	--	15,696	5.0%	8,306	3.7%
281 OTHER DEFICIENCY ANEMIA	--	--	--	--	--	--	--	--	2,334	1.1%
All Others	113,436	27.6%	63,451	22.0%	22,772	12.8%	40,466	13.0%	--	--

Source: Verispan, Physician Drug and Diagnosis Audit. Years 2003 – 2007. Extracted 2-08. File: PDDA ESA Dx3ConcurDx 2-11-08.qry

CONCLUSIONS

- Wholesale distribution data show that the outpatient clinic setting is the largest setting of use for Epogen[®] and Aranesp[®], each accounting for approximately 97% and 54% sales, respectively. The largest setting of use for Procrit[®] was non-federal hospitals, accounting for approximately 39% of vials sold to that channel. Outpatient retail pharmacy distribution accounted for approximately 11%, 5%, and less than 1% of wholesale distribution for Procrit[®], Aranesp[®], and Epogen[®], respectively. Interestingly, the long-term care channel accounted for approximately 10% and 5% of sales distribution for Procrit[®] and Aranesp[®], respectively.
- The most common ESA product dispensed from outpatient retail pharmacies was Procrit[®], accounting for approximately 66% to 70% of the outpatient prescription market during years

2003 through 2007. Use appears to have declined between year 2006 and 2007 for all three of these agents. Likewise, patient count data also showed similar results.

- The top two diagnoses or indications associated with the use of Procrit[®] and Aranesp[®] as reported by office-based physician practices were “other and unspecified anemias” (ICD-9 285), and “chronic kidney disease” (ICD-9 585), each accounting for roughly 60% and 12% of use during year 2007. “Chronic kidney disease” (ICD-9 585) and “other and unspecified anemias” (ICD-9 285) accounted for approximately 38% and 37% of use for Epogen[®].
- “Lymphoid leukemia” was the only cancer-related diagnosis reported as the primary reason for treatment for Procrit[®]. “Malignant neoplasm of prostate” (ICD-9 185) also appeared as a concurrent cancer-related diagnosis with “other and unspecified anemias” (ICD-9 285) as the primary diagnosis for Procrit[®].¹⁷
- No cancer-related diagnoses were reported as the primary reason for treatment visit for Aranesp[®], however, “malignant neoplasm of trachea, bronchus, and lung” (ICD-9 162) and malignant neoplasm of colon” (ICD-9 153) were reported as concurrent diagnoses with “other and unspecified anemias” (ICD-9 285) as the primary diagnosis for Aranesp[®].
- No cancer-related diagnoses were reported as the primary or concurrent diagnosis for Epogen[®].

¹⁷ Source: Verispan, Physician Drug and Diagnosis Audit. Years 2003 – 2007. Extracted 2-08. File: PDDA ESA Dx3ConcurDx 2-11-08.qry

APPENDIX B: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

Verispan, LLC: Vector One®: National (VONA)

Verispan's VONA measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, mail order pharmacies, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 1.5 billion prescription claims per year, representing over 100 million unique patients. Since 2002 Vector One® has captured information on over 8 billion prescriptions representing 200 million unique patients.

Prescriptions are captured from a sample of approximately 59,000 pharmacies throughout the US. The pharmacies in the data base account for nearly all retail pharmacies and represent nearly half of retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores.

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and

trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.