

CMS Manual System	Department of Health & Human Services (DHHS)
Pub 100-02 Medicare Benefit Policy	Centers for Medicare & Medicaid Services (CMS)
Transmittal 212	Date: November 6, 2015
	Change Request 9386

SUBJECT: Update to the List of Compendia as Authoritative Sources for Use in the Determination of a “Medically-Accepted Indication” of Drugs and Biologicals Used Off-label in an Anti-Cancer Chemotherapeutic Regimen

I. SUMMARY OF CHANGES: CMS is adding Wolters Kluwer Lexi-Drugs® to the list of authoritative compendia in chapter 15, section 50.4.5 of the Medicare Benefit Policy Manual for use in the determination of a medically accepted indication of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen.

EFFECTIVE DATE: August 12, 2015

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

IMPLEMENTATION DATE: February 10, 2016

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-Only One Per Row.

R/N/D	CHAPTER / SECTION / SUBSECTION / TITLE
R	15/50.4.5/Off-Label Use of Anti-Cancer Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen

III. FUNDING:

For Medicare Administrative Contractors (MACs):

The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted 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.

IV. ATTACHMENTS:

One Time Notification

Attachment - One-Time Notification

Pub. 100-02	Transmittal: 212	Date: November 6, 2015	Change Request: 9386
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SUBJECT: Update to the List of Compendia as Authoritative Sources for Use in the Determination of a “Medically-Accepted Indication” of Drugs and Biologicals Used Off-label in an Anti-Cancer Chemotherapeutic Regimen

EFFECTIVE DATE: August 12, 2015

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

IMPLEMENTATION DATE: February 10, 2016

I. GENERAL INFORMATION

A. Background: Section 1861(t)(2)(B)(ii)(I) of the Social Security Act (the Act) as amended by section 6001(f)(1) of the Deficit Reduction Act of 2005, Pub. Law 109-171, recognizes three compendia -- American Medical Association Drug Evaluations (AMA-DE), United States Pharmacopoeia-Drug Information (USP-DI) or its successor publication, and American Hospital Formulary Service-Drug Information (AHFS-DI) -- as authoritative sources for use in the determination of a "medically-accepted indication" of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia. This provision was implemented through instructions to Medicare contractors that are in Pub. 100-02, Medicare Benefit Policy Manual, chapter 15, section 50.4.5.

Due to changes in the pharmaceutical reference industry, AHFS-DI was the only remaining statutorily-named compendia available for our reference; the AMA-DE and USP-DI are no longer published; Thomson Micromedex designated Drug Points as the successor to USP-DI, but Drug Points has since been deleted from the list of recognized compendia.

On March 30, 2006, the Centers for Medicare & Medicaid Services (CMS) held a public session of Medicare Evidence Development and Coverage Advisory Committee (MEDCAC) and developed a list of desirable compendium characteristics as criteria for use in the determination of medically-accepted indications of drugs and biologicals in anti-cancer therapy.

Beginning in January 2008, via the Physician Fee Schedule Final Rule for calendar year 2008, CMS established a process for revising the list of compendia, as authorized under section 1861(t)(2) of the Act, and also established a definition for “compendium.” This sub-regulatory process for revising the list of compendia is described in Pub. 100-02, Medicare Benefit Policy Manual, chapter 15, section 50.4.5.1. Based on this process, CMS updated the list in 2008 to include the following four compendia:

- American Hospital Formulary Service-Drug Information (AHFS-DI),
- National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium,
- Truven Health Analytics Micromedex DrugDEX, and
- Elsevier/Gold Standard Clinical Pharmacology

On August 12, 2015, CMS announced the addition of Lexi-Drugs to the above list of compendia used by the Medicare program in the determination of a "medically accepted indication" for off-label drugs and biologics used in an anticancer chemotherapeutic treatment regimen.

B. Policy: Effective for services on or after August 12, 2015, CMS is adding Wolters Kluwer Lexi-Drugs to the list of authoritative compendia for use in the determination of a “medically-accepted indication” of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen.

Note the complete list of the recognized compendia in Pub. 100-02, Medicare Benefit Policy Manual, chapter 15, section 50.4.5:

- American Hospital Formulary Service-Drug Information (AHFS-DI),
- National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium,
- Truven Health Analytics Micromedex DrugDEX, and
- Elsevier/Gold Standard Clinical Pharmacology
- Wolters Kluwer Lexi-Drugs

Contractors shall recognize medically accepted indications as those that:

- are favorably listed in one or more of the compendia listed, or,
- the contractor determines from a review of the peer-reviewed literature as described above that it is a medically accepted indication,

unless CMS has determined that the use is not medically accepted, or any of the above listed compendia list the use as not medically accepted, or words to that effect.

CMS is aware that the listed compendia employ various rating and recommendation systems that may not be readily cross-walked from compendium to compendium. In general, a use is identified by a compendium as **medically accepted** if the:

1. indication is a Category 1 or 2A in NCCN, or Class I, Class IIa, or Class IIb in DrugDex; or,
2. narrative text in AHFS-DI or Clinical Pharmacology is supportive, or
3. indication is listed in Lexi-Drugs as “Use: Off-Label” and rated as “Evidence Level A”

A use is **not medically accepted** by a compendium if the:

1. indication is a Category 3 in NCCN or a Class III in DrugDex; or,
2. narrative text in AHFS or Clinical Pharmacology is “not supportive,” or
3. indication is listed in Lexi-Drugs as “Use: Unsupported”

The complete absence of narrative text on a use is considered neither supportive nor non-supportive.

NOTE: Referencing compendia for off-label anti-cancer chemotherapeutic drug use is an ongoing contractor instruction. The Secretary has the authority under section 1861(t)(2) of the Act to revise the compendia list as is appropriate for identifying medically acceptable off-label drug use. This instruction constitutes an update to the existing compendia list found at Pub. 100-02, Medicare Benefit Policy Manual, chapter 15, section 50.4.5.

NOTE: The contractor may maintain its own subscriptions to the listed compendia updates or peer-reviewed publications to determine the medically accepted indication of drugs or biologicals used off-label in an anti-cancer chemotherapeutic regimen. Compendia documentation or peer-reviewed literature supporting off-label use by the treating physician may also be requested of the physician by the contractor.

II. BUSINESS REQUIREMENTS TABLE

"Shall" denotes a mandatory requirement, and "should" denotes an optional requirement.

Number	Requirement	Responsibility									
		A/B MAC			D M E M A C S	Shared-System Maintainers				Other	
		A	B	H H H		F I S S	M C S	V M S	C W F		
9386.1	Effective August 12, 2015, in processing claims, contractors shall be aware of the addition to the list of compendia as authoritative sources for use in the determination of a "medically-accepted indication" of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen, unless the Secretary has determined that the use is not medically appropriate or the use is identified as not indicated in one or more such compendia as described in Pub. 100-02, chapter 15, section 50.4.5.	X	X	X	X						

III. PROVIDER EDUCATION TABLE

Number	Requirement	Responsibility					
		A/B MAC			D M E M A C	C E D I	
		A	B	H H H			
9386.2	MLN Article: A provider education article related to this instruction will be available at http://www.cms.gov/Outreach-and-Education/Medicare-Learning-Network-MLN/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 sites and include information about it in a listserv message within 5 business days after receipt of the notification from CMS announcing the availability of the article. In addition, the provider education article shall be included in the contractor's 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	X	X		

IV. SUPPORTING INFORMATION

Section A: Recommendations and supporting information associated with listed requirements: N/A

"Should" denotes a recommendation.

X-Ref Requirement Number	Recommendations or other supporting information:
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Section B: All other recommendations and supporting information: N/A

V. CONTACTS

Pre-Implementation Contact(s): Cheryl Gilbreath, 410-786-5919 or cheryl.gilbreath@cms.hhs.gov

Post-Implementation Contact(s): Contact your Contracting Officer's Representative (COR).

VI. FUNDING

Section A: For Medicare Administrative Contractors (MACs):

The Medicare Administrative Contractor is hereby advised that this constitutes technical direction as defined in your contract. CMS does not construe this as a change to the MAC Statement of Work. The contractor is not obligated to incur costs in excess of the amounts allotted 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.

ATTACHMENTS: 1

Medicare Benefit Policy Manual

Chapter 15 – Covered Medical and Other Health Services

Table of Contents *(Rev. 212, 11-06-15)*

50.4.5 – *Off-Label* Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen

50.4.5 - Off-Label Use of Drugs and Biologicals in an Anti-Cancer Chemotherapeutic Regimen

(Rev. 212, Issued: 11-06-15, Effective: 08-12-15, Implementation: 02-10-16)

A. Overview

Effective January 1, 1994, off-label, medically accepted indications of Food and Drug Administration-(FDA) approved drugs and biologicals used in an anti-cancer chemotherapeutic regimen are identified under the conditions described below. A regimen is a combination of anti-cancer agents clinically recognized for the treatment of a specific type of cancer. Off-label, medically accepted indications are supported in either one or more of the compendia or in peer-reviewed medical literature. The contractor may maintain its own subscriptions to the listed compendia or peer-reviewed publications to determine the medically accepted indication of drugs or biologicals used off-label in an anti-cancer chemotherapeutic regimen. Compendia documentation or peer-reviewed literature supporting off-label use by the treating physician may also be requested of the physician by the contractor.

B. Recent Revisions to the Compendia List

Do not deny coverage based solely on the absence of FDA-approved labeling for the use, if the use is supported by any of the following compendia and the use is **not** listed as unsupported, not indicated, not recommended, or equivalent terms, in any of the following compendia:

Existing - American Hospital Formulary Service-Drug Information (AHFS-DI)

Effective June 5, 2008 - National Comprehensive Cancer Network (NCCN) Drugs and Biologics Compendium

Effective June 10, 2008 - Micromedex DrugDex

Effective July 2, 2008 - Clinical Pharmacology

Effective August 12, 2015 – Lexi-Drugs

The listed compendia employ various rating and recommendation systems that may not be readily cross-walked from compendium to compendium. In general, a use is identified by a compendium as **medically accepted** if the:

1. indication is a Category 1 or 2A in NCCN, or Class I, Class IIa, or Class IIb in DrugDex; or,
2. narrative text in AHFS-DI or Clinical Pharmacology is supportive, or
3. *indication is listed in Lexi-Drugs as “Use: Off-Label” and rated as “Evidence Level A”*

A use is **not medically accepted** by a compendium if the:

1. indication is a Category 3 in NCCN or a Class III in DrugDex; or,
2. narrative text in AHFS or Clinical Pharmacology is “not supportive,” or
3. *indication is listed in Lexi-Drugs as “Use: Unsupported”*

The complete absence of narrative text on a use is considered neither supportive nor non-supportive.

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

Contractors may also identify off-label uses that are supported by clinical research under the conditions identified in this section. Peer-reviewed medical literature may appear in 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 prior to publication. In-house publications of entities whose business relates to the manufacture, sale, or distribution of pharmaceutical products are excluded from consideration. Abstracts (including meeting abstracts) are excluded from consideration.

In determining whether an off-label use is supported, the contractors will evaluate the evidence in published, peer-reviewed medical literature listed below. When evaluating this literature, they will consider (among other things) the following:

- Whether the clinical characteristics of the beneficiary and the cancer are adequately represented in the published evidence
- Whether the administered chemotherapy regimen is adequately represented in the published evidence.
- Whether the reported study outcomes represent clinically meaningful outcomes experienced by patients.
- Whether the study is appropriate to address the clinical question. The contractor 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 contractor 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

D. Generally

FDA-approved drugs and biologicals may also be considered for use in the determination of medically accepted indications for off-label use if determined by the contractor to be reasonable and necessary.

If a use is identified as not indicated by the Centers for Medicare and Medicaid Services (CMS) or the FDA, or if a use is specifically identified as not indicated in one or more of the compendia listed, or if the contractor determines, based on peer-reviewed medical literature, that a particular use of a drug is not safe and effective, the off-label usage is not supported and, therefore, the drug is not covered.