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DARBEPOETIN ALFA (ARANESP®): PRACTICAL ISSUES IN THE MANAGEMENT OF CHEMOTHERAPY-RELATED ANEMIA

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Introduction

Erythropoietic agents were developed as a non-transfusion-based treatment of mild to moderate anemia. Administration of epoetin alfa (Procrit®, Ortho Biotech Products, L.P., Raritan, NJ), the first erythropoietic agent approved by the Food and Drug Administration (FDA) more than a decade ago, to patients with nonmyeloid malignancies receiving chemotherapy raises hemoglobin (Hgb) levels in 50% to 60% of patients, decreases red blood cell (RBC) transfusion requirements and, most importantly, improves quality of life (QOL) in many patients.¹ However, thrice-weekly or weekly administration of epoetin alfa requires frequent physician visits, consuming patient and provider time.²

Darbepoetin alfa (Aranesp®, Amgen Inc., Thousand Oaks, Calif), approved by the FDA in July 2002 for the treatment of chemotherapy-induced anemia in patients with nonmyeloid malignancies, is a novel, erythropoiesis-stimulating protein. Darbepoetin alfa is biochemically distinct from epoetin alfa, because it has 2 more N-glycosylation sites that contain additional sialic acid.^{2,4} The increase in sialic-acid content confers an approximately 3-fold longer terminal half-life and greater in vivo activity to darbepoetin alfa compared with epoetin alfa.^{1,5} The prolonged half-life allows for less frequent administration without a compromise in hematopoietic response.² Thus, darbepoetin alfa has the potential to further improve the QOL of cancer patients by reducing the number of physician visits required to administer erythropoietic therapy and, consequently, decreasing resource use.⁵

With the availability of 2 erythropoietic agents that produce the same patient response, a number of practical issues must be considered so that clinicians can prescribe the most effective and efficient therapy for chemotherapy-related anemia (Table 1). A summary of these issues follows.

Table 1. Practical Questions About the Role of Darbepoetin Alfa in the Management of Chemotherapy-Related Anemia

- Do clinically significant differences in the efficacy of darbepoetin alfa and epoetin alfa as treatment of chemotherapy-related anemia exist?
- What is the most cost-effective and efficient dosage of darbepoetin alfa as treatment of chemotherapy-related anemia?
- What is the appropriate dose-conversion ratio for epoetin alfa and darbepoetin alfa?
- How does reimbursement of darbepoetin alfa as treatment of chemotherapy-related anemia vary among insurance carriers?
- What research is needed to define further the role of darbepoetin alfa as treatment of chemotherapy-related anemia?

Do clinically significant differences in the efficacy of darbepoetin alfa and epoetin alfa as treatment of chemotherapy-related anemia exist?

Although the number of informal and formal studies comparing epoetin alfa with darbepoetin alfa as treatment of chemotherapy-related anemia is increasing, the results of published, prospective trials comparing these agents are limited. The results of a 2-part, comparative trial showed that these agents were equally effective in achieving a hematologic response in patients with solid tumors who received multicycle chemotherapy (Table 2).^{2,6} In part A of the study, darbepoetin alfa 1.5 µg/kg administered subcutaneously (SQ) weekly and epoetin alfa 150 to 300 U/kg administered SQ 3 times weekly produced a similar mean increase in Hgb levels from baseline and incidence of RBC transfusions.² In part B of the study, which compared less frequent administration schedules of the erythropoietic agents, the minimally effective dosage of darbepoetin alfa was 3 µg/kg administered every 2 weeks (see Table 2); this dosage produced

Table 2. Results of a 2-Part, Open-Label, Randomized, Dose-Determining Study Comparing Darbepoetin Alfa and Epoetin Alfa^{2,6}

Part A	Darb 1.5 µg/kg SQ q wk	Darb 2.25 µg/kg SQ q wk	Darb 4.5 µg/kg SQ q wk	Epo 150 U/kg SQ tiw ^a
No. of patients	35	59	29	53
Mean change in Hgb level after 4 wk, g/dL	0.3	0.7	0.9	0.3
Mean change in Hgb level after 12 wk, g/dL	1.1	1.3	1.9	1.1
Patients requiring RBC transfusion, %*	26	13	6	23
Part B	Darb 3 µg/kg q 2 wk	Darb 5 µg/kg q 2 wk	Epo 40,000 U q wk ¹¹	
No. of patients	33	31	32	
Patients with ≥ 2-g/dL increase in Hgb level, % [†]	60	79	60	
Patients with Hgb level ≥ 12 g/dL, % [†]	57	62	53	
Patients requiring RBC transfusion, % ^{**††}	4	22	36	

*From week 5 to end-of-treatment phase.

[†]Kaplan-Meier proportion.

^{**}Thirty patients included in analysis.

[§]Dose increased to 300 U/kg at week 8 in patients with inadequate response.

¹¹Dose increased to 60,000 U weekly at week 6 in patients with inadequate response.

Darb=darbepoetin alfa; Epo=epoetin alfa; Hgb=hemoglobin; RBC=red blood cell; SQ=subcutaneously; tiw=3 times weekly.

hematopoietic responses similar to those produced by epoetin alfa 40,000 U administered weekly.²

The results of a pooled analysis of data from 3 studies evaluating darbepoetin alfa 3 µg/kg every 2 weeks and epoetin alfa 40,000 U weekly or 150 U/kg 3 times weekly in patients receiving multicycle chemotherapy also demonstrated comparable efficacy (ie, 71% hematopoietic response in both groups). Of note, fewer RBC transfusions were required in darbepoetin alfa-treated patients.⁷

The impact of epoetin alfa compared with darbepoetin alfa administration on QOL has not been evaluated. Results of an interim analysis of a noncomparative trial assessing QOL, specifically fatigue, in darbepoetin alfa-treated cancer patients demonstrated improved fatigue scores (Functional Assessment of Cancer Therapy–Fatigue subscale) in the majority of patients receiving an every-2-week regimen; improvements in fatigue scores correlated with increases in Hgb levels.⁸

The results of these studies confirm that epoetin alfa and darbepoetin alfa produce similar effects on Hgb levels and suggest that darbepoetin alfa may be associated with fewer RBC transfusions.^{2,7} Based on these data, the Centers for Medicare & Medicaid Services (CMS) has determined these agents to be “functionally equivalent,” stating “both products use the same biological mechanism to produce the same clinical result, stimulation of the bone marrow to produce RBCs.”⁹ This concept of functional equivalence has created a controversy in the oncology healthcare community because of its impact on reimbursement for these agents, especially in the outpatient setting.

What is the most cost-effective and efficient dosage of darbepoetin alfa as treatment of chemotherapy-related anemia?

Using either a weight-based or fixed-dose regimen, darbepoetin alfa is administered less frequently than epoetin alfa because of its prolonged half-life. The FDA recommends the use of weight-based regimens when initiating treatment with either agent: epoetin alfa 150 U/kg SQ 3 times a week or darbepoetin alfa 2.25 µg/kg SQ weekly.^{4,9} The *United States Pharmacopeia Drug Information (USP DI)* supports less frequent administration of darbepoetin alfa and the use of a range of weight-based dosages (ie, 1.5–2.25 µg/kg q wk or 3–5 µg/kg q 2 wk).¹⁰ Results of a trial evaluating dose and schedule support even less frequent administration of darbepoetin alfa.¹¹ In the placebo-controlled, double-blind portion of the study, at least 60% of anemic cancer patients receiving darbepoetin alfa 6.75 µg/kg every 3 weeks, 6.75 µg/kg every 4 weeks, or 10 µg/kg every 4 weeks achieved a hematopoietic response.¹¹

Despite recommendations for using weight-based dosages, most clinicians prescribe fixed doses and less frequent administration schedules than those recommended in the package insert (PI). For epoetin alfa, a fixed dosage of 40,000 U weekly produced hematopoietic responses similar to those observed with a thrice weekly dosage; thus, epoetin alfa 40,000 U weekly is the dosage most commonly used in clinical practice.¹²

Although no prospective, controlled study results have been published, the results of uncontrolled, retrospective studies support the use of fixed-dosage darbepoetin alfa.^{13,14} For example, in a multicenter retrospective cohort study evaluating the records of 1,293 patients receiving a single erythropoietic agent as treatment of chemotherapy-related anemia, 735 patients (57%) received darbepoetin alfa, with approximately 75% of these patients receiving an initial darbepoetin alfa dosage of 200 µg every 2 weeks.¹³ The mean change in Hgb levels and the incidence of RBC transfusions were similar between patients receiving this fixed dosage of darbepoetin alfa and patients receiving epoetin alfa 40,000 U every week.¹³ Furthermore, the results of a chart review of 166 patients receiving fixed dosages of darbepoetin alfa indicate that a fixed darbepoetin alfa dosage of 200 µg or less administered every 2 weeks is effective in the majority of patients receiving either an erythropoietic agent for the first time or darbepoetin alfa after having initially received epoetin alfa.¹⁴ A fixed dosage of darbepoetin alfa, 200 µg every 2 weeks, was recently granted preliminary approval by a United States Pharmacopeia Expert Committee as the dosage for the initial treatment of anemia of malignancy (D. Penn, personal communication, October 2003).¹⁵

Recently updated National Comprehensive Cancer Network (NCCN) clinical practice guidelines for cancer- and treatment-related anemia support the use of darbepoetin alfa.¹⁶ These guidelines provide options for initial administration of darbepoetin alfa, including the weekly dosage recommended in the manufacturer’s PI (2.25 µg/kg/wk) and 2 commonly used biweekly dosages, one weight based (3 µg/kg q 2 wk) and the other a fixed dosage (200 µg q 2 wk).¹⁶ The NCCN support of the 2 non-FDA-approved biweekly regimens is based on current market-usage patterns and considers the practical, economic, and humanistic aspects of delivering drug therapy to cancer patients.

Some clinicians question the appropriateness of a fixed dosage for a dose-responsive agent like darbepoetin alfa. With a 200-µg fixed dose, a 50-kg patient receives 30% more drug than does a 70-kg patient; this difference could be clinically significant in terms of response. The concept of a fixed-dose is also confounded by the FDA-approved recommendation to increase the dose in nonresponders. These concerns prompted the

Department of Pharmacy at the Moffitt Cancer Center & Research Institute in Tampa, Florida, to adopt a tiered, fixed-dosage strategy that bases the initial dosage on 3 weight ranges: darbepoetin alfa 150 µg SQ every 2 weeks for patients weighing < 55 kg; 200 µg SQ every 2 weeks for patients weighing 56 to 75 kg; and 250 µg SQ every 2 weeks for patients weighing > 75 kg (P. Johnson, oral communication, March 2003). Dosages are further adjusted based on specified monitoring and response criteria.

Other administration strategies for darbepoetin alfa, including a front-loading technique, are under investigation. Front-loading involves the administration of an induction course of high weekly doses of darbepoetin alfa followed by a maintenance course of lower doses.¹⁷

What is the appropriate dose-conversion ratio for epoetin alfa and darbepoetin alfa?

No standard formula exists for converting amounts of biologic agents administered in units to amounts of agents administered according to weight.³ To determine equivalent reimbursement rates for darbepoetin alfa and epoetin alfa for use in the 2003 Medicare Hospital Outpatient Prospective Payment System (OPPS), the CMS developed a reimbursement dose-conversion ratio for these 2 agents. In 2003, the conversion ratio was 260 U of epoetin alfa to 1 µg of darbepoetin alfa.³ Using this ratio, administration of epoetin alfa 40,000 U SQ weekly is equivalent to that of darbepoetin alfa 154 µg SQ weekly (ie, for a 70-kg patient, approximately 2.25 µg/kg/wk). After reviewing the results of observational, retrospective, cohort studies comparing the erythropoietic agents and analyzing claims data from 2002 and 2003, the CMS published a more accurate reimbursement conversion ratio of 330 U of epoetin alfa to 1 µg of darbepoetin alfa for use in the 2004 OPPS.¹⁸ Using this ratio, administration of epoetin alfa 40,000 U SQ weekly is equivalent to darbepoetin alfa 121 µg SQ weekly (ie, for a 70-kg patient, approximately 1.75 µg/kg/wk). In the 2004 Hospital OPPS Final Rule, the CMS emphasizes that the reimbursement conversion ratio is not a clinical conversion ratio and should not be used to determine therapeutic dosages for patients.¹⁸

How does reimbursement of darbepoetin alfa as treatment of chemotherapy-related anemia vary among insurance carriers?

Major insurance plans, including Medicare, Medicaid, and private insurance (indemnity or managed care) plans, are

likely to cover darbepoetin alfa when it is used for its approved indication in cancer patients.¹⁹ Reimbursement rates and restrictions typically vary based on the carrier and the administration setting (ie, inpatient or outpatient) (Table 3).¹⁹ Outpatient reimbursement, particularly as defined by the CMS, varies depending on whether the outpatient environment is a physician's office or hospital outpatient department (see Table 3).

With the exception of reimbursement under Medicare's Hospital OPPS, darbepoetin alfa is generally reimbursed at favorable rates. Medicare covers 95% of the average wholesale price (AWP) of darbepoetin alfa administered in a physician's office.¹⁹ Many private insurers reimburse for darbepoetin alfa at rates comparable to or above these Medicare standards. Medicaid reimbursement rates vary among states, but commonly allow for reimbursement at 80% to 85% of AWP, according to Amgen Inc., the manufacturer of darbepoetin alfa (L. Carter, oral communication, February 2003).

With the implementation of the Medicare Hospital OPPS, reimbursement was reduced for erythropoietic agents administered in a hospital outpatient department. Under the 2003 OPPS ruling, which considers epoetin alfa and darbepoetin alfa to be "functionally equivalent," each agent is reimbursed at a fixed amount per unit of drug to ensure equitable payments. In 2003, using the CMS dose-conversion ratio of 260 U of epoetin alfa to 1 µg of darbepoetin alfa, Medicare pays \$9.10 per 1,000 U of epoetin alfa and \$2.37 per µg for darbepoetin alfa.³ Thus, Medicare reimburses \$364 for either epoetin alfa 40,000 U or darbepoetin alfa 154 µg. Effective January 1, 2004, the CMS dose-conversion ratio will increase from 260 U of epoetin alfa to 1 µg of darbepoetin alfa to 330 U of epoetin alfa to 1 µg of darbepoetin alfa.¹⁸ Therefore, Medicare will increase payment for epoetin alfa by 8% (\$9.83 per 1,000 U) and darbepoetin alfa by 37% (\$3.24 per µg).^{3,18} By applying these new 2004 Medicare payment rates to commonly used regimens, providers will receive approximately \$393 for a weekly, fixed epoetin alfa dose of 40,000 U, \$512 for a weekly, weight-based darbepoetin alfa dose of 158 µg (eg, 2.25 µg/kg/wk administered to a 70-kg patient), and \$648 for a biweekly, fixed darbepoetin alfa dose of 200 µg.

Additional information about coverage and reimbursement for darbepoetin alfa is available through Amgen's Reimbursement Connection[®], online at www.reimbursement-connection.com or by calling 1-800-272-9376.¹⁹ The Reimbursement Connection also includes information about Amgen's patient-assistance program, SAFETY NET[®], which provides information about obtaining darbepoetin alfa for qualifying patients who are uninsured or underinsured.

Table 3. Insurance Coverage and Reimbursement for Darbepoetin Alfa Used as Treatment of Chemotherapy-Related Anemia ¹⁹			
Provider Setting	Medicare	Medicaid	Private Insurers (Indemnity, Managed Care Plans)
Physician's office	<ul style="list-style-type: none"> Coverage likely when use is reasonable and necessary Administration must be "incident to a physician's service" Reimbursement rate is 95% of AWP (80% paid to provider by Medicare; 20% paid to provider by patient or patient's coinsurance) 	<ul style="list-style-type: none"> Reimbursement varies among states Reimbursement may require preauthorization 	<ul style="list-style-type: none"> Coverage and reimbursement are plan dependent Reimbursement may require preauthorization and/or patient monitoring
Hospital, outpatient	<ul style="list-style-type: none"> Reimbursement based on OPPS designated amount for assigned APC 	<ul style="list-style-type: none"> Some states allow reimbursement Reimbursement may be based on cost, charges, or per diem rate 	<ul style="list-style-type: none"> Coverage likely Reimbursement is plan dependent
Hospital, inpatient	<ul style="list-style-type: none"> Reimbursement included in assigned DRG 	<ul style="list-style-type: none"> Coverage likely Reimbursement varies among states Reimbursement may be based on per diem rate, DRG, or allowable costs 	<ul style="list-style-type: none"> Coverage likely Reimbursement is plan dependent
Pharmacy	<ul style="list-style-type: none"> Reimbursement unavailable when agent obtained from retail pharmacy or home health agency 	<ul style="list-style-type: none"> Coverage likely Reimbursement varies among states and may require preauthorization Dispensing fees often reimbursable 	<ul style="list-style-type: none"> Coverage likely Reimbursement is plan dependent Cost-sharing requirements for patient are dependent on plan and formulary status

APC=ambulatory payment classification; AWP=average wholesale price; DRG=diagnosis-related group; OPPS=outpatient prospective payment system.

What research is needed to define further the role of darbepoetin alfa as treatment of chemotherapy-related anemia?

Although data supporting less frequent administration of darbepoetin alfa compared with epoetin alfa has led many clinicians to prescribe darbepoetin alfa, a number of questions must be answered before the optimal erythropoietic agent can be recommended. Some of these questions will be addressed in ongoing studies evaluating the impact of darbepoetin alfa on QOL, transfusion requirements, cognitive function, response rate, and survival times.¹ Other issues that require additional research include establishing 1) optimal initial treatment dosages, perhaps fixed dosages based on weight; 2) evidence-based dose-adjustment guidelines for nonresponders; 3) predictors of epoetin alfa and darbepoetin alfa resistance; 4) evidence-based criteria for discontinuing therapy; and 5) evidence-based monitoring guidelines.

References

1. Valley AW. Overview of cancer-related anemia: focus on the potential role of darbepoetin alfa. *Pharmacotherapy*. 2002;22(pt 2):150S-159S.
2. Glaspy JA, Tchekmedyan NS. Darbepoetin alfa administered every 2 weeks alleviates anemia in cancer patients receiving chemotherapy. *Oncology (Huntingt)*. 2002;16(suppl 11):23-29.
3. Centers for Medicare & Medicaid Services. CY2003 hospital outpatient prospective payment system. Fact sheet: payment for Epogen, Procrit, and Aranesp. Available at: www.cms.hhs.gov/regulations/hopps/change/cy2003.asp. Accessed March 24, 2003.
4. Aranesp [package insert]. Thousand Oaks, Calif: Amgen Inc.; 2002.
5. Zamboni WC, Stewart CF. An overview of the pharmacokinetic disposition of darbepoetin alfa. *Pharmacotherapy*. 2002;22(pt 2):133S-140S.
6. Glaspy JA, Jadeja JS, Justice G, et al. Darbepoetin alfa given every 1 or 2 weeks alleviates anaemia associated with cancer chemotherapy. *Br J Cancer*. 2002;87:268-276.
7. Mirtsching B, Charu V, Vadhan-Raj S, et al. Every-2-week darbepoetin alfa is comparable to rHuEPO in treating chemotherapy-induced anemia. Results of a combined analysis. *Oncology (Huntingt)*. 2002;16 (suppl 11):31-36.
8. Vadhan-Raj S, Mirtsching B, Charu V, et al. Assessment of hematologic effects and fatigue in cancer patients with chemotherapy-induced anemia given darbepoetin alfa every two weeks. *J Support Oncol*. 2003;1:131-138.
9. Procrit [package insert]. Raritan, NJ: Ortho Biotech Products, L.P.; 2000.
10. Darbepoetin alfa. In: *USP DI® Drug Information for the Health Care Professional*. Greenwood Village, Colo: MICROMEDEX; 2003.
11. Smith RE Jr, Tchekmedyan NS, Chan D, et al. A dose- and schedule-finding study of darbepoetin alfa for the treatment of chronic anaemia of cancer. *Br J Cancer*. 2003;88:1851-1858.
12. Gabrilove JL, Cleeland CS, Livingston RB, Sarokhan B, Winer E, Einhorn LH. Clinical evaluation of once-weekly dosing of epoetin alfa in chemotherapy patients: improvements in hemoglobin and quality of life are similar to three-times-weekly dosing. *J Clin Oncol*. 2001;19:2875-2882.
13. Schwartzberg L, Shiffman R, Tomita D, Stolshek B, Rossi G, Adamson R. A multicenter retrospective cohort study of practice patterns and clinical outcomes of the use of darbepoetin alfa and epoetin alfa for chemotherapy-induced anemia. *Clin Ther*. 2003;25:2781-2796.
14. Thames W, Dozier N, Alley JL, Yao B. Initial experience with darbepoetin alfa administered at a fixed dose of 200 mcg every 2 weeks (Q2W) in anemia cancer patients undergoing chemotherapy. *Blood*. 2002;100(suppl). Abstract 3522.
15. USP DI off-label uses in public review. Available at: <http://www.usp.org/druginformation/revisions/monographsOffLabel.html>. Accessed October 16, 2003.
16. Sabbatini P, Cella D, Chanan-Khan A, et al. The NCCN Cancer and Treatment-Related Anemia Clinical Practice Guidelines in Oncology (v.1.2004). Available at: http://www.nccn.org/physician_gls/f_guidelines.html. Accessed October 31, 2003.
17. Glaspy J, Sinh Jadeja J, Justice G, Fleishman A, Rossi G, Colowick AB. A randomized, active-control, pilot trial of front-loaded dosing regimens of darbepoetin-alfa for the treatment of patients with anemia during chemotherapy for malignant disease. *Cancer*. 2003;97:1312-1320.
18. Final rule: Medicare program: changes to the hospital outpatient prospective payment system and calendar year 2004 payment rates. (CMS-1471-FC). Available at: <http://www.cms.gov/regulations/hopps/2004/f/>. Accessed November 3, 2003.
19. Coverage and reimbursement. Aranesp® (darbepoetin alfa). Available at: <http://www.reimbursementconnection.com>. Accessed October 16, 2003.

IN THE NEWS

FDA Approvals and News

Final Approvals

July 25, 2003: Aloxi™ (palonosetron hydrochloride, MGI Pharma, Inc. and Helsinn Healthcare SA), a selective 5-HT₃ receptor antagonist, received Food and Drug Administration (FDA) approval for the prevention of 1) acute nausea and vomiting associated with initial and repeated courses of moderately and highly emetogenic chemotherapy, and 2) delayed nausea and vomiting associated with initial and repeated courses of moderately emetogenic chemotherapy. Aloxi is the first 5-HT₃ receptor antagonist to receive FDA approval for the prevention of delayed chemotherapy-induced nausea and vomiting associated with moderately emetogenic chemotherapy.

September 18, 2003: Ganite™ (gallium nitrate injection, Genta Incorporated) was approved for the treatment of cancer-related hypercalcemia that is resistant to hydration.

October 14, 2003: BSD Medical Corporation received approval for 4 new operating systems (BSD-500i-4, BSD-500c-4, BSD-500i-8 and BSD-500c-8) that deliver superficial and interstitial hyperthermia therapy. Superficial hyperthermia is a noninvasive method of treating cancerous tumors anatomically located near the skin's surface, such as melanoma and breast cancer. Interstitial hyperthermia is used to treat breast, prostate, head and neck, and other cancers.

Abbreviated New Drug Applications

August 28, 2003: SICOR Pharmaceuticals, Inc. was granted permission for an Abbreviated New Drug Application (ANDA) for fludarabine phosphate injection. This product is the generic equivalent of Berlex Laboratories' Fludara®, the patent for which expired in February of this year.

Fast-Track Designations

September 3, 2003: Telcyta™ (TLK286, Telik Inc.) was granted fast-track designation for the treatment of ovarian cancer. Telcyta, which requires activation by glutathione S-transferase P1-1 (GST P1-1), an enzyme present in higher levels in cancer cells than in normal cells, initiates apoptosis in ovarian cancer cells.

September 4, 2003: Provenge® (Dendreon Corporation), an investigational therapeutic vaccine, was granted fast-track designation. Provenge is being developed for treatment of asymptomatic, metastatic, androgen-independent prostate cancer. Provenge stimulates a patient's immune response to prostate cancer through Dendreon's proprietary Antigen Delivery Cassette™ technology, which uses a recombinant form of prostatic acid phosphatase, an antigen found in 95% of prostate cancers.

Orphan Drug Designations

August 21, 2003: Combretastatin A4 Prodrug (CA4P, OXiGENE, Inc.) was awarded orphan drug status for the treatment of anaplastic thyroid, medullary, stage IV papillary, and stage IV, follicular thyroid cancers. Combretastatin, a synthetic compound originally derived from the root of the Combretum caffrum tree, represents a new class of compounds known as vascular targeting agents, which are capable of drastically reducing blood flow to tumors.

September 8, 2003: REXIN-G™ (Retroviral Expression Vectors Bearing Inhibitory Genes, Epeius Biotechnologies Corporation) was granted orphan drug status for pancreatic cancer. REXIN-G is the world's first tumor-targeted, injectable gene-therapy vector.

ODAC Update

October 9, 2003: The **Pediatric Oncology Subcommittee of the Oncologic Drugs Advisory Committee (ODAC)** met in October 2003. The subcommittee discussed off-patent oncology drugs for which pediatric studies are needed, discussed the availability of information concerning the safe and effective use of off-patent oncology drugs in pediatric patients, and determined whether additional studies evaluating the health benefits of using off-patent oncology drugs in pediatric patients are required, as mandated by the Best Pharmaceuticals for Children Act. The subcommittee also discussed age-appropriate formulation changes required to facilitate appropriate administration of oncology drugs to pediatric patients. A summary of the meeting minutes is available at: <http://www.fda.gov/ohrms/dockets/ac/03/minutes/3995M1.htm>.

Legislative and Regulatory News

CMS Proposes New Payment Models for Part B Covered Drugs

August 20, 2003: The Center for Medicare and Medicaid Services (CMS) published a proposed rule in the Federal Register offering 4 new models that would reform the current average wholesale price (AWP) system; these models have been termed 1) Comparability, 2) AWP Discount, 3) Market Monitoring, and 4) Competitive Acquisition Program and Average Sales Prices. According to the proposed payment models, Medicare would 1) reimburse at the lower of the existing Medicare payment levels or the amounts paid by preferred provider organization and indemnity plans operated by Medicare carriers; 2) apply a 10% to 20% discount to AWP in 2004 and establish more reasonable payments for subsequent years; 3) redefine AWP as the “widely available market price,” a price based initially on reports from the US General Accounting Office and the US Office of the Inspector General, and, subsequently, on systems designed to monitor changes in market prices; or 4) directly pay vendors based on a mandatory vendor imposition-style process or physicians based on the average sales price (ASP) of the drug plus an “add-on” percentage, which varies from 1% to 12% of the ASP.

Reform of Medicare's OPPS Drug Reimbursement Rates

September 10, 2003: House and Senate conferees charged with reconciling differences between the 2 Medicare prescription coverage bills (H.R. 1/S. 1) passed in June 2003 agreed to restore Medicare reimbursement for drugs and biologics in the outpatient hospital setting. Under this agreement, payment for sole-source drugs covered by Medicare's OPPS could not fall below 88% of AWP in 2004 and 83% of AWP in 2005. Reimbursement rates for 2006 and beyond were not defined, but may be based on the actual costs of drugs and biologics to hospitals. Also under this agreement, multisource and generic drugs would be reimbursed at 68% and 46% of AWP, respectively. New drugs that do not have a Medicare code (eg, C-code) would be reimbursed at 95% of AWP, and orphan drugs would be reimbursed based on a reasonable cost basis for the next 2 years. These agreements have been incorporated into the final Medicare prescription drug coverage bill that must be voted on by Congress.

ASCO and ACCC Reject Adoption of CMS Proposed Rule on Payment Reform for Part B Drugs

October 10, 2003: The American Society of Clinical Oncology (ASCO) and the Association of Community Cancer Centers (ACCC) both submitted comments in response to the Payment Reform for Part B Drugs Proposed Rule published in the Federal Register on August 20, 2003. ASCO states that the proposed rule has serious deficiencies and should not be adopted. ASCO fears that adoption of the proposed rule

would lead to inadequate overall payments for cancer treatment and create patient access problems. Their detailed comments question CMS' authority to implement the proposal and the legality of the schedule for implementation. ASCO critiques the 4 proposed AWP reform methodologies and suggests none of them are reasonable. Despite CMS' proposal to change its policy to pay for multiple intravenous push administrations of medications, ASCO states that the lack of change in payment for other drug administration services would result in wholly inadequate payment amounts. ACCC notes the proposed reductions in drug payments are excessive and proposed increases in practice expense relative value units (RVUs) for drug administration and other related services are insufficient. ACCC urges CMS to issue another proposed rule that considers other options or modifies the proposed options to reduce the magnitude of payment cuts; ACCC requests that the public be given an opportunity to comment on a new proposed rule before it is finalized.

Medicare Prescription Drug Benefit Update

October 26, 2003: Members of Congress missed a working deadline of October 17, 2003 to develop a final resolution of the House and Senate bills passed in June 2003 that would provide prescription drug coverage for Medicare beneficiaries. The 2 bills differed significantly. Although resolution of these differences has been slower than expected, a final bill is expected to be passed later this year. Although no details on the final bill have been established, lawmakers have proposed that higher-income seniors pay higher premiums for Medicare coverage than lower-income seniors. CMS also announced premiums for current Medicare beneficiaries will increase by 13% next year to \$66.60 per month.

Other News

CMS Qualifies Velcade™ for Pass-Through Status

October 2, 2003: **Velcade (bortezomib)**, Millennium Pharmaceuticals), approved for the treatment of refractory multiple myeloma, qualified for pass-through payment status under Medicare's Hospital OPPS. Velcade 3.5 mg was assigned billing and ambulatory payment classification codes of C9207 and 9207, respectively. Pass-through payments will be retroactive to October 1, 2003.

Medicare Coding Instructions for Bexxar® Released

October 2, 2003: Coding and reimbursement instructions were released by CMS for **Bexxar (tositumomab and iodine I 131 tositumomab)**, Corixa Corporation and GlaxoSmith Kline). These codes are retroactive to July 1, 2003; instructions for using these codes are available on CMS' new Internet-only manual at http://www.cms.hhs.gov/manuals/pm_trans/R1OTSN.pdf. Depending on the radiological or pharmaceutical services provided, hospitals are to bill using 1 or more Healthcare Common Procedure Coding System (HCPCS) codes, G3001, G0273, G0274, or CPT 77300, which cover the dosimetric and therapeutic steps involved in Bexxar delivery.

CMS Decides to Increase Access to High-Dose IL-2 Treatment

October 20, 2003: A multicenter study documenting the discrepancy between a hospital's actual cost to deliver high-dose interleukin-2 (IL-2) therapy and Medicare's reimbursement for such therapy prompted the CMS to increase reimbursement rates for high-dose IL-2 therapy effective October 1, 2003. The study results showed that hospitals require reimbursement of approximately \$25,000 to adequately cover their costs of delivering IL-2 therapy. Medicare previously allotted less than \$10,000 as payment for high-dose IL-2 therapy. Patients most affected by this change include metastatic melanoma and renal cell carcinoma patients.

NETWORKING COLUMN

How to Ensure You Are Getting Paid for Billed Drug Charges

David Kvancz, MS, RPh, FASHP

Director of Pharmacy, The Cleveland Clinic Foundation

So, your organization has obtained a contract for the lowest possible acquisition cost of a drug. You have met all of the volume or market share criteria required to qualify for the highest possible discount or rebate for the drug. You have worked diligently to ensure that hospital staff has properly coded for drug charges and included all of the required documentation in the medical record to support these charges in order to minimize or eliminate claim rejections or denials. Feeling good about this process, you report to upper-level administration that “everything is under control.” Then, upper-level administration asks the question: **“How do we know if we are getting paid for a specific drug claim and whether we are making a profit?”**

To answer this question, you review the monthly budget reports, which include data on the acquisition costs and charges billed for drugs administered in the hospital outpatient department or physicians’ clinics, and show that the profit margin for these billed services is as expected. You know, however, that budget reports do not correlate payments received with specific drug charges submitted and services provided during a patient visit are commonly reimbursed as a lump-sum payment, without providing drug- or service-specific details. You turn to your Patient Accounting or Financial Services Department for help, but, to your surprise and consternation, these departments can not provide you with the information requested.

Sound familiar? The ability to track drug- or service-specific payments and assess profit margins has remained an elusive dilemma for many health-system pharmacy administrators for the past 25 years. There are, however, a few financial models that can reasonably estimate the payments received for specific drug charges billed. Most of these models require manual accounting, because automated programs designed to answer this question are unavailable. The availability of computerized databases, spreadsheets, and health-system cost accounting software programs that include the ability to receive patient-specific payment postings from the Patient Accounting Department, have, however, made this process easier. The steps one should consider when constructing a financial model to assess whether payment is being received for specific drug charges are outlined below. This process requires extensive collaboration between the Patient Accounting and Pharmacy Departments. Before embarking on such a process, one should review the feasibility of the process and achieve consensus from the involved departments on the scope of the project, the methods to be used, and the individual responsibilities and timeframe for completing the process.

The process outlined below is based on 2 assumptions. First, you are interested in determining whether payments received cover the cost of drugs for the majority of payors and/or drugs. If you are assessing only Medicare-related charges, a direct comparison of the drug’s acquisition cost with Medicare’s assigned payment for the drug, adjusted for appropriate utilization volumes, is all that is required. This model also assumes that the explanation of benefits (EOB) statements, including drug-specific payments, are either difficult to obtain or the volume of EOBs required for an accurate review of all payors would be overwhelming. If the scope of your review is limited to a few drugs or a few payors, then requesting EOB statements may be the preferred method for a line-item payment-versus-cost analysis. Otherwise, a model such as the one described below may help you determine specific profit margins.

1. **Identify a timeframe for a retrospective review of patient accounts and payments received.** A 1-month period that coincides with the monthly billing cycle is recommended for oncology therapies. Select a month with a complete data set (eg, a month in which most payments received have been posted).
2. **Identify the target drug(s) or payor(s).** For example, you may wish to focus on a specific drug, a class of drugs, or 10 to 20 commonly used drugs that represent 50% to 70% of the total drug costs or charges for the hospital outpatient or physician’s clinic settings. You may also wish to focus your review on a specific payor or analyze all payors.
3. **Extract drug-specific data from your pharmacy computer system for the established timeframe; create a report of the extracted data.** At a minimum, the report should include the patient account and/or episode number, the name of the drug, the drug acquisition cost, and the amount charged to the patient for the drug.
4. **Provide the drug-specific data report to your Patient Accounting Department.** The Patient Accounting Department should manually or electronically provide the dollar amount charged and received and the payor or payor class for each patient included on the drug-specific data report.
5. **Integrate the patient accounting and drug-specific data reports.** Using spreadsheet software (eg, Access or Excel, Microsoft® Software, Redmond, Wash), integrate the data and sort the information by a specific drug or drug class and payor or payor type.
6. **Determine the percentage of total charges paid versus the total charges submitted. Apply this percentage to the total billed drug charges to determine the dollar amount paid for drug charges. Compare the dollar amount paid for drug charges to the actual acquisition cost for the drug in question to determine the profit margin.** This process should be repeated for all patients in the drug-specific or payor-specific data sets.

Using this model, drug- or payor-specific profit margins can be reasonably estimated. Further refinement of this model may include use of specific payment rates for all drugs with Medicare ambulatory payment classifications rather than the percentage of charges estimate. In addition, institution-specific contract carve-outs or other contract provisions which may provide for an increase or decrease in the estimated payment for specific drugs can be factored into the model.

Determining the actual payment received for hospital outpatient or physician’s office drug charges can be a complex and labor intensive process. However, it is important that each healthcare facility knows whether drug acquisition costs are being covered and if the profit margin generated covers the costs of providing drugs to patients.

COMPENDIA UPDATE

Drugs Indicated for Chronic Anemia Associated With Malignancy*			
Generic Drug Name	Brand Name	Compendia Listing	Billing Code (Billing Unit) [†]
Darbepoetin alfa	Aranesp®	USP DI	Q0137 (1 µg) [‡]
Epoetin alfa	Procrit®	AHFS; USP DI	Q0136 (1,000 U)

*Information as listed in *Compendia-Based Drug Bulletin*, volume 12, August 2003.

[†]Codes and units for injectable formulations, unless otherwise indicated.

[‡]Code and unit for Medicare’s Hospital Outpatient Prospective Payment System.

AHFS=American Hospital Formulary Service Drug Information; USP DI=United States Pharmacopeia Drug Information.

Drugs and Indications Added or Changed in Compendia in August 2003*				
Generic Drug Name	Brand Name	Indication	Compendia Listing	Billing Code (Billing Unit)*
New drugs				
Bortezomib	Velcade™	Multiple myeloma	AHFS	C9207 (3.5 mg)
New indications				
Arsenic trioxide	Trisenox®	Chronic lymphocytic leukemia Liver cancer	Orphan drug status† Orphan drug status†	J9017 (1 mg) J9017 (1 mg)
Irinotecan HCl	Camptosar®	Non-small cell lung cancer	USP DI	J9206 (20 mg)

*Information as listed in *Compendia-Based Drug Bulletin*, volume 12, August 2003.

†Codes and units for injectable formulations, unless otherwise indicated.

‡Drug has orphan drug status and may not be reimbursed by local carrier.

AHFS=American Hospital Formulary Service Drug Information; HCl=hydrochloride; USP DI=United States Pharmacopeia Drug Information.

REIMBURSEMENT HOTLINES AND RESOURCES FOR ONCOLOGY DRUGS

Reimbursement Hotlines for Recently Approved Oncology Drugs*

Manufacturer	Drugs Covered; Generic Name (Brand Name)	Program Name; Web Site	Phone Number	Information Available
Genta Incorporated	Gallium nitrate injection (Ganite™)	GentaCARES™ (Creating Access to Reimbursement Expertise Solutions); www.gentaCARES.com	888.864.3682	PRA, PAP
GlaxoSmithKline Corixa Corporation	Tositumomab and Iodine I 131 Tositumomab (Bexxar®)	GSK Oncology Reimbursement HELpline™; http://www.bexxar.com/hcp/reimbursement.html †	800.699.3806	PRA
		Commitment to Access Program; http://commitmenttoaccess.gsk.com	866.265.6491	PAP
MGI PHARMA, Incorporated and Helsinn Healthcare SA	Palonosetron HCl (Aloxi™)	Aloxi Alliance Services	866.302.5694	PRA, PAP

*Reimbursement hotline information for other oncology drugs available at www.accc-cancer.org and other Web sites (see Reimbursement Resources in this newsletter).

†Web site provides billing code information only.

HCl=hydrochloride; PAP=patient-assistance program; PRA=provider reimbursement assistance.

Reimbursement Resources

Resource Name	Web Site or Phone Number	Description of Resource and/or Reimbursement Information Provided
Government-Based Sites		
CMS	www.cms.gov	Official site of federal agency that runs Medicare and Medicaid programs; site provides <ul style="list-style-type: none"> • Information about specific government insurance programs • Information about coverage laws and regulations • CMS-related news • Glossary of terms
FDA	www.fda.gov	Official site for FDA news and other related information; site provides <ul style="list-style-type: none"> • Information about recent FDA product approvals • Information about recent ODAC activities
Medicare	www.medicare.gov	Official site of Medicare; site provides <ul style="list-style-type: none"> • Online access to policy and coverage manuals • List of prescription drug-assistance programs and other assistance programs
THOMAS	thomas.loc.gov	Online access to federal information, including <ul style="list-style-type: none"> • Legislation and bill summaries • Congressional records • Committee records
National Organizations		
American Society of Clinical Oncology	www.asco.org	Official site of largest professional organization representing physicians who treat patients with cancer; site provides <ul style="list-style-type: none"> • Legislative and organizational news affecting reimbursement and clinical news • Online access to practice guidelines
Association of Community Cancer Centers	www.accc-cancer.org	Organization charged with helping oncology professionals adapt to challenges of program management, cuts in reimbursement, hospital consolidation and mergers, and legislation and regulations that threaten delivery of high-quality cancer care; site provides <ul style="list-style-type: none"> • Online access to <i>Compendia-Based Drug Bulletins</i> and <i>United States Pharmacopeia Drug Information (USP DI)</i> • List of oncology drug reimbursement hotlines • Oncology-related news
Pharmaceutical Research and Manufacturers of America Foundation	www.helpingpatients.org	Interactive Web site designed to help patients, health care providers, and/or family members/caregivers find information on patient-assistance programs; site provides <ul style="list-style-type: none"> • List of available patient-assistance programs based on specific patient characteristics • List of pharmaceutical company-based patient-assistance programs • Links to other reimbursement resources

Reimbursement Resources — continued on page 10.

ONCOLOGY REIMBURSEMENT CONNECTION NEWSLETTER EVALUATION FORM

Name _____ Degree _____

Title _____

Institution/Practice Site _____

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Please tick (✓) box if you would like to be added to our mailing list and receive more complimentary copies of *Oncology Reimbursement Connection*.

Feature Article Feedback (Please tick (✓) the box that best answers the following questions)

1) Which erythropoietic agent(s) is/are primarily prescribed to treat chemotherapy-related anemia at your institution?

Darbepoetin alfa Epoetin alfa Darbepoetin alfa > Epoetin alfa Epoetin alfa > Darbepoetin alfa Both agents are prescribed at comparable rates

2) For treatment of chemotherapy-related anemia, what initial dosage of an erythropoietic agent is most commonly used?

(Tick all that apply)

Darbepoetin alfa 2.25 µg/kg/wk Darbepoetin alfa 3 µg/kg every 2 weeks Darbepoetin alfa 200 µg every 2 weeks Epoetin alfa 40,000 U/wk
 Other (please specify agent and dosage) _____

3) What percentage of erythropoietic therapy administered in the outpatient setting is reimbursed by Medicare according to the Outpatient Prospective Payment System (OPPS) ruling?

25% 26%–50% 51%–75% > 75%

4) How have changes in reimbursement for erythropoietic agents as mandated by the OPPS affected financial performance in the outpatient department of your institution?

Significantly Modestly Minimally Not at all Do not know

Using a scale of 1 to 5, with 1 indicating that you strongly disagree and 5 indicating that you strongly agree, please complete the following survey.

N/A=not applicable.

Newsletter Effectiveness Assessment (Please tick (✓) the rating that best represents your opinion)

Disagree  Agree

How well was the information presented?	N/A	1	2	3	4	5
1) The newsletter provided information that was relevant to my practice.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2) The newsletter's content was presented at an appropriate level of learning.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3) The newsletter was organized efficiently and effectively.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4) The length of the newsletter was appropriate.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please rate the overall value of the feature article and newsletter columns in this issue of the *Oncology Reimbursement Connection* newsletter using the following 5 point scale.

1=not valuable 2=slightly valuable 3=valuable 4=very valuable 5=extremely valuable

Feature Articles/Columns Value Assessment (Please tick (✓) the rating that best represents your opinion)

How valuable were the following articles/columns to your practice?	N/A	1	2	3	4	5
1. Feature Article: Darbepoetin Alfa (Aranesp®): Practical Issues in the Management of Chemotherapy-Related Anemia	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. "In the News"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. "Compendia Update"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. "Networking Column"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. "Hotlines and Resources"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
6. Feature Insert: 2004 Outpatient Prospective Payment System Final Rule: Summary of Oncology-Related Medications	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Audience Assessment (Please tick (✓) the rating that best represents your opinion)

Yes No

1) Would you like to have ACPE-accredited continuing education credits awarded for the material in this newsletter?	<input type="checkbox"/>	<input type="checkbox"/>
2) Would you like to have ACCN-accredited continuing education credits awarded for the material in this newsletter?	<input type="checkbox"/>	<input type="checkbox"/>
3) Would you like to have ACCME-accredited continuing education credits awarded for the material in the newsletter?	<input type="checkbox"/>	<input type="checkbox"/>
4) Would you be interested in receiving this newsletter online (with printable text)?	<input type="checkbox"/>	<input type="checkbox"/>

If you answered "Disagree," "Not Valuable," or "No" to any of the questions, would you please explain: _____

Suggestions for improving the value of the newsletter: _____



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Resource Name	Web Site or Phone Number	Description of Resource and/or Reimbursement Information Provided
Rx Hope	www.rxhope.com	Web portal for physicians and other healthcare providers to submit applications for patient-assistance programs over the Internet; site provides <ul style="list-style-type: none"> • Online patient-assistance application process • List of patient-assistance programs accessible by product or manufacturer name • Information on state and federal financial-assistance programs • Links to Web sites for pharmaceutical companies, healthcare organizations, and patient support networks • Drug information (prescribing information only)
Other Resources		
CANCERcare®	www.cancercares.org	Web site that lists programs providing medications to underinsured or uninsured patients, including state-based patient-assistance programs and pharmaceutical manufacturers' indigent drug programs
Copayment Assistance Program	800.272.9376	Program that provides copayment financial assistance to patients who meet objective financial eligibility criteria; program administered by Patient Services Incorporated
NeedyMeds.com	www.needyMeds.com	Regularly updated Web site that provides reimbursement and/or patient-assistance program information to patients and healthcare workers; site provides <ul style="list-style-type: none"> • List of reimbursement and patient-assistance programs accessible by drug or manufacturer name • Printed version of Web site information (available for \$100.00) • Downloads for patient-assistance program applications • Links to Medicaid sites
Patient Advocate Foundation	www.patientadvocate.org	National nonprofit organization that serves as active liaison between the patient and insurer, employer and/or creditors to resolve insurance, job retention, and/or debt crisis matters
ProCert	888.776.2378	Service provided by Bristol-Myers Squibb Oncology that conducts appeals for Medicare denials for off-label use of ProCert-covered products on provider's behalf; service reimburses provider with drug if appeal is not won; drugs covered include bleomycin, carboplatin, carmustine, cisplatin, cyclophosphamide, etoposide, ifosfamide, mesna, mitomycin, paclitaxel, teniposide
PROCRIline	www.procritline.com	Program that provides reimbursement assistance for Procrit®; site provides <ul style="list-style-type: none"> • Educational primer, "Oncology Coding and Reimbursement for Beginners" • 2002 Reference Guide to Oncology Diagnosis Codes • 2003 Online Reimbursement & Health Care Resources (an extensive list of Web sites)
Reimbursement Connection	800.272.9376; www.reimbursementconnection.com	Program that provides reimbursement assistance for Amgen's oncology products; site provides <ul style="list-style-type: none"> • Summaries of coverage and reimbursement for various insurers • Information about coding and claims processing, including sample forms and letters • Assistance with insurance verification
RxAssist	www.rxassist.org	Online service that provides healthcare providers with information needed to access various patient-assistance programs, including <ul style="list-style-type: none"> • Pharmaceutical company programs • Federal programs for military personnel or veterans • State Medicaid programs • State programs for senior, disabled, or low-income patients • City, county, or community programs • Drug discount cards, some of which are designed for seniors

CMS=Centers for Medicare & Medicaid Services; FDA=Food and Drug Administration; ODAC=Oncology Drugs Advisory Committee.

Oncology Reimbursement Connection

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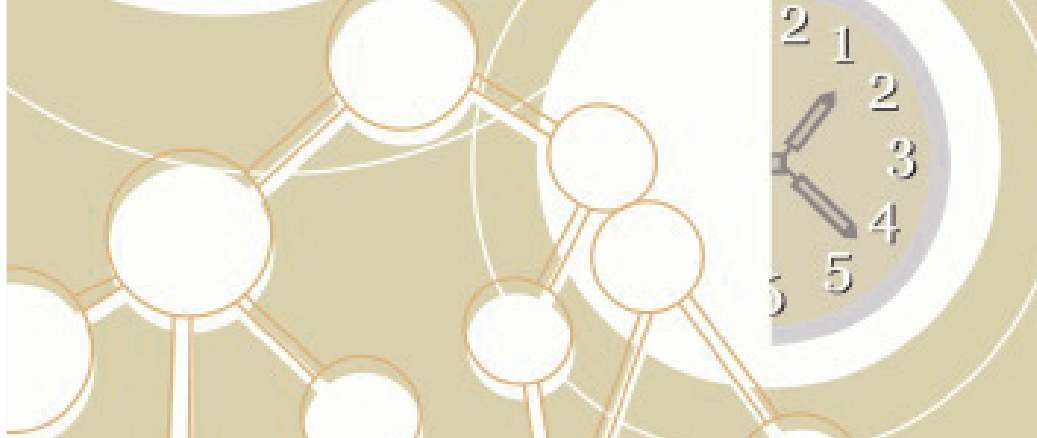
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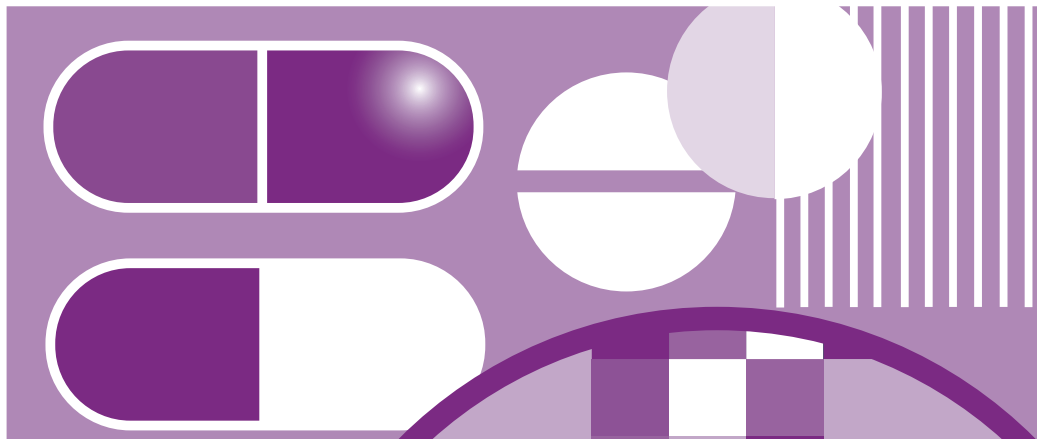
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Special Feature



2004 Outpatient Prospective Payment System Final Rule:

Summary of Oncology-Related Medications



Introduction

Medicare's 2004 Outpatient Prospective Payment System (OPPS) Final Rule, defining payment rates for hospital-based outpatient services, was released on October 31, 2003 and will become effective January 1, 2004. This feature insert of the *Oncology Reimbursement Connection* newsletter summarizes the key differences between the 2003 and 2004 OPPS Final Rules and categorizes oncology-related medications according to 2004 OPPS payment classifications. For more information about OPPS payment classification, please see the feature article entitled "Understanding the Outpatient Prospective Payment System" published in the 2003 Summer Issue (volume 1, issue 2) of *Oncology Reimbursement Connection*.

Table 1

Key Differences in the 2003 and 2004 Outpatient Prospective Payment System Final Rules¹⁻⁴

- The relative weight and payment rate for each ambulatory payment classification (APC) was updated using median unadjusted hospital costs derived from Outpatient Prospective Payment System (OPPS) claims submitted between April 1, 2002 and December 31, 2002. Oncology-related exceptions include amifostine and daunorubicin, for which adjusted median costs did not adequately represent actual costs; payment rates for these drugs were based on adjusted median costs derived from 2002 OPPS and external claims data. (*Note: OPPS will not accept midyear or quarterly revisions in APC payment rates based on the final Medicare Part B Average Wholesale Price [AWP] rule or quarterly AWP updates as suggested in the 2004 OPPS Proposed Rule and will continue to calculate payment rates for generic drugs using the same methodology for other separately payable drugs, rather than using the proposed generic drug payment methodology outlined in the 2004 OPPS Proposed Rule*).
- The threshold for packaging drugs into procedural APCs (eg, chemotherapy administration APCs) was reduced from \$150 to \$50. Carmustine, diethylstilbestrol diphosphonate, and pegaspargase lost drug-specific APC status for 2004; these drugs will now be paid under chemotherapy administration APCs (*see Table 2*). Asparaginase, Bacillus Calmette and Guérin (live), cyclophosphamide (lyophilized and nonlyophilized injections), cytarabine, liposomal cytarabine, dacarbazine, oral dolasetron, doxorubicin, etoposide, intravenous and oral granisetron, interferon alfa-2a, interferon alfa-2b, plicamycin, sargamostim, and thiotepa have been assigned drug-specific APCs for 2004 (*see Table 3*).
- Darbepoetin alfa and epoetin alfa are still considered by CMS to be functional equivalents when administered as treatment of chemotherapy-induced anemia, but the reimbursement conversion ratio was increased. The 2004 conversion ratio is 330 IU of epoetin alfa to 1 µg of darbepoetin alfa (330:1) (*see Table 3*).
- No across-the-board reduction of transitional pass-through payment drugs was required for 2004. Alemtuzumab, arsenic trioxide, and leuprolide acetate implant lost transitional pass-through payment status for 2004; these drugs are now paid under drug-specific APCs (*see Table 3*). Bortezomib and palonosetron were granted transitional pass-through payment status for 2004 (*see Table 4*).
- The chemotherapy administration APC, chemotherapy by both infusion and noninfusion (0118), was deleted from the 2004 OPPS Final Rule; hospitals will be allowed to bill and receive payment for both APC 0116 (chemotherapy administration by other than infusion) and 0117 (chemotherapy administration by infusion) if performed during the same patient visit. OPPS will not split APC 0116 into 3 APC codes according to method of administration (eg, subcutaneous or intramuscular, intravenous push, and central nervous system administration) and will not require use of Current Procedural Terminology (CPT) codes for administration of chemotherapy as suggested by the expert panel in the 2004 OPPS Proposed Rule, but will consider these revisions for 2005.
- The proper use of chemotherapy administration APCs 0116 and 0117 was not revised in the 2004 OPPS Final Rule, but OPPS clarified the proper method for using these codes when multiple drugs are administered in 1 or 2 patient visits on the same day. OPPS will only reimburse APC 0016 and 0017 once during a single visit, regardless of the number of drugs administered during the visit. Thus, if 2 chemotherapy drugs are administered by injection and 3 chemotherapy drugs are administered by infusion, the hospital can only bill one APC 0016 and one APC 0017 for that visit. If the patient, however, leaves the outpatient department after completing the first chemotherapy administration and returns later that day for another chemotherapy drug administration, the appropriate APC (either 0016 or 0017) may be billed again.
- Single-indication orphan drugs, including aldesleukin, denileukin diftitox, gemtuzumab ozogamicin, oprelvekin, and thyrotropin alpha, will be paid under separate APCs in 2004, rather than on a reasonable-cost basis as in 2003, using 88% of AWP for payment rates (*see Table 3*).

Table 2

Oncology-Related Medications Without Separate APC Payments in 2004* 1,3,5,6

GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	USUAL ROUTE(S)	GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	USUAL ROUTE(S)
Carmustine [†]	BiCNU [®]	J9050 (100 mg)	IV	Hydrocortisone acetate	Hydrocortone [®] Acetate	J1700 (up to 25 mg)	IV, IM, SQ
Corticotropin	ACTH [®] ; Acthar [®]	J0800 (up to 40 units)	IV, IM, SQ	Hydrocortisone sodium phosphate	Solu-Cortef [®] ; others	J1710 (up to 50 mg)	IV, IM, SQ
Cyclophosphamide, oral [†]	Cytosan	J8530 (25 mg)	Oral	Hydrocortisone succinate sodium	Solu-Cortef [®]	J1720 (up to 100 mg)	IV, IM, SQ
Dactinomycin	Cosmegen [®]	J9120 (0.5 mg)	IV	Leucovorin calcium	Wellcovorin [®]	J0640 (50 mg)	IM, IV
Dexamethasone acetate	Decadron [®] LA; others	J1094 (1 mg)	IM, IV	Mechlorethamine HCl	Mustargen [®]	J9230 (10 mg)	IV
Dexamethasone sodium phosphate	Decadron [®] ; others	J1100 (1 mg)	IM, IV	Medroxyprogesterone acetate	Depo-Provera [®] ; Provera [®]	J1051 (50 mg)	IM
Diethylstilbestrol diphosphate [†]	Stilphostrol [®]	J9165 (250 mg)	IV	Melphalan, oral [†]	Alkeran [®]	J8600 (2 mg)	Oral
Dolasetron mesylate [‡]	Anzemet [®]	J1260 (10 mg)	IV	Methotrexate	NA	J9250 (5 mg) J8610 (2.5 mg oral)	IA, IM, IT, IV Oral
Estradiol cypionate	Estro-Cyp [®] ; others	J1000 (up to 5 mg)	IM	Nandrolone decanoate	Deca-Durabolin [®] ; Hybolin [™] Decanoate	J2320 (up to 50 mg) J2321 (up to 100 mg) J2322 (up to 200 mg)	IM IM IM
Estradiol valerate	Valergen [®] ; others	J1380 (up to 10 mg) J1390 (up to 20 mg) J0970 (up to 40 mg)	IM IM IM	Ondansetron HCl	Zofran [®]	J2405 (1 mg) Q0179 (8 mg, oral)	IV Oral
Estrogens, conjugated	Premarin [®]	J1410 (25 mg)	IV, IM	Pegaspargase [†]	Oncaspar [®]	J9266 (single-dose vial)	IM, IV
Estrone	Kestron-5 [®] ; Theelin [™]	J1435 (1 mg)	IM	Prednisone	Deltasone [®] ; others	J7506 (any dose, 100 tablets)	Oral
Etidronate disodium	Didronel [®]	J1436 (300 mg)	IV	Testosterone cypionate	DepAndro [®] ; others	J1070 (up to 100 mg) J1080 (200 mg)	IM IM
Fluorouracil	Adrucil [®]	J9190 (500 mg)	IV				

Table 2

continued

Oncology-Related Medications Without Separate APC Payments in 2004* 1,3,5,6

GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	USUAL ROUTE(S)
Testosterone enanthate	Delatest®; others	J3120 (up to 100 mg)	IM
		J3130 (up to 200 mg)	IM
Testosterone propionate	NA	J3150 (up to 100 mg)	IM
Testosterone suspension	Testaqua®	J3140 (up to 50 mg)	IM
Vinblastine sulfate	Velban®; others	J9360 (1 mg)	IV
Vincristine sulfate	Oncovin®; Vincasar PFS®	J9370 (1 mg)	IV



*Reimbursed by Medicare in 2004 through packaged ambulatory payment classifications (APC).

†Assigned drug-specific APC status in 2003.

‡Intravenous formulation has its own APC (see Table 3).

§Oral formulation has its own APC (see Table 3)

APC=ambulatory payment classification; HCl=hydrochloride; IA=intraarterial; IM=intramuscular; IT=intrathecal; IV=intravenous; NA=not applicable; SQ=subcutaneous.

Table 3

Oncology-Related Medications With 2004 APC Payments* 1,3,5,7

GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	APC	2004 PAYMENT RATE, \$
Aldesleukin†	Proleukin®	J9015 (single-use vial)	0807	680.35
Alemtuzumab†	CamPath®	J9010 (10 mg)	9110	424.88
Amifostine	Ethyol®	J0207 (500 mg)	7000	289.40
Arsenic trioxide†	Trisenox®	J9017 (1 mg)	9012	26.91
Asparaginase‡	Elspar®	J9020 (10,000 units)	0814	16.13
Bacillus Calmette and Guérin, live‡	TheraCys®; Tice® BCG	J9031 (per vial)	0809	103.75
Bleomycin sulfate	Blenoxane®	J9040 (15 units)	0857	160.56
Busulfan	Busulfex™	C1178 (6 mg)	1178	299.70
Busulfan, oral	Myleran®	J8510 (2 mg)	7015	1.57

Table 3

continued

Oncology-Related Medications With 2004 APC Payments* 1,3,5,7

GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	APC	2004 PAYMENT RATE, \$
Capecitabine, oral	Xeloda®	J8520 (150 mg)	7042	1.65
Carboplatin	Paraplatin®	J9045 (50 mg)	0811	86.47
Cisplatin	Platinol®-AQ	J9060 (10 mg)	0813	21.74
Cladribine	Leustatin®	J9065 (1 mg)	0858	37.82
Cyclophosphamide ^{III}	Cytosan®; Neosar®	<i>Nonlyophilized:</i> J9070 (100 mg)	0815	4.74
	Cytosan® Lyophilized	<i>Lyophilized:</i> J9093 (100 mg)	0816	4.50
Cytarabine [§]	Cytosar-U®	J9100 (100 mg)	0817	5.07
Cytarabine liposome [§]	DepoCyt®	J9098 (10 mg) ^{††}	1116	278.99
Dacarbazine [§]	DTIC-Dome®	J9130 (100 mg)	0819	5.31
Darbepoetin alfa [†]	Aranesp®	Q0137 (1 µg) ^{††}	0734	3.24
Daunorubicin HCl	Cerubidine®	J9150 (10 mg)	0820	73.97
Daunorubicin citrate liposome	DaunoXome®	J9151 (10 mg)	0821	163.55
Denileukin diftitox [†]	Ontak®	J9160 (300 µg)	1084	1,232.88
Dexrazoxane HCl	Zinecard®	J1190 (250 mg)	0726	112.48
Docetaxel	Taxotere®	J9170 (20 mg)	0823	220.97
Dolasetron mesylate, oral [§]	Anzemet®	Q0180 (100 mg)	0763	41.00
Doxorubicin HCl [§]	Adriamycin®; Rubex®	J9000 (10 mg)	0847	6.61
Doxorubicin HCl liposome	Doxil®	J9001 (10 mg)	7046	256.34
Epirubicin HCl	Ellence®	J9178 (2 mg) ^{§§}	1167	20.43
Epoetin alfa [†]	Procrit®, Epogen®	Q0136 (1,000 units)	0733	9.83
Etoposide [§]	VePesid®, Toposar™	J9181 (10 mg)	0824	4.56
Etoposide, oral	VePesid®	J8560 (50 mg)	0802	27.37
Filgrastim	Neupogen®	J1440 (300 µg)	0728	123.48
Filgrastim	Neupogen®	J1441 (480 µg)	7049	175.96
Floxuridine	FUDR™	J9200 (500 mg)	0827	114.19

Table 3

continued

Oncology-Related Medications With 2004 APC Payments* 1,3,5,7

GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	APC	2004 PAYMENT RATE, \$
Fludarabine phosphate	Fludara [®]	J9185 (50 mg)	0842	205.74
Gemcitabine HCl	Gemzar [®]	J9201 (200 mg)	0828	80.43
Gemtuzumab ozogamicin [†]	Mylotarg [®]	J9300 (5 mg)	9004	2,022.90
Goserelin acetate implant	Zoladex [®]	J9202 (3.6 mg)	0810	285.16
Granisetron HCl [§]	Kytril [®]	J1626 (100 µg)	0764	5.70
Granisetron HCl, oral [§]	Kytril [®]	Q0166 (1 mg)	0765	34.49
Idarubicin HCl	Idamycin [®]	J9211 (5 mg)	0832	178.21
Ifosfamide	Ifex [®]	J9208 (1 g)	0831	106.04
Immune globulin [®]	Gamimune [®] ; Gammagard [®] ; others	J1564 (10 mg)	9021	.44
Immune globulin**	Gamimune [®] ; Gammagard [®] ; others	J1563 (1 g)	0905	43.96
Interferon alfa-2a [§]	Roferon [®] -A	J9213 (3 million units)	0834	20.61
Interferon alfa-2b [§]	Intron [®] -A	J9214 (1 million units)	0836	10.93
Irinotecan	Camptosar [®]	J9206 (20 mg)	0830	100.55
Leuprolide acetate	Lupron [®]	J9218 (1 mg)	0861	43.60
Leuprolide acetate for depot suspension	Lupron Depot [®]	J1950 (3.75 mg)	0800	182.92
Leuprolide acetate for depot suspension	Lupron Depot [®]	J9217 (7.5 mg)	9217	312.37
Leuprolide acetate implant [†]	Viadur [®]	J9219 (65 mg)	7051	3,666.71
Melphalan HCl	Alkeran [®]	J9245 (50 mg)	0840	254.90
Mesna	Mesnex [®]	J9209 (200 mg)	0732	28.43
Mitomycin	Mutamycin [®]	J9280 (5 mg)	0862	53.03
Mitoxantrone	Novantrone [®]	J9293 (5 mg)	0864	173.68
Octreotide acetate	Sandostatin [®]	J2354 (1 mg) ^{¶¶}	7031	1.44
Octreotide acetate depot	Sandostatin LAR [®]	J2353 (1 mg) ^{¶¶}	1207	65.74
Oprelvekin [†]	Neumega [®]	J2355 (5 mg)	7011	248.16
Paclitaxel	Taxol [®]	J9265 (30 mg)	0863	112.14
Pamidronate disodium	Aredia [®]	J2430 (30 mg)	0730	174.32
Pentostatin	Nipent [®]	J9268 (10 mg)	0844	965.98
Plicamycin [§]	Mithracin [®]	J9270 (2,500 µg)	0860	15.42
Porfimer sodium	Photofrin [®]	J9600 (75 mg)	0856	1,594.30
Rituximab	Rituxan [™]	J9310 (100 mg)	0849	306.40
Sargramostim [§]	Leukine [®]	J2820 (50 µg)	0731	16.32
Streptozocin	Zanosar [®]	J9320 (1 g)	0850	65.19
Temozolomide, oral	Temodar [®]	J8700 (5 mg)	1086	3.76
Teniposide	Vumon [®]	Q2017 (50 mg)	7035	137.41
Thiotepa [§]	Thioplex [®]	J9340 (15 mg)	0851	59.93
Thyrotropin alpha injection [†]	Thyrogen [®]	J3240 (0.9 mg)	9108	572.00

Table 3

continued

Oncology-Related Medications With 2004 APC Payments* 1,3,5,7

GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	APC	2004 PAYMENT RATE, \$
Topotecan HCl	Hycamtin®	J9350 (4 mg)	0852	433.41
Trastuzumab	Herceptin®	J9355 (10 mg)	1613	40.56
Trimetrexate glucuronate	Neutrexin®	J3305 (25 mg)	7045	61.36
Valrubicin	Valsar®	J9357 (200 mg)	1614	461.78
Vinorelbine tartrate	Navelbine®	J9390 (10 mg)	0855	64.79

*Injectable drugs, unless otherwise stated.

†Paid on a reasonable-cost basis in 2003.

‡Assigned transitional pass-through payment status in 2003.

§Paid through packaged APCs in 2003.

¶Oral formulation packaged under chemotherapy administration APCs (see Table 2).

‡For non-endstage renal disease.

¶Used for reporting quantities <0.75 g.

**Used for reporting quantities >0.75 g; relative weight not reported.

††HCPCS code revised in 2004; C1166 deleted, but payment will be made under C1166 through 3/30/04.

‡‡HCPCS code revised in 2004; C1774 deleted, but payment will be made under C1774 through 3/30/04.

§§HCPCS code revised in 2004; C1167 deleted, but payment will be made under C1167 through 3/30/04.

¶¶HCPCS code revised in 2004; J2352 deleted as of 12/31/03.

‡‡‡HCPCS code revised in 2004; Q4052 deleted, but payment will be made under Q4052 through 3/30/04.

APC=ambulatory payment classification; HCl=hydrochloride; HCPCS=Healthcare Common Procedure Coding System.

Table 4

Oncology-Related Medications With 2004 Transitional Pass-Through Payment Status* 3,4

GENERIC DRUG NAME	BRAND NAME	BILLING CODE (BILLING UNIT)	APC	PASS-THROUGH PAYMENT, \$	NON PASS-THROUGH PAYMENT, \$ Medicare Portion [†]	Copayment [‡]	TOTAL PAYMENT, \$
Bortezomib [†]	Velcade [™]	C9207 (3.5 mg)	9207	262.66	621.62	155.40	1,039.68
Fulvestrant	Faslodex [®]	J9395 (25 mg) [§]	9120	22.13	52.36	13.09	87.58
Oxaliplatin	Eloxatin [™]	C9205 (5 mg)	9205	23.86	56.48	14.12	94.46
Palonosetron ^{††}	Aloxi [™]	NA	NA	NA	NA	NA	NA
Pegfilgrastim	Neulasta [™]	J2505 (6 mg) [¶]	9119	708.00	1,675.60	418.90	2,802.50
Triptorelin pamoate	Trelstar [®] Depot	J3315 (3.75 mg)	9122	100.70	238.33	59.58	398.62
Zoledronic acid	Zometa [®]	J3487 (1 mg)	9115	54.93	130.00	32.50	217.43

*All medications listed had transitional pass-through payment status for at least part of 2003, unless otherwise stated.

†Assigned transitional pass-through payment status beginning January 1, 2004.

‡Pass-through status assigned after publication of 2004 OPPS Final Rule; specific coding and payment instructions will be announced in the CMS program memorandum implementing the January 2004 OPPS updates. CMS program memorandums are generally available at: <http://www.cms.gov>.

§HCPCS code revised in 2004; C9120 deleted as of 12/31/03.

¶HCPCS code revised in 2004; C9119 deleted as of 12/31/03.

††Medicare portion of nonpass-through payment calculated by subtracting sum of copayment and pass-through payment from total payment.

‡Based on the minimum unadjusted copayment.

APC=ambulatory payment classification; CMS=Centers for Medicare & Medicaid Services; HCPCS=Healthcare Common Procedure Coding System; NA=not available; OPPS=Outpatient Prospective Payment System.

References

1. Federal Register. Centers for Medicare & Medicaid. 2002;67:66717-67046. Available at: http://www.access.gpo.gov/su_docs/fedreg/a021101c.html. Accessed July 28, 2003.
2. Federal Register. Centers for Medicare & Medicaid. 2003;68:47965-48248. Available at: http://www.access.gpo.gov/su_docs/fedreg/a030812c.html. Accessed August 12, 2003.
3. Final rule: Medicare program; changes to the hospital outpatient prospective payment system and calendar year 2004 payment rates. (CMS-1471-FC). Available at: <http://www.cms.gov/regulations/hopps/2004f/>. Accessed November 3, 2003.
4. MGI PHARMA announces that Aloxi qualifies for pass-through status; hospital OPPS code available January 1, 2004. Available at: http://www.corporate-ir.net/ireye/ir_site.zhtml?ticker=MOGN&script=410&layout=6&item_id=465268. Accessed November 13, 2003.
5. Appendix 3: Table of drugs. In: *American Medical Association Healthcare Common Procedure Coding System 2003*. Atlanta, Ga: Ingenix, Inc; 2002:Appendix-7-Appendix-38.
6. McEvoy GK, ed. *AHFS Drug Information*® (2003). [textbook online]. Bethesda, Md: American Society of Health-Systems Pharmacists, Inc.; 2003.
7. CMS publication 60A; transmittal A-03-020: April 2003 update of the hospital outpatient prospective payment system (OPPS). Available at: <http://www.cms.gov/providerupdate/previousinstruct.asp>. Accessed July 29, 2003.

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