CMS Manual System	**Department of Health & Human Services (DHHS)**
Pub 100-02 Medicare Benefit Policy	**Centers for Medicare & Medicaid Services (CMS)**
Transmittal 78	**Date: SEPTEMBER 21, 2007**
	Change Request 5729

Subject: Unlabeled Use for Anti-Cancer Drugs: Medical Literature Used to Determine Medically Accepted Indications for Drugs and Biologicals Used in Anti-Cancer Treatment

I. SUMMARY OF CHANGES: CMS is adding to the current list at chapter 15, section 50.4.5 of the Medicare Benefit Policy Manual the following journals:

Annals of Oncology
Biology of Blood and Marrow Transplantation
Bone Marrow Transplantation
Gynecologic Oncology
Clinical Cancer Research
International Journal of Radiation, Oncology, Biology, and Physics
Journal of NCCN
Radiation Oncology
Annals of Surgical Oncology
Journal of Urology
Lancet Oncology

CMS is not deleting any of the current journals at this time.

New / Revised Material
Effective Date: October 22, 2007
Implementation Date: October 22, 2007

Disclaimer for manual changes only: The revision date and transmittal number apply only to red italicized material. Any other material was previously published and remains unchanged. However, if this revision contains a table of contents, you will receive the new/revised information only, and not the entire table of contents.

II. CHANGES IN MANUAL INSTRUCTIONS: (N/A if manual is not updated)
R=REVISED, N=NEW, D=DELETED

R/N/D	CHAPTER / SECTION / SUBSECTION / TITLE
R	15/50.4.5/Unlabeled Use for Anti-Cancer Drugs

III. FUNDING:
No additional funding will be provided by CMS; contractor activities are to be carried out within their operating budgets.

IV. ATTACHMENTS:

Business Requirements

Manual Instruction

Unless otherwise specified, the effective date is the date of service.

Attachment - Business Requirements

Pub. 100-02	Transmittal: 78	Date: September 21, 2007	Change Request: 5729

SUBJECT: Unlabeled Use for Anti-Cancer Drugs: Medical Literature Used to Determine Medically Accepted Indications for Drugs and Biologicals Used in Anti-Cancer Treatment

Effective Date: October 22, 2007

Implementation Date: October 22, 2007

I. GENERAL INFORMATION

A. Background: Section 1861(t)(2)(B)(ii)(II) of the Social Security Act states that "the carrier involved determines, based upon guidance provided by the Secretary to carriers for determining accepted uses of drugs, that such use is medically accepted based on supportive clinical evidence in peer reviewed medical literature appearing in publications which have been identified for purposes of this subclause by the Secretary." Accordingly, chapter 15, section 50.4.5 of Pub.100-02, the Medicare Benefit Policy Manual lists 15 peer-reviewed journals that a contractor must use to determine "whether there is supportive clinical evidence for a particular use of a drug."

In letters dated May 21, 2003 (2003 letter) and May 4, 2006 (2006 letter), the American Society of Clinical Oncology (ASCO) noted that this list was created in 1993 and has not been revised since. Therefore, ASCO formally submitted requests for the Centers for Medicare & Medicaid Services (CMS) to revise the list by adding 14 journals.

CMS staff conducted an ad hoc review of the journals listed in the ASCO requests. In addition, CMS informally consulted oncology experts from the National Cancer Institute at the National Institutes of Health and from the Center for Drug Evaluation and Research at the Food and Drug Administration to request their opinions about the ASCO-recommended journals. CMS also provided public notice and solicited public comment through a CMS Web site posting from October 27, 2006, through December 26, 2006. CMS staff integrated the data from its review and from the above sources into a final decision.

B. Policy: CMS is adding the following journals to the current list at chapter 15, section 50.4.5 of the Medicare Benefit Policy Manual, Publication 100-02:

- Annals of Oncology
- Biology of Blood and Marrow Transplantation
- Bone Marrow Transplantation
- Gynecologic Oncology
- Clinical Cancer Research
- International Journal of Radiation, Oncology, Biology, and Physics
- Journal of NCCN
- Radiation Oncology
- Annals of Surgical Oncology
- Journal of Urology
- Lancet Oncology

CMS is not deleting any of the current journals at this time.

II. BUSINESS REQUIREMENTS TABLE

Use "Shall" to denote a mandatory requirement

Number	Requirement	Responsibility (place an "X" in each applicable column)										
		A/B MAC	DME MAC	FI	CARRIER	DMERC	RHHI	Shared-System Maintainers				OTHER
								FISS	MCS	VMS	CWF	
5729.1	Contractors shall be aware of the revised list of publications specified in Pub. 100-02, chapter 15, section 50.4.5.D when determining unlabeled use for anti-cancer drugs.	X			X							

III. PROVIDER EDUCATION TABLE

Number	Requirement	Responsibility (place an "X" in each applicable column)										
		A/B MAC	DME MAC	FI	CARRIER	DMERC	RHHI	Shared-System Maintainers				OTHER
								FISS	MCS	VMS	CWF	
5729.2	A provider education article related to this instruction will be available at http://www.cms.hhs.gov/MLNMattersArticles/ shortly after the CR is released. You will receive notification of the article release via the established "MLN Matters" listserv. Contractors shall post this article, or a direct link to this article, on their Web site and include information about it in a listserv message within one week of the availability of the provider education article. In addition, the provider education article shall be included in your next regularly scheduled bulletin. Contractors are free to supplement MLN Matters articles with localized information that would benefit their provider community in billing and administering the Medicare program correctly.	X			X							

IV. SUPPORTING INFORMATION

A. For any recommendations and supporting information associated with listed requirements, use the box below:

Use "Should" to denote a recommendation.

X-Ref Requirement Number	Recommendations or other supporting information:

B. For all other recommendations and supporting information, use the space below:

V. CONTACTS

Pre-Implementation Contact(s):

Coverage: Kate Tillman, katherine.tillman@cms.hhs.gov or 410-786-9252
Coverage: Pat Brocato-Simons patricia.brocatosimons@cms.hhs.gov or 410-786-0261

Post-Implementation Contact(s): Regional Office

VI. FUNDING

A. *For Fiscal Intermediaries, Carriers, and the Durable Medical Equipment Regional Carrier (DMERC)*:

No additional funding will be provided by CMS; Contractor activities are to be carried out within their operating budgets.

B. *For Medicare Administrative Contractors (MAC)*:

The Medicare Administrative Contractor (MAC) is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as changes to the MAC Statement of Work (SOW). The contractor is not obligated to incur costs in excess of the amounts specified in your contract unless and until specifically authorized by the Contracting Officer. If the contractor considers anything provided, as described above, to be outside the current scope of work, the contractor shall withhold performance on the part(s) in question and immediately notify the Contracting Officer, in writing or by e-mail, and request formal directions regarding continued performance requirements.

50.4.5 - Unlabeled Use for Anti-Cancer Drugs

(Rev. 78, Issued: 09-21-07, Effective: 10-22-07, Implementation: 10-22-07)

Effective January 1, 1994, unlabeled uses of *Food and Drug Administration- (*FDA) approved drugs and biologicals used in an anti-cancer chemotherapeutic regimen for a medically accepted indication are evaluated under the conditions described in this paragraph. A regimen is a combination of anti-cancer agents clinically recognized for the treatment of a specific type of cancer. An example of a drug regimen is: Cyclophosphamide + vincristine + prednisone (CVP) for non-Hodgkin's lymphoma.

In addition to listing the combination of drugs for a type of cancer, there may be a different regimen or combinations which are used at *various* times in the history of the cancer (induction, prophylaxis of *central nervous system* involvement, post remission, and relapsed or refractory disease). A protocol may specify the combination of drugs, doses, and schedules for administration of the drugs. For purposes of this provision, a cancer treatment regimen includes drugs used to treat toxicities or side effects of the cancer treatment regimen when the drug is administered incident to a chemotherapy treatment.

Do not deny coverage based solely on the absence of FDA-approved labeling for the use, if the use is supported by one of the following and the use is **not** listed as "not indicated" in any of the three compendia. (See note at the end of this subsection.)

A. American Hospital Formulary Service Drug Information

Drug monographs are arranged in alphabetical order within therapeutic classifications. Within the text of the monograph, information concerning indications is provided; including both labeled and unlabeled uses. Unlabeled uses are identified with daggers. The text must be analyzed to make a determination whether a particular use is supported.

B. American Medical Association *(AMA)* Drug Evaluations

Drug evaluations are organized into sections and chapters that are based on therapeutic classifications. The evaluation of a drug provides information concerning indications, including both labeled and unlabeled uses. Unlabeled uses are not specifically identified as such. The text must be analyzed to make a determination whether a particular use is supported. In making these determinations, also refer to the "AMA Drug Evaluations Subscription," Volume III, section 17 (Oncolytic Drugs), chapter 1 (Principles of Cancer Chemotherapy), tables 1 and 2.

Table 1, Specific Agents Used *in* Cancer Chemotherapy, lists the anti-neoplastic agents currently available for use in various cancers. The indications presented in this table for a particular anti-cancer drug include labeled and unlabeled uses (although they are not identified as such). Any indication appearing in this table is considered to be a medically accepted use.

Table 2, Clinical Responses *to* Chemotherapy, lists some of the currently preferred regimens for various cancers. The table headings include: (1) type of cancer; (2) drugs or regimens currently preferred; (3) alternative or secondary drugs or regimens; and, (4) other drugs or regimens with reported activity.

A regimen appearing under the preferred or alternative/secondary headings is considered to be a medically accepted use.

A regimen appearing under the heading "Other Drugs or Regimens *with* Reported Activity" is considered to be for a medically accepted use provided:

- The preferred and alternative/secondary drugs or regimens are contraindicated;
- A preferred and/or alternative/secondary drug or regimen was used but was not tolerated or was ineffective; or,
- There was tumor progression or recurrence after an initial response.

C. United States Pharmacopoeia Drug Information (USPDI)

Monographs are arranged in alphabetic order by generic or family name. Indications for use appear as accepted, unaccepted, or insufficient data. An indication is considered to be a medically accepted use only if the indication is listed as accepted. Unlabeled uses are identified with brackets. A separate indications index lists all indications included in USPDI along with the medically accepted drugs used in treatment or diagnosis.

D. A Use Supported by Clinical Research That Appears in Peer-Reviewed Medical Literature

This applies only when an unlabeled use does not appear in any of the compendia or is listed as insufficient data or investigational. If an unlabeled use of a drug meets these criteria, the carrier will contact the compendia to see if a report regarding this use is forthcoming. If a report is forthcoming, the carrier uses this information as a basis for making decisions. The compendium process for making decisions concerning unlabeled uses is very thorough and continuously updated. Peer-reviewed medical literature includes scientific, medical, and pharmaceutical publications in which original manuscripts are published, only after having been critically reviewed for scientific accuracy, validity, and reliability by unbiased independent experts. This does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts).

In determining whether there is supportive clinical evidence for a particular use of a drug, carrier medical staff (in consultation with local medical specialty groups) will evaluate the quality of the evidence in published peer-reviewed medical literature. When evaluating this literature, they will consider (among other things) the following:

- The prevalence and life history of the disease when evaluating the adequacy of the number of subjects and the response rate. While a 20% response rate may be adequate for highly prevalent disease states, a lower rate may be adequate for rare diseases or highly unresponsive conditions.

- The effect on the patient's well-being and other responses to therapy that indicate effectiveness, e.g., a significant increase in survival rate or life expectancy or an objective and significant decrease in the size of the tumor or a reduction in symptoms related to the tumor. Stabilization is not considered a response to therapy.

- The appropriateness of the study design. The carrier will consider:

    1. Whether the experimental design in light of the drugs and conditions under investigation is appropriate to address the investigative question. (For example, in some clinical studies, it may be unnecessary or not feasible to use randomization, double blind trials, placebos, or crossover.);

    2. That non-randomized clinical trials with a significant number of subjects may be a basis for supportive clinical evidence for determining accepted uses of drugs; and,

    3. That case reports are generally considered uncontrolled and anecdotal information and do not provide adequate supportive clinical evidence for determining accepted uses of drugs.

The carrier will use peer-reviewed medical literature appearing *in the regular editions of* the following publications*, not to include supplement editions privately funded by parties with a vested interest in the recommendations of the authors*.

- American Journal of Medicine;
- Annals of Internal Medicine;
- *Annals of Oncology;*
- *Annals of Surgical Oncology;*
- *Biology of Blood and Marrow Transplantation;*
- Blood;
- *Bone Marrow Transplantation;*
- British Journal of Cancer;
- British Journal of Hematology;
- British Medical Journal;
- Cancer;
- *Clinical Cancer Research;*
- Drugs;

- European Journal of Cancer (formerly the European Journal of Cancer and Clinical Oncology);
- *Gynecologic Oncology;*
- *International Journal of Radiation, Oncology, Biology, and Physics;*
- The Journal of the American Medical Association;
- Journal of Clinical Oncology;
- Journal of the National Cancer Institute;
- *Journal of the National Comprehensive Cancer Network (NCCN);*
- *Journal of Urology;*
- Lancet;
- *Lancet Oncology;*
- Leukemia;
- The New England Journal of Medicine; or
- *Radiation Oncology*

The carrier is not required to maintain copies of these publications. If a claim raises a question about the use of a drug for a purpose not included in the FDA-approved labeling or the compendia, the carrier will ask the physician to submit copies of relevant supporting literature.

Unlabeled uses may also be considered medically accepted if determined by the carrier to be medically accepted generally as safe and effective for the particular use.

NOTE: If a use is identified as not indicated *by the Centers for Medicare & Medicaid Services* or the FDA, or if a use is specifically identified as not indicated in one or more of the three compendia mentioned, or if the carrier determines, based on peer-reviewed medical literature, that a particular use of a drug is not safe and effective, the *unlabeled* usage is not supported and, therefore, the drug is not covered.