

Medical Policy Bulletin

Title:

Ocrelizumab (Ocrevus®) and Ocrelizumab and Hyaluronidase-ocsq (Ocrevus Zunovo™)

Policy #:

MA08.088e

The Company makes decisions on coverage based on the Centers for Medicare and Medicaid Services (CMS) regulations and guidance, benefit plan documents and contracts, and the member's medical history and condition. If CMS does not have a position addressing a service, the Company makes decisions based on Company Policy Bulletins. Benefits may vary based on contract, and individual member benefits must be verified. The Company determines medical necessity only if the benefit exists and no contract exclusions are applicable. Although the Medicare Advantage Policy Bulletin is consistent with Medicare's regulations and guidance, the Company's payment methodology may differ from Medicare.

When services can be administered in various settings, the Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition. This decision is based on the member's current medical condition and any required monitoring or additional services that may coincide with the delivery of this service.

This Policy Bulletin document describes the status of CMS coverage, medical terminology, and/or benefit plan documents and contracts at the time the document was developed. This Policy Bulletin will be reviewed regularly and be updated as Medicare changes their regulations and guidance, scientific and medical literature becomes available, and/or the benefit plan documents and/or contracts are changed.

Policy

Coverage is subject to the terms, conditions, and limitations of the member's Evidence of Coverage.

The Company reserves the right to reimburse only those services that are furnished in the most appropriate and cost-effective setting that is appropriate to the member's medical needs and condition.

In the absence of coverage criteria from applicable Medicare statutes, regulations, NCDs, LCDs, CMS manuals, or other Medicare coverage documents, this policy uses internal coverage criteria developed by the Company in consideration of peer-reviewed medical literature, clinical practice guidelines, and/or regulatory status.

MEDICALLY NECESSARY

Ocrelizumab (Ocrevus®), administered as an intravenous (IV) infusion, or ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™), as a subcutaneous (SC) injection, are considered medically necessary and, therefore, covered for the treatment of adults with either relapsing forms of multiple sclerosis (RMS) (including clinically isolated syndrome (CIS), relapsing-remitting disease, and active secondary progressive disease) or primary progressive forms of multiple sclerosis (PPMS) when the individual is hepatitis B negative (i.e., has negative results for hepatitis B surface antigen [HBsAg] and anti-hepatitis B virus tests).

EXPERIMENTAL/INVESTIGATIONAL

All other uses for ocrelizumab (Ocrevus) or ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo), including nonrelapsing secondary progressive MS, are considered experimental/investigational and, therefore, not covered unless the indication is supported as an accepted off-label use, as defined in the Company medical policy on off-label coverage for prescription drugs and biologics.

REQUIRED DOCUMENTATION

The individual's medical record must reflect the medical necessity for the care provided. These medical records may include, but are not limited to: records from the professional provider's office, hospital, nursing home, home health agencies, therapies, and test reports.

The Company may conduct reviews and audits of services to our members, regardless of the participation status of

the provider. All documentation is to be available to the Company upon request. Failure to produce the requested information may result in a denial for the drug.

Guidelines

There is no Medicare coverage determination addressing ocrelizumab (Ocrevus); therefore, the Company policy is applicable.

DRUG ADMINISTRATION

The dosing of ocrelizumab (Ocrevus) is as follows:

- Initial dose: 300 mg intravenous (IV) infusion, followed two weeks later by a second 300 mg IV infusion
- Subsequent doses: single 600 mg IV infusion every six months

The dosing of ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo), administered every 6 months as a subcutaneous (SC) injection, is as follows:

- 920 mg ocrelizumab
- 23,000 units of hyaluronidase

HEPATITIS B SEROLOGIC MARKER DEFINITIONS

According to the Centers for Disease Control (CDC):

- Hepatitis B surface antigen (HBsAg): The presence of HBsAg, a protein on the surface of the hepatitis B virus (HBV), indicates that the person is infectious. It can be detected in high levels in serum during acute or chronic HBV infection. The body normally produces antibodies to HBsAg as part of the normal immune response to infection. HBsAg is the antigen used to make hepatitis B vaccine.
- Hepatitis B surface antibody (anti-HBs): The presence of anti-HBs is generally interpreted as indicating recovery and immunity from HBV infection. Anti-HBs also develops in a person who has been successfully vaccinated against hepatitis B.

BENEFIT APPLICATION

Subject to the applicable Evidence of Coverage, ocrelizumab (Ocrevus) or ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo) are covered under the medical benefits of the Company's Medicare Advantage products when the medical necessity criteria listed in this medical policy are met.

For Medicare Advantage members, certain drugs are available through either the member's medical benefit (Part B benefit) or pharmacy benefit (Part D benefit), depending on how the drug is prescribed, dispensed, or administered. This medical policy only addresses instances when ocrelizumab (Ocrevus) is covered under a member's medical benefit (Part B benefit). It does not address instances when ocrelizumab (Ocrevus) is covered under a member's pharmacy benefit (Part D benefit).

US FOOD AND DRUG ADMINISTRATION STATUS

Ocrelizumab (Ocrevus) was approved by the US Food and Drug Administration (FDA) on March 28, 2017 for the treatment of adults with relapsing or primary progressive forms of multiple sclerosis (MS). Supplemental approvals for ocrelizumab (Ocrevus) have since been issued by the FDA.

Ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo) was approved by the FDA on September 13, 2024 for the treatment of adults with relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, or primary progressive forms of multiple sclerosis.

PEDIATRIC USE

The safety and effectiveness of ocrelizumab (Ocrevus) or ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo) in the pediatric population have not been established.

Description

MULTIPLE SCLEROSIS BACKGROUND

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) where the immune system attacks nerve fibers (called axons) and the protective coating that surrounds them (called myelin sheath). Myelin that has been damaged forms scar tissue called sclerosis or plaques that can be seen with a magnetic resonance imaging (MRI) scan of the brain in individuals with MS. The myelin sheath sends nerve impulses throughout the CNS. Once damaged, communication between the nerve impulses and the targeted area of the body are distorted or interrupted, producing a variety of symptoms. Symptoms of MS vary between individuals. Even in those who relapse, symptoms may differ with each episode. Examples of common symptoms include: motor weakness, limb ataxia, gait or balance problems, vertigo, bladder/bowel dysfunction, sensory loss, heat intolerance, fatigue, visual and cognitive impairment, depression, and pain. There are many hypotheses as to the causes of MS, including those with a basis of infection, genetics, immunological, and environmental, however, the causes of MS have not been established. It is estimated that 250,000 to 400,000 individuals in the United States and 2.5 million individuals worldwide are affected by MS.

TYPES OF MULTIPLE SCLEROSIS AND THEIR TREATMENTS

There is currently no cure for MS. Medications can be used to treat acute relapses (e.g., corticosteroids), slow the progression of the disease and reduce the number and severity of relapses (e.g., MS disease-modifying therapies), and improve symptoms that occur, such as fatigue, pain, and depression.

The four major types of MS include:

- Clinical isolated syndrome (CIS) is the first episode of a neurologic event associated with inflammation and demyelination involving the central nervous system that lasts at least 24 hours. There is a high chance (60-80 percent) of developing a secondary episode and a diagnosis of relapsing/remitting MS (RRMS) when CIS is accompanied by lesions on a brain MRI that are similar to those seen in MS. When not accompanied by MS-like lesions on a brain MRI, there is a lower chance (20 percent) of developing MS.
 - Treatment of CIS may consist of the following medications:
 - Ocrelizumab (Ocrevus) and siponimod (Mayzent®) are US Food and Drug Administration (FDA)-approved for CIS; however, there is a paucity of published data for siponimod (Mayzent®)
 - Glatiramer acetate and interferon beta 1a (IFN- β -1a) are more effective than placebo in reducing the proportion of individuals converting to MS (Rae-Grant 2018)
 - Per the authors of the systematic review, the following disease modifying therapies (DMTs) are probably more effective than placebo in reducing the proportion of individuals converting to MS: cladribine (safety concerns), immunoglobulins, IFN- β -1a (Avonex®, Rebif®), IFN- β -1b (Betaseron®), and teriflunomide (Aubagio®) (Rae-Grant 2018)
- Relapsing-remitting MS (RRMS): RRMS is the most common form of MS, accounting for approximately 85 percent of all MS cases. It is characterized by recurrent attacks to the nervous system, followed by complete recovery or partial recovery where some symptoms become permanent. There is no or minimal disease progression during remission.
 - Treatment of RRMS progression may consist of the following medications (Filippini 2013, Rae-Grant 2018):
 - MS disease-modifying therapies (e.g., alemtuzumab [Lemtrada®], dimethyl fumarate [Tecfidera®], fingolimod [Gilenya®]), glatiramer acetate [Copaxone®], IFN- β -1a [Avonex®, Rebif®], IFN- β -1b [Betaseron®], natalizumab [Tysabri®], ocrelizumab [Ocrevus], rituximab [Rituxan®], siponimod (Mayzent®), teriflunomide [Aubagio®].
 - Azathioprine (Imuran®)
 - Cladribine
 - Intravenous immunoglobulin (IVIG)
 - Mitoxantrone
 - Stem cell transplantations
 - The results of a Cochrane review and Practice Guideline suggested an unfavorable risk-benefit balance for the following drugs: IFN- β -1a [Avonex®], IVIG, cyclophosphamide, and long-term steroids. The Cochrane review also noted the paucity of high-quality data regarding the use of azathioprine (Filippini 2013, Rae-Grant 2018)
- Primary progressive MS (PPMS): PPMS represents about 10-15 percent of all MS cases. It is characterized by gradual disease progression from symptom onset. There are periods of active disease, occasional plateaus, and temporary minor improvement of symptoms, but there are no distinct relapses or remissions.

- Ocrelizumab (Ocrevus) was the first and only drug FDA-approved for the treatment of PPSM.
- Some individuals may respond to the following treatments; however, randomized controlled trials have failed to show consistent benefit for the treatment of PPMS: azathioprine, cladribine, intravenous (IV) bimonthly glucocorticoid pulses, IV cyclophosphamide, MS disease-modifying therapies (e.g., interferons, glatiramer acetate [Copaxone®], fingolimod [Gilenya®]), IVIG, methotrexate, mitoxantrone, rituximab (Rituxan®), stem cell transplantations. The results of a Cochrane review in 2013 showed a paucity of high-quality data for the following drugs, since they were ineffective in preventing disability progression over two to three years: IFN- β -1a [Avonex®, Rebif®], IFN- β -1b [Betaseron®], glatiramer acetate [Copaxone®]), mitoxantrone, methotrexate, cyclophosphamide, IVIG, rituximab (Rituxan®), and long-term corticosteroids. (Filippini 2013, Rae-Grant 2018)
- Secondary progressive MS (SPMS): SPMS initially presents as RRMS, but later transitions to a condition similar to PPMS. It is a progressive disease that may or may not have relapses. It is estimated that 80 percent of all individuals with RRMS will develop this type of MS.
 - Treatments for SPSM may consist of the following: MS disease-modifying therapies (e.g., ocrelizumab [Ocrevus], siponimod [Mayzent®]), cladribine, mitoxantrone, IV bimonthly glucocorticoid pulses, or IV cyclophosphamide
 - Some individuals may respond to the following treatments, however randomized controlled trials have failed to show consistent benefit for the treatment of PPMS: azathioprine, cladribine, IV cyclophosphamide, interferons, IVIG, methotrexate, mitoxantrone, stem cell transplantation (Rae-Grant 2018)

In addition to the major types of MS listed above, all types of MS can further be characterized into the following stages of disease:

- Active disease: i.e., whether there are relapses or MRI changes
- Not active disease: i.e., showing no evidence of disease activity
- Disease worsening, or with progression: e.g., increased disability over a specific time period, with or without relapses; or objective measure of disease worsening over a specific time period, with or without relapses
- Non-worsening or stable or without progression: e.g., no evidence of disease worsening or increased disability over a specific time period

OCRELIZUMAB (OCREVUS) AND OCRELIZUMAB AND HYALURONIDASE-OCSQ (OCREVUS ZUNOVO)

Ocrelizumab (Ocrevus) was approved by the FDA on March 28, 2017 for the treatment of adults with relapsing or primary progressive forms of multiple sclerosis. Ocrelizumab (Ocrevus) was the first drug FDA-approved for the treatment of PPMS. On July 16, 2019, the FDA expanded the indication of relapsing forms of MS to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, in adults. Ocrelizumab (Ocrevus) is a recombinant humanized monoclonal antibody that selectively targets Cluster of Differentiation 20 (CD20), a cell surface antigen expressed on only certain B-cells (pre-B, mature B, and memory B-cells, but not lymphoid stem cells and plasma cells). Following cell surface binding to B lymphocytes, ocrelizumab (Ocrevus) is thought to cause apoptosis, antibody-dependent cellular cytotoxicity (cell membrane destruction), and complement-mediated lysis involving macrophages, natural killer cells, etc. to cause cell destruction. The specificity for targeting only certain B-cells allows the immune function to remain intact, since the levels of immunoglobulin G (IgG) and IgM are not diminished. Hyaluronidase is an endoglycosidase used to increase dispersion and absorption of co-administered drugs when administered as a subcutaneous (SC) injection.

Peer-reviewed Literature

Intravenous Administration

Primary Progressive Multiple Sclerosis

In 2017, Montalban et al. performed the ORATORIO (A Study of Ocrelizumab in Participants With Primary Progressive Multiple Sclerosis) trial, a Phase 3, randomized (2:1), double-blind, placebo-controlled trial that investigated the safety and effectiveness of ocrelizumab (Ocrevus) in the treatment of PPMS. A total of 732 participants were diagnosed with PPMS per 2005 revised McDonald criteria and had a score on the Expanded Disability Status Scale (EDSS) of 3 to 6.5 at screening (range, 0–10, where higher scores indicate greater disability). Approximately 88 percent of participants had not received a previous disease-modifying therapy for MS. Participants received ocrelizumab (Ocrevus) 600 mg (N=488) or placebo (N=244) every 24 weeks for at least 120 weeks. The primary endpoint of the study was the percentage of individuals with disability progression confirmed at 12 weeks in a time-to-event analysis where disability progression was defined as an increase in EDSS of at least one point from baseline if baseline was 5.5 or less, or an increase of 0.5 if baseline was more than 5.5. Disability progression at 12-weeks was confirmed in 32.9 percent of those in the ocrelizumab (Ocrevus) group and 39.3 percent in the placebo group, which was statistically significant. The adverse event that was most frequently reported was infusion-related

reactions: 39.9 percent in the ocrelizumab (Ocrevus) group and 25.5 percent in the placebo group. There was an increased incidence of neoplasms in the ocrelizumab (Ocrevus) group (2.3 percent) compared to those in the placebo group (0.8 percent). No cases of progressive multifocal leukoencephalopathy (PML) have been reported during clinical studies. The authors reported that further evaluation of the occurrence of neoplasms and PML risk is warranted.

Relapsing Multiple Sclerosis

In 2017, Hauser et al. investigated the safety and effectiveness of ocrelizumab (Ocrevus) in the treatment of RMS in the OPERA I (A Study of Ocrelizumab in Comparison With Interferon Beta-1a [Rebif] in Participants With Relapsing Multiple Sclerosis) (N=821) and OPERA II (N=835) studies, which are identical, Phase 3, randomized (1:1) trials. Eligibility included a diagnosis of RMS per 2010 revised McDonald criteria, a score on the Expanded Disability Status Scale (EDSS) of 0 to 5.5 at screening (range, 0–10, where higher scores indicate greater disability), and at least two documented clinical relapses within the previous 2 years or one clinical relapse within the year before screening. Approximately 73 percent of participants had not received a previous disease-modifying therapy for MS. Participants received ocrelizumab (Ocrevus) 600 mg every 24 weeks and placebo subcutaneous injection three times weekly or subcutaneous IFN- β -1a 44 mcg three times weekly and placebo IV infusion every 24 weeks for 96 weeks. The primary endpoint was the annualized relapse rate by 96 weeks. Ocrelizumab (Ocrevus) significantly decreased the annualized relapse rate at week 96 as follows: Trial 1 (0.16 vs 0.29) 46 percent lower rate in the ocrelizumab (Ocrevus) group and Trial 2 (0.16 vs 0.29) 47 percent lower rate in the ocrelizumab (Ocrevus) group. Infusion reactions occurred more frequently in the ocrelizumab (Ocrevus) group (34.3 percent) compared to the IFN- β -1a group who received placebo IV infusions (9.7 percent). There was an increase incidence of neoplasms in the ocrelizumab (Ocrevus) group (0.5 percent) compared to those in the placebo group (0.2 percent). During the open-label extension study where all participants received ocrelizumab (Ocrevus), five more cases of neoplasm occurred. No cases of PML have been reported during clinical studies. The authors reported that further evaluation of the occurrence of neoplasms and PML risk is warranted.

Subcutaneous Administration

In 2024, Newsome et al. investigated the noninferiority of ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo) administered as a SC injection to ocrelizumab (Ocrevus) administered as an IV injection in the OCARINA II (A Phase III, Non-Inferiority, Randomized, Open-Label, Parallel Group, Multicenter Study To Investigate The Pharmacokinetics, Pharmacodynamics, Safety And Radiological And Clinical Effects Of Subcutaneous Ocrelizumab Versus Intravenous Ocrelizumab In Patients With Multiple Sclerosisclinical trial). This phase 3, randomized, open-label trial enrolled 213 individuals with RMS and 23 individuals with PPMS. Participants were randomly assigned 1:1 to receive either the IV injection or the SC injection. The primary endpoint was serum ocrelizumab area under the concentration-time curve at week 12 (AUCW1-12). A key secondary endpoint was the total number of new or enlarging T2 lesions as detected by brain magnetic resonance imaging (MRI). At week 12, the geometric mean ratio for AUCW 1–12 for the SC injection versus the IV injection was 1.29 (1.23–1.35). The results of the MRI demonstrated near-complete suppression of new or enlarging lesions for both cohorts. No new safety concerns were identified for the SC injection.

OFF-LABEL INDICATIONS

There may be additional indications contained in the Policy section of this document due to evaluation of criteria highlighted in the Company's off-label policy, and/or review of clinical guidelines issued by leading professional organizations and government entities.

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Coding

Inclusion of a code in this table does not imply reimbursement. Eligibility, benefits, limitations, exclusions, precertification/referral requirements, provider contracts, and Company policies apply.

The codes listed below are updated on a regular basis, in accordance with nationally accepted coding guidelines. Therefore, this policy applies to any and all future applicable coding changes, revisions, or updates.

In order to ensure optimal reimbursement, all health care services, devices, and pharmaceuticals should be

reported using the billing codes and modifiers that most accurately represent the services rendered, unless otherwise directed by the Company.

The Coding Table lists any CPT, ICD-10, and HCPCS billing codes related only to the specific policy in which they appear.

CPT Procedure Code Number(s)

N/A

ICD - 10 Procedure Code Number(s)

N/A

ICD - 10 Diagnosis Code Number(s)

- G35.A Relapsing-remitting multiple sclerosis
- G35.B1 Active primary progressive multiple sclerosis
- G35.C1 Active secondary progressive multiple sclerosis
- G35.D Multiple sclerosis, unspecified

HCPCS Level II Code Number(s)

HCPCS Level II Code Number(s)

THE FOLLOWING CODE IS USED TO REPRESENT OCRELIZUMAB (OCREVUS)

J2350 Injection, ocrelizumab, 1 mg

THE FOLLOWING CODES ARE USED TO REPRESENT OCRELIZUMAB AND HYALURONIDASE-OCSQ (OCREVUS ZUNOVO)

J2351 Injection, ocrelizumab, 1 mg and hyaluronidase-ocsq

Revenue Code Number(s)

N/A

Policy History

Revisions From MA08.088e:

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| 12/15/2025 | <p>This version of the policy will become effective 12/15/2025.</p> <p>Inclusion of a policy in a Code Update memo does not imply that a full review of the policy was completed at this time.</p> <p>The following ICD-10 codes have been added to this policy: G35.A Relapsing-remitting multiple sclerosis G35.B1 Active primary progressive multiple sclerosis G35.C1 Active secondary progressive multiple sclerosis G35.D Multiple sclerosis, unspecified</p> <p>The following ICD-10 code has been removed from this policy: G35 Multiple sclerosis</p> |
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Revisions From MA08.088d:

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| 06/13/2025 | <p>This version of the policy will become effective 06/13/2025.</p> <p>The following new medication has been added to this policy in accordance with the US Food and Drug Administration labeling (09/13/2024): Ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™)</p> |
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| | The following HCPCS code has been added to this policy to represent ocrelizumab and hyaluronidase-ocsq (Ocrevus Zunovo™): J2351 Injection, ocrelizumab, 1 mg and hyaluronidase-ocsq |
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Revisions From MA08.088c:

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| 03/28/2025 | The policy has been reviewed and reissued to communicate the Company's continuing position on ocrelizumab (Ocrevus). |
| 05/07/2024 | The policy has been reviewed and reissued to communicate the Company's continuing position on ocrelizumab (Ocrevus). |
| 09/05/2023 | The policy has been reviewed and reissued to communicate the Company's continuing position on ocrelizumab (Ocrevus). |
| 06/15/2022 | The policy has been reviewed and reissued to communicate the Company's continuing position on ocrelizumab (Ocrevus). |
| 05/24/2021 | The policy has been reviewed and reissued to communicate the Company's continuing position on ocrelizumab (Ocrevus). |
| 06/17/2020 | This version of the policy will become effective 06/17/2020. The policy has been reviewed and reissued to communicate the Company's continuing position on ocrelizumab (Ocrevus). |
| 09/23/2019 | This policy has undergone a routine review and the medical necessity criteria have been revised to reflect the updated FDA labeling for relapsing forms of multiple sclerosis (RMS), including clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. Experimental/Investigational coverage position has been added for nonrelapsing secondary progressive MS. |

Revisions From MA08.088b:

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| 05/22/2019 | This policy has been reissued in accordance with the Company's annual review process. |
| 07/03/2018 | The policy has been reviewed and reissued to communicate the Company's continuing position on Ocrelizumab (Ocrevus™). Definitions of two hepatitis B serologic markers have been added to the Guidelines Section. |
| 01/01/2018 | This policy has been identified for the HCPCS code update, effective 01/01/2018. The following HCPCS code has been added to this policy: J2350 Injection, ocrelizumab, 1 mg The following HCPCS codes have been removed from this policy: C9494 Injection, ocrelizumab, 1 mg J3590 Unclassified biologics |

Revisions From MA08.088a:

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| 10/01/2017 | This policy has been identified for the HCPCS code update, effective 10/01/2017. The following HCPCS code has been added to this policy: C9494 Injection, ocrelizumab, 1 mg |
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Revisions From MA08.088:

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| 08/23/2017 | The following new policy has been developed to communicate the Company's coverage criteria for ocrelizumab (Ocrevus™). |
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Version Effective Date:

12/15/2025

Version Issued Date:

12/15/2025

Version Reissued Date:

N/A