

<b>CMS Manual System</b>	<b>Department of Health &amp; Human Services (DHHS)</b>
<b>Pub 100-03 Medicare National Coverage Determinations</b>	<b>Centers for Medicare &amp; Medicaid Services (CMS)</b>
<b>Transmittal 11692</b>	<b>Date: November 9, 2022</b>
	<b>Change Request 12950</b>

**SUBJECT: National Coverage Determination (NCD) 200.3 - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (AD)**

**I. SUMMARY OF CHANGES:** The purpose of this Change Request (CR) is to provide business instructions for the National Coverage Determination (NCD) 200.3 - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (AD).

**EFFECTIVE DATE: April 7, 2022**

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

**IMPLEMENTATION DATE: December 12, 2022**

*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.

<b>R/N/D</b>	<b>CHAPTER / SECTION / SUBSECTION / TITLE</b>
R	1/200/3/Table of Contents
N	1/200/3/Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (AD)

**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:**

**Business Requirements  
Manual Instruction**

# Attachment - Business Requirements

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**SUBJECT: National Coverage Determination (NCD) 200.3 - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer’s Disease (AD)**

**EFFECTIVE DATE: April 7, 2022**

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**IMPLEMENTATION DATE: December 12, 2022**

## I. GENERAL INFORMATION

**A. Background:** Alzheimer’s disease (AD) is a currently irreversible brain disorder that progressively degrades memory, cognitive function, and ability to carry out tasks of daily living. AD is the number one cause of dementia in older Americans.

Anti-amyloid-beta monoclonal antibodies (anti-amyloid mAbs) are laboratory-made proteins designed to bind a specific substance in the body, with the goal of marking it for destruction by the body’s immune system. Scientists design various mAbs as treatments with the goal of targeting and neutralizing or clearing infections (like the COVID-19 virus), cancer cells, and in the case of AD, amyloid accumulation in the brain.

**B. Policy:** Effective April 7, 2022, CMS covers Food and Drug Administration (FDA)-approved monoclonal antibodies directed against amyloid for the treatment of AD when furnished in accordance with the coverage criteria below, under coverage with evidence development (CED) for patients who have a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia, both with confirmed presence of amyloid beta pathology consistent with AD.

Coverage Criteria:

- 1) Monoclonal antibodies directed against amyloid that are approved by FDA for the treatment of AD based upon evidence of efficacy from a change in a surrogate endpoint (e.g., amyloid reduction) considered as reasonably likely to predict clinical benefit may be covered in a randomized controlled trial conducted under an investigational new drug (IND) application.
- 2) Monoclonal antibodies directed against amyloid that are approved by FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry.
- 3) For CMS-approved studies, the protocol, including the analysis plan, must include specific criteria specified in the NCD.
- 4) CMS-approved studies of a monoclonal antibody directed against amyloid (anti-amyloid mAb) approved by FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit must address specific questions specified in the NCD.
- 5) CMS-approved studies must adhere to the standards of scientific integrity specified in the NCD that have been identified by the Agency for Healthcare Research and Quality (AHRQ).

Monoclonal antibodies directed against amyloid indicated for the treatment of AD are covered when furnished according to the FDA-approved indication in National Institutes of Health (NIH)-supported trials.

For any CMS-approved study, or NIH-supported trial, that includes a beta amyloid positron emission tomography (PET) scan as part of the protocol, it has been determined that these trials or studies also meet the CED requirements included in the Beta Amyloid PET in Dementia and Neurodegenerative Disease NCD (220.6.20).

Monoclonal antibodies directed against amyloid for the treatment of AD provided outside of an FDA-approved randomized controlled trial, CMS approved studies, or studies supported by the NIH, are nationally non-covered.

**NOTE:** Individually approved clinical trials require a new HCPCS code specific to the therapy being studied. Therapies with FDA approval that have not been assigned a dedicated HCPCS code would be identified by existing HCPCS codes J3490, J3590. Subsequent CRs to follow.

**NOTE:** There is no action to be taken by the MACs at this time until the subsequent CR is issued.

## II. BUSINESS REQUIREMENTS TABLE

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

Number	Requirement	Responsibility								
		A/B MAC			DME MAC	Shared-System Maintainers				Other
		A	B	HHH		FISS	MCS	VMS	CWF	
12950.1	<p>Effective April 7, 2022 CMS covers FDA-approved monoclonal antibodies directed against amyloid for the treatment of AD when furnished in accordance with the coverage criteria below, under CED for patients who have a clinical diagnosis of MCI due to AD or mild AD dementia, both with confirmed presence of amyloid beta pathology consistent with AD.</p> <p>Contractors shall use required ICD-10 diagnosis code Z00.6, along with one of the following additional diagnosis codes: G30.0, G30.1, G30.8, G30.9, G31.84.</p> <p>Please refer to the NCD manual section 200.3 for further information. Please note that a Change Request with further claims processing instructions will be issued at a later date.</p>	X	X							

## III. PROVIDER EDUCATION TABLE

Number	Requirement	Responsibility				
		A/B MAC			DME MAC	CEDI
		A	B	HHH		
12950.2	Medicare Learning Network® (MLN): CMS will market provider education content through the MLN Connects® newsletter shortly after CMS releases the CR. MACs shall follow IOM Pub. No. 100-09 Chapter 6, Section 50.2.4.1 instructions for distributing the MLN Connects newsletter information to providers and link to relevant information on your website. You may supplement MLN content with your local information after we release the MLN Connects newsletter. Subscribe to the “MLN Connects” listserv to get MLN content notifications. You don’t need to separately track and report MLN content releases when you distribute MLN Connects newsletter content per the manual section referenced above.	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:

**Section B: All other recommendations and supporting information: N/A**

#### V. CONTACTS

**Pre-Implementation Contact(s):** Lisa Davis, lisa.davis@cms.hhs.gov (Coverage and Analysis) , Wanda Belle, wanda.belle@cms.hhs.gov (Coverage and Analysis) , David Dolan, David.Dolan@cms.hhs.gov (Coverage and Analysis) , Patricia Brocato-Simons, Patricia.Brocatosimons@cms.hhs.gov (Coverage and Analysis)

**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: 0**

# **Medicare National Coverage Determinations Manual Chapter 1, Part 1 Coverage Determinations**

**Table of Contents**  
*(Rev.1169, Issued: 11-09-22)*

*200.3 - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)*

## **200.3 - Monoclonal Antibodies Directed Against Amyloid for the Treatment of Alzheimer's Disease (AD)**

**(Rev.:11692, Issued:11-09-22, Effective: 04-07-22, Implementation: 12-12-22)**

### **A. General**

*Alzheimer's disease (AD) is a currently irreversible brain disorder that progressively degrades memory, cognitive function, and ability to carry out tasks of daily living. AD is the number one cause of dementia in older Americans.*

*Anti-amyloid-beta monoclonal antibodies (anti-amyloid mAbs) are laboratory-made proteins designed to bind a specific substance in the body, with the goal of marking it for destruction by the body's immune system. Scientists design various mAbs as treatments with the goal of targeting and neutralizing or clearing infections (like the COVID-19 virus), cancer cells, and in the case of AD, amyloid accumulation in the brain.*

### **B. Nationally Covered Indications**

*Effective April 7, 2022, the Centers for Medicare & Medicaid Services (CMS) covers Food and Drug Administration (FDA) approved monoclonal antibodies directed against amyloid for the treatment of AD when furnished in accordance with Section B under coverage with evidence development (CED) for patients who have a clinical diagnosis of mild cognitive impairment (MCI) due to AD or mild AD dementia, both with confirmed presence of amyloid beta pathology consistent with AD.*

*Coverage Criteria:*

- 1) Monoclonal antibodies directed against amyloid that are approved by the FDA for the treatment of AD based upon evidence of efficacy from a change in a surrogate endpoint (e.g., amyloid reduction) considered as reasonably likely to predict clinical benefit may be covered in a randomized controlled trial conducted under an investigational new drug (IND) application.*
- 2) Monoclonal antibodies directed against amyloid that are approved by the FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit may be covered in CMS-approved prospective comparative studies. Study data for CMS-approved prospective comparative studies may be collected in a registry.*
- 3) For CMS-approved studies, the protocol, including the analysis plan, must include:*
  - a. A study population whose diversity of patients are representative of the national population with MCI due to AD or mild AD dementia.*
  - b. A neurocognitive evaluation and a description of the instruments used to assess cognition and function for the clinical diagnosis of MCI due to AD or mild AD dementia for study enrollment and outcomes assessment.*
  - c. A description of:*
    - i. The multidisciplinary dementia team and optimal medical management.*
    - ii. Study sites with clinical expertise and infrastructure to provide treatments consistent with the safety monitoring outlined in the FDA-approved label.*
- 4) CMS-approved studies of a monoclonal antibody directed against amyloid (anti-amyloid mAb) approved by the FDA for the treatment of AD based upon evidence of efficacy from a direct measure of clinical benefit must address all of the questions below:*
  - a. Does the anti-amyloid mAb meaningfully improve health outcomes (i.e., slow the decline of cognition and function) for patients in broad community practice?*

- b. *Do benefits, and harms such as brain hemorrhage and edema, associated with use of the anti-amyloid mAb, depend on characteristics of patients, treating clinicians, and settings?*
- c. *How do the benefits and harms change over time?*

5) *CMS-approved studies must adhere to the following standards of scientific integrity that have been identified by the Agency for Healthcare Research and Quality (AHRQ):*

- a. *The principal purpose of the study is to test whether the item or service meaningfully improves health outcomes of affected beneficiaries who are represented by the enrolled subjects.*
- b. *The rationale for the study is well supported by available scientific and medical evidence.*
- c. *The study results are not anticipated to unjustifiably duplicate existing knowledge.*
- d. *The study design is methodologically appropriate and the anticipated number of enrolled subjects is sufficient to answer the research question(s) being asked in the National Coverage Determination (NCD).*
- e. *The study is sponsored by an organization or individual capable of completing it successfully.*
- f. *The research study is in compliance with all applicable Federal regulations concerning the protection of human subjects found in the Code of Federal Regulations (CFR) at 45 CFR Part 46. If a study is regulated by the FDA, it is also in compliance with 21 CFR Parts 50 and 56. In addition, to further enhance the protection of human subjects in studies conducted under CED, the study must provide and obtain meaningful informed consent from patients regarding the risks associated with the study items and/or services, and the use and eventual disposition of the collected data.*
- g. *All aspects of the study are conducted according to appropriate standards of scientific integrity.*
- h. *The study has a written protocol that clearly demonstrates adherence to the standards listed here as Medicare requirements.*
- i. *The study is not designed to exclusively test toxicity or disease pathophysiology in healthy individuals. Such studies may meet this requirement only if the disease or condition being studied is life threatening as defined in 21 CFR §312.81(a) and the patient has no other viable treatment options.*
- j. *The clinical research studies and registries are registered on the [www.ClinicalTrials.gov](http://www.ClinicalTrials.gov) website by the principal sponsor/investigator prior to the enrollment of the first study subject. Registries are also registered in the AHRQ Registry of Patient Registries (RoPR).*
- k. *The research study protocol specifies the method and timing of public release of all prespecified outcomes to be measured including release of outcomes if outcomes are negative or study is terminated early. The results must be made public within 12 months of the study's primary completion date, which is the date the final subject had final data collection for the primary endpoint, even if the trial does not achieve its primary aim. The results must include number started/completed, summary results for primary and secondary outcome measures, statistical analyses, and adverse events. Final results must be reported in a publicly accessible manner; either in a peer-reviewed scientific journal (in print or on-line), in an on-line publicly accessible registry dedicated to the dissemination of clinical trial information such as [ClinicalTrials.gov](http://ClinicalTrials.gov), or in journals willing to publish in abbreviated format (e.g., for studies with negative or incomplete results).*
- l. *The study protocol must explicitly discuss beneficiary subpopulations affected by the item or service under investigation, particularly traditionally underrepresented groups in clinical studies, how the inclusion and exclusion criteria affect enrollment of these populations, and a plan for the retention and reporting of said populations in the trial. If the inclusion and exclusion criteria are expected to have a negative effect on the recruitment or retention of underrepresented populations, the protocol must discuss why these criteria are necessary.*
- m. *The study protocol explicitly discusses how the results are or are not expected to be generalizable to affected beneficiary subpopulations. Separate discussions in the protocol may be necessary for populations eligible for Medicare due to age, disability or Medicaid eligibility.*

*The principal investigator must submit the complete trial protocol, cite where the detailed analysis plan for the CMS CED questions occurs in the protocol, and provide a statement addressing how the study satisfies each of the standards of scientific integrity (a. through m. listed above), as well as the investigator's contact information, to the email address below. The information will be reviewed, and approved trials will be identified on the CMS Website.*

*The Email address for protocol submissions is: [clinicalstudynotification@cms.hhs.gov](mailto:clinicalstudynotification@cms.hhs.gov). The Email subject line should be: "CED Monoclonal Antibodies for the Treatment of Alzheimer's Disease [name of sponsor/primary investigator]"*

*Monoclonal antibodies directed against amyloid indicated for the treatment of AD are covered when furnished according to the FDA approved indication in National Institutes of Health (NIH)-supported trials.*

*For any CMS-approved study, or NIH-supported trial, that includes a beta amyloid positron emission tomography (PET) scan as part of the protocol, it has been determined that these trials or studies also meet the CED requirements included in the Beta Amyloid PET in Dementia and Neurodegenerative Disease NCD (220.6.20).*

***C. Nationally Non-Covered Indications***

*Monoclonal antibodies directed against amyloid for the treatment of AD provided outside of an FDA-approved randomized controlled trial, CMS-approved studies, or studies supported by the NIH, are nationally non-covered.*

***D. Other***

*N/A.*

*(This NCD last reviewed April 2022.)*