## Contractor Information

<table>
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<th>Contractor Name</th>
<th>Contract Type</th>
<th>Contract Number</th>
<th>Jurisdiction State(s)</th>
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<td>06101 - MAC A</td>
<td>Illinois</td>
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## LCD Information

Local Coverage Determination (LCD): Drugs and Biologicals, Coverage of, for Label and Off-Label Uses (L33394)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

## Document Information

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CMS National Coverage Policy Language quoted from Centers for Medicare and Medicaid Services (CMS), National Coverage Determinations (NCDs) and coverage provisions in interpretive manuals is italicized throughout the policy. NCDs and coverage provisions in interpretive manuals are not subject to the LCD Review Process (42 CFR 405.860[b] and 42 CFR 426 [Subpart D]). In addition, an administrative law judge may not review an NCD. See Section 1869(f)(1)(A)(i) of the Social Security Act.

Unless otherwise specified, *italicized* text represents quotation from one or more of the following CMS sources:

**Title XVIII of the Social Security Act (SSA):**

Section 1862(a)(1)(A) excludes expenses incurred for items or services which are not reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member.

Section 1833(e) prohibits Medicare payment for any claim which lacks the necessary information to process the claim.

**CMS Publications**


50 - Drugs and Biologicals

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

**Coverage Indications, Limitations, and/or Medical Necessity**

Abstract:

An off-label/unlabeled use of a drug is defined as a use for a non-FDA approved indication, that is, one that is not listed on the drug’s official label/prescribing information. An indication is defined as a diagnosis, illness, injury, syndrome, condition, or other clinical parameter for which a drug may be given. Off-label use is further defined as giving the drug in a way that deviates significantly from the labeled prescribing information for a particular indication. This includes but is not necessarily limited to, dosage, route of administration, duration and frequency of administration, and population to whom the drug would be administered. Drugs used for indications other than those in the approved labeling may be covered under Medicare if it is determined that the use is medically accepted, taking into consideration the major drug compendia, authoritative medical literatures and/or accepted standards of medical practice. Determinations as to whether medication is reasonable and necessary for an individual patient are made on appeal on the same basis as all other such determinations (i.e., with support from the peer-reviewed literature, with the advice of medical consultants, with reference to accepted standards of medical practice, and in consideration of the medical circumstance of the individual case).

In the case of drugs used in an anti-cancer chemotherapeutic regimen, off-label uses are covered for a medically accepted indication as defined in the *Medicare Benefit Policy Manual* (CMS publication 100-2, Chapter 15, Section 50.4.5).

In order to meet the requirement that the use of the drug is reasonable and necessary for the treatment of disease, the drugs must be safe and effective. Drugs approved for marketing by the Food and Drug Administration (FDA) are considered safe and effective when used for indications specified on the labeling. Therefore, Medicare pays for the use of a FDA-approved drug, if:

- It was injected on or after the date of the FDA’s approval;
- It is reasonable and necessary for the individual patient; and
- All other applicable coverage requirements are met.

**Indications:**

A medically accepted indication, which is covered by National Government Services is one of the following:

1. An FDA approved, labeled indication or a use supported in the American Hospital Formulary Service Drug Information (AHFS-DI), NCCN Drugs and Biologics Compendium, Truven Health Analytics Micromedex DrugDex®, Elsevier/Gold Standard Clinical Pharmacology and Wolters Kluwer Lexi-Drugs® as the acceptable compendia based on CMS’ Change Request 6191 (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); or
2. Articles or Local Coverage Determinations (LCDs) published by National Government Services.

The compendia listed above will be accepted at the following levels;

- American Hospital Formulary Service-Drug Information (AHFS-DI) – indication is supportive
- NCCN Drugs and Biologics Compendium - indication is a Category 1 or 2A
- Micromedex DrugDex® – indication is Class I, Class IIa, or Class IIb or
- Clinical Pharmacology – indication is supportive

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Lexi-Drugs - indication is rated as “Evidence Level A”

When new off-label uses for drugs are published in the above compendia at the accepted level of recommendation, the effective date for National Government Services coverage of those off-label uses is the date of publication of our revised coverage article, not the date of inclusion in the compendia.

In an effort to limit the number of LCD’s or articles related to off label indications for drug use, National Government Services will publish articles relating to drugs approved for off-label use for which there is a need for education or concern about utilization. These articles will include drugs with their FDA approved and off-label indications, as well as their uses listed in the American Hospital Formulary Services (AHFS), Elsevier/Gold Standard Clinical Pharmacology, NCCN Drugs and Biologics Compendium, Truven Health Analytics Micromedex DrugDex® compendium and/or Wolters Kluwer Lexi-Drugs®. Only off-label uses requested by providers according to the following criteria will be considered for inclusion in an article. These articles are searchable on the CMS Website http://www.cms.gov/medicare-coverage-database. A brief tutorial on how to use the site is included in the Supplemental Information Article attached to this LCD.

Providers may request that a drug be approved for off-label use by submitting this request in writing and including the data supporting its use. The data must include:

a. A use supported by clinical research that appears in at least two Phase III clinical trials that definitively demonstrate safety and effectiveness; or,

b. If no Phase III trial evidence is available, at least two Phase II clinical trials with reasonably large patient samples showing consistent results of safety and efficacy may be considered in certain instances such as use in rare diseases in which a Phase III study might be difficult to complete in a reasonable period of time after completion of the Phase II studies, or when overwhelmingly good evidence of safety and effectiveness is noted in the Phase II studies.

c. A use that is an accepted standard of medical practice. "Are there published recommendations from specialty societies or in other authoritative evidence-based guidelines?" (For example, a state of the art review article published in a recognized textbook or a reputable publication) It should be noted that acceptance by individual health care practitioners, or even a limited group of health care practitioners normally does not indicate general acceptance by the medical community. Testimonials indicating such limited acceptance, and limited case studies distributed by sponsors with potential financial conflict of interest in the outcome, are not sufficient evidence of general acceptance by the medical community. The broad range of available evidence must be considered and its quality must be evaluated before a conclusion is reached.

The Phase III or Phase II trials must come from different centers and be published in national or international peer-reviewed (editorial committee is comprised of physicians) journals. Peer reviewed medical literature includes scientific and medical publications. It does not include in-house publications of pharmaceutical manufacturing companies or abstracts (including meeting abstracts).

In principle, rankings of research design have been based on the ability of each study design category to minimize bias. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series and
- Single case reports

The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size.

In determining whether there is supportive clinical evidence for a particular use of a drug, the quality of the published evidence must be considered. Such consideration involves the assessment of the following study characteristics:

- The adequacy of the number of subjects;
- The response rate;

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• The effect on key status and survival indications. That is, the effect on the patient's well-being and other responses to therapy that indicate effectiveness (e.g., reduction in mortality, morbidity, signs and symptoms);
• The appropriateness of the study design, that is, 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.); and
• The prevalence and life history of the disease when evaluating the adequacy of the number of subjects and the response rate.

After such evidence is received, National Government Services will, with appropriate help of specialty-specific consultants as indicated, make a coverage determination for the non-FDA approved indication (off-label use) of the drug or biological.

National Government Services may determine a drug use to be reasonable and necessary for the treatment of illness or injury if, on the basis of available or presented evidence, it is shown to be safe and effective and does not violate national or local Medicare determinations and regulations. The approval will include, but is not limited to, diagnosis, dose and route of administration, duration and frequency, and appropriate patient population.

Limitations:

If a use is identified as not indicated by CMS or the FDA, or if a use is specifically identified as not indicated in the American Hospital Formulary Services (AHFS), Elsevier/Gold Standard Clinical Pharmacology, NCCN Drugs and Biologics Compendium, Truven Health Analytics Micromedex DrugDex® and/or Wolters Kluwer Lexi-Drugs® compendium, the off-label use is not supported and the drug will not be covered.

Regardless of the evidence supporting coverage for a particular off-label use, payment may only be made if the use is reasonable and necessary for the treatment of illness or injury of the specific patient receiving the drug.

Services related to non-covered services or drugs are also not covered (e.g., administration services).

Upon review, if the drug use is not on the FDA label, does not appear on the American Hospital Formulary Services (AHFS), Elsevier/Gold Standard Clinical Pharmacology, NCCN Drugs and Biologics Compendium, Truven Health Analytics Micromedex DrugDex® and/or National Government Services has not published an LCD or article covering the off-label use, the drug use is not approved and the use of the drug may be denied. However, determinations as to whether medication is reasonable and necessary for an individual patient may be made on appeal on the same basis as all other such determinations (i.e., with support from the peer-reviewed literature, with the advice of medical consultants, with reference to accepted standards of medical practice, and in consideration of the medical circumstance of the individual case).

Contractors must continue to apply the policy that not only the drug is medically reasonable and necessary for any individual claim, but also that the route of administration is medically reasonable and necessary. (Pub 100-02, Medicare Benefit Policy Manual, Chapter 15, Section 50.2 - Determining Self-Administration of Drug or Biological (Rev. 91; Issued: 06-20-08; Effective/Implementation Date: 07-21-08)). National Government Services will use evidence-based clinical guidelines to determine medical necessity of the route of administration.

Specific Drugs and Biological Coverage

The clinical criteria in the medical policy drug articles linked under “Related Local Coverage Documents” are hereby incorporated by reference as if fully set forth herein.

A52370 - Bevacizumab (e.g., Avastin™) - Related to LCD L33394
A52371 - Bortezomib (e.g., Velcade®) – Related to LCD L33394
A52399 - Denosumab (Prolia™, Xgeva™) - Related to LCD L33394
A54548 - Eculizumab (Soliris®) - Related to LCD L33394
A52408 - Filgrastim, Pegfilgrastim, Tbo-filgrastim, Filgrastim-sndz (e.g., Neupogen®, Neulasta™, Granix™, Zarxio™) - Related to LCD L33394
A52420 - Hyaluronans Intra-articular Injections of - Related to LCD L33394
A52421 - Ibandronate Sodium (e.g., Boniva®) – Related to LCD L33394
A52423 - Infliximab (e.g., Remicade™) – Related to LCD L33394
A52446 - Intravenous Immune Globulin (IVIG) - Related to LCD L33394
A52453 - Luteinizing Hormone-Releasing Hormone (LHRH) Analogs – Related to LCD L33394
A52455 - Luteinizing Hormone-Releasing Hormone (LHRH) Analogs – Related to LCD L33394
A52456 - Paclitaxel (e.g., Taxol®/Abraxane™) - Related to LCD L33394
A52451 - Ranibizumab (e.g., Lucentis™) and Aflibercept (e.g., Eylea™) – Related to LCD L33394
A52452 - Rituximab (Rituxan®) - Related to LCD L33394

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Coding Information

Bill Type Codes:

Contractors may specify Bill Types to help providers identify those Bill Types typically used to report this service. Absence of a Bill Type does not guarantee that the policy does not apply to that Bill Type. Complete absence of all Bill Types indicates that coverage is not influenced by Bill Type and the policy should be assumed to apply equally to all claims.

N/A

Revenue Codes:

Contractors may specify Revenue Codes to help providers identify those Revenue Codes typically used to report this service. In most instances Revenue Codes are purely advisory. Unless specified in the policy, services reported under other Revenue Codes are equally subject to this coverage determination. Complete absence of all Revenue Codes indicates that coverage is not influenced by Revenue Code and the policy should be assumed to apply equally to all Revenue Codes.

Revenue codes only apply to providers who bill these services to the Part A MAC. Revenue codes do not apply to physicians, other professionals and suppliers who bill these services to the carrier or Part B MAC. Specific revenue code advice will be provided in the specific drug or biological coverage article attached to this LCD.

Please note that not all revenue codes apply to every type of bill code. Providers are encouraged to refer to the FISS revenue code file for allowable bill types. Similarly, not all revenue codes apply to each CPT/HCPCS code. Providers are encouraged to refer to the FISS HCPCS file for allowable revenue codes.

All revenue codes billed on the inpatient claim for the dates of service in question may be subject to review.

0250 Pharmacy - General Classification
0260 IV Therapy - General Classification
028X Oncology - General Classification
0636 Pharmacy - Drugs Requiring Detailed Coding

CPT/HCPCS Codes

Group 1 Paragraph: Specific CPT/HCPCS coding advice will be provided in the specific drug or biological coverage article attached to this LCD.

Group 1 Codes:

XX000 Not Applicable

ICD-10 Codes that Support Medical Necessity

Group 1 Codes:

ICD-10 Codes Description

XX000 Not Applicable

ICD-10 Codes that DO NOT Support Medical Necessity

Group 1 Codes:

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ICD-10 Codes Description
XX000 Not Applicable

ICD-10 Additional Information

General Information

Associated Information
Documentation Requirements:
The patient's medical record must contain documentation that fully supports the medical necessity for services included within this LCD. (See "Indications and Limitations of Coverage.") This documentation includes, but is not limited to, relevant medical history, physical examination, and results of pertinent diagnostic tests or procedures.

The medical record must include the following information:

• The name of the drug or biological administered;
• The route of administration;
• The dosage (e.g., mgs, mcgs, cc's or IU's);
• The duration of the administration (for CPT codes that are time based); and
• When modifier –JW is used to report that a portion of the drug or biological is discarded, from single use vials, the medical record must clearly document the amount administered and the amount wasted or discarded.

Appendices:
Not applicable

Utilization Guidelines:
Not applicable

Sources of Information and Basis for Decision
This bibliography presents those sources that were obtained during the development of this policy. National Government Services is not responsible for the continuing viability of Web site addresses listed below.


Based on a reconsideration the following sources have been added:


Tsavaris N, Kosmas C, Mylonakis N, et al. Parameters that influence the outcome of nausea and emesis in
Based on a reconsideration request for infliximab, Infliximab article (A52423), the indication for ankylosing spondylitis has been revised to indicate treatment with TNF alpha-inhibitors as “second line” after NSAIDS and the American College of Rheumatology guidelines have been added to the “Sources of Information” section. The Bevacizumab article (A52370) has been revised to add ICD-10-CM codes.

The LCD has been revised to add article A54862 - Nivolumab (Opdvo®) to the LCD effective for dates of service on or after 04/01/2016. Article A54863 has been added as the Comment and Response document for nivolumab.

Based on a reconsideration request for graft vs host disease (GVHD) for infliximab, the Infliximab article (A52423) has been revised to add sources. The Rituximab article (A52452) has also been revised to add sources for neuropathy with IgM monoclonal gammopathy based on a reconsideration request. The Denosumab article (A52399) has been revised to add ICD-10-CM codes.

Based on CMS Transmittal 212, the list of compendia has been updated to add Wolters Kluwer Lexi-Drugs® as an authoritative source for use in the determination of a medically accepted indication of drugs and biologicals used off-label in an anti-cancer chemotherapeutic regimen effective for services on or after August 12, 2015. Clinical Pharmacology has been revised to Elsevier/Gold Standard Clinical Pharmacology and Thomson Micromedex DrugDex has been revised to Truven Health Analytics Micromedex DrugDex. The following articles have been revised based on ICD-10-CM updates, Denosumab (A52399), IVIG (A52446), Omalizumab (A52448) and Rituximab (A52452) and the following articles have been updated based on the annual 2016 HCPCS update, Filgrastim (A52408) and Hyaluronans (A52420).

Based on a reconsideration request, the indication for psoriatic arthropathy has been revised in the Infliximab article (A52423). The Bevacizumab article (A52370) has been revised to add an indication for malignant pleural mesothelioma. The Rituximab article (A52452) has been revised to add Microscopic Polyangiitis (MPA) which was inadvertently removed with the last update to the ICD-9-CM article. ICD-10-CM codes have been added to the following drug articles: Bevacizumab (A52370), Paclitaxel (A52450), IVIG (A52446) and Rituximab (A52452).

The LCD has been revised to add a "Specific Drugs and Biological Coverage" section to the "Coverage Indications, Limitations and/or Medical Necessity" section of the LCD. The following articles have been updated to add ICD-10-CM codes: Ibandronate article (A52421), Infliximab article (A52423) and the Zoledronic Acid article (A52455). The Filgrastim article (A52408) has been updated to include information on filgrastim-sndz in addition to an ICD-10-CM code addition.

Based on provider comment, ICD-10-CM code M85.88 has been added to the Ibandronate article (A52421) and the Zoledronic Acide article (A52455).
## Revision History

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<th>Revision Number</th>
<th>Explanation</th>
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<td>10/01/2015</td>
<td>R1</td>
<td>The LCD has been revised to add article A54548 for eculizumab (Soliris®) to the LCD effective for dates of service on or after 10/01/2015. Article A54549 has been added as the Comment and Response document for eculizumab.</td>
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### Associated Documents

#### Related Local Coverage Documents

- Article(s) A52370 - Bevacizumab (e.g., Avastin™) - Related to LCD L33394
- A52371 - Bortezomib (e.g., Velcade®) – Related to LCD L33394 A52399 - Denosumab (Prolia™, Xgeva™) - Related to LCD L33394 A52855 - Drugs and Biologicals, Coverage of, for Label and Off-Label Uses - Supplemental Instructions Article A54548 - Eculizumab (Soliris®) - Related to LCD L33394 A52408 - Filgrastim, Pegfilgrastim, Tbo-filgrastim, Filgrastim-sndz (e.g., Neupogen®, Neulasta™, Granix™, Zarzio™) - Related to LCD L33394 A52420 - Hyaluronans Intra-articular Injections of - Related to LCD L33394 A52421 - Ibandronate Sodium (e.g., Boniva®) – Related to LCD L33394 A52423 - Infliximab (e.g., Remicade™) – Related to LCD L33394 A52446 - Intravenous Immune Globulin (IVIG) - Related to LCD L33394 A52453 - Luteinizing Hormone-Releasing Hormone (LHRH) Analogs – Related to LCD L33394 A54862 - Nivolumab (Opdivo®) - Related to LCD L33394 A52448 - Omalizumab (e.g., Xolair®) – Related to LCD L33394 A52450 - Paclitaxel (e.g., Taxol®/Abraxane™) - Related to LCD L33394 A52451 - Ranibizumab (e.g., Lucentis™) and Aflibercept (e.g., Eylea™) – Related to LCD L33394 A54549 - Response to Comments: Eculizumab (Soliris®) - Related to LCD L33394 A54863 - Response to Comments: Nivolumab (Opdivo®) - Related to LCD L33394 A52452 - Rituximab (Rituxan®) - Related to LCD L33394 A52445 - Verteporfin (e.g., Visudyne™) - Related to LCD L33394 A52455 - Zoledronic Acid (e.g., Zometa® , Reclast® ) – Related to LCD L33394

#### Related National Coverage Documents

- N/A

### Keywords

- N/A Read the [LCD Disclaimer](#)