Aetna

Intermittent Intravenous Insulin Therapy

- Clinical Policy Bulletins
- Medical Clinical Policy Bulletins

Number: 0742

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Policy

Scope of Policy

This Clinical Policy Bulletin addresses intermittent intravenous insulin therapy.

1. **Experimental, Investigational, or Unproven**

   Aetna considers the following procedures experimental, investigational, or unproven because the effectiveness of these approaches has not been established:

   1. Diagnostic tests of blood glucose or potassium, respiratory quotient, and urine urea nitrogen when performed in the context of intermittent intravenous insulin therapy because the clinical value of these tests in this context has not been established;
   2. Insulin potentiation therapy for treatment of arthritis, cancer (e.g., breast, prostate; not an all-inclusive list), infectious diseases, and other conditions;
   3. Intermittent intravenous insulin therapy (also known as hepatic activation therapy, metabolic activation therapy, physiologic insulin re-sensitization (PIR) infusions, pulse insulin therapy, pulsatile intravenous insulin therapy, and Trina Health artificial pancreas treatment) for the management of diabetes mellitus and all other indications.

   Note: This policy does not apply to the use of insulin infusions for treatment of diabetic ketoacidosis or hyperosmolar coma.

2. **Related Policies**

   - CPB 0070 - Diabetes Tests, Programs and Supplies

CPT Codes / HCPCS Codes / ICD-10 Codes

There are no specific codes for intermittent intravenous insulin therapy (also known as hepatic activation therapy, metabolic activation therapy, and pulsatile intravenous insulin therapy), Trina Health artificial pancreas:

Code	Code Description
CPT codes not covered for indications listed in the CPB [when performed in the context of intermittent intravenous insulin therapy]:	
82947	Glucose; quantitative, blood (except reagent strip)
82948	Glucose; blood, reagent strip
82950	post glucose dose (includes glucose)
84132	Potassium; serum, plasma or whole blood

Code	Code Description
84133	Potassium; urine
84540	Urea nitrogen, urine

HCPCS codes not covered for indications listed in the CPB:

G9147	Outpatient Intravenous Insulin Treatment (OIVIT) either pulsatile or continuous, by any means, guided by the results of measurements for: respiratory quotient; and/or, urine urea nitrogen (UUN); and/or, arterial, venous or capillary glucose; and/or potassium concentration

Other HCPCS codes related to the CPB:

J1811 - J1815, J1817, S5550 - S5571	Insulin

ICD-10 codes not covered for indications listed in the CPB: (not all-inclusive):

A00.0 - B99.9	Certain infections and parasitic disease
C00.0 - D49.9	Neoplasms
E08.3211 - E13.37X2	Diabetes mellitus
M00.00 - M25.9	Arthropathies

Background

According to Aoki and colleagues (1993), the limited success of conventional insulin therapy (IT) attained in the management of patients with diabetes mellitus (DM) and its complications suggested that there is a need for re-evaluation of the appropriateness of standard insulin administration protocols. Conventional subcutaneous IT produces slowly changing blood insulin levels and sub-optimal hepatocyte insulinization resulting in impaired hepatic capacity for processing incoming dietary glucose. Chronic intermittent intravenous insulin therapy (CIIIT), also known as hepatic activation therapy, metabolic activation therapy, and pulsatile intravenous insulin therapy (PIVIT), is an IT that delivers insulin in a pulsatile fashion and supposedly achieves physiological insulin concentration in the portal vein. The Trina Health Artificial Pancreas Treatment is intermittent pulsatile intravenous insulin therapy that should be used in combination with standard hypoglycemic treatments for the treatment of type I and type II DM.

Chronic intermittent intravenous IT is usually performed as a weekly procedure in conjunction with daily intensive subcutaneous IT. According to the Aoki Diabetes Research Institute, a CIIIT treatment session entails a 6-hour period in an out-patient (or in-patient) setting. The patient receives intermittent pulses of insulin through an intravenous catheter in a peripheral vein in the hand or arm. The intermittent pulses are controlled by a computerized program, which produces the desired geometric waveforms and the doses are adjusted based on frequent monitoring of blood glucose levels, respiratory quotient response, and the timing of a glucose load ingested by the patient. Chronic intermittent intravenous IT has been reported to

1. improve significantly glycemic control while reducing the incidence of hypoglycemic events,
2. improve hypertension control,
3. slow the progression of overt diabetic nephropathy (DN), and
4. reverse some manifestations of diabetic autonomic neuropathy including abnormal circadian blood pressure (BP) pattern, severe postural hypotension, and hypoglycemia unawareness (Aoki et al, 1995a; Aoki et al, 1995b; Aoki et al, 1995c; Aoki et al, 2001; Aoki Diabetes Research Institute, 2006)

Aoki and colleagues (1993) examined the effects of long-term CIIIT in patients with insulin-dependent diabetes mellitus (IDDM, also known as type 1 DM), with the aim of achieving high portal vein concentrations during and after a glucose meal.
They studied 20 IDDM patients with brittle disease. Despite the use of a 4-injection regimen with manipulation of insulin doses, diet, and physical activity, as well as frequent clinic visits for at least a year, these patients still had wide fluctuations in blood glucose and frequent hypoglycemic reactions. Chronic intermittent intravenous IT consisted of 7 to 10 pulses of intravenous insulin, infused while the patient was ingesting carbohydrate (primarily glucose) during the first hour of a 3-hour treatment; 3 treatments were given in a day. After 2 consecutive days' treatment, patients were treated for 1 day per week. No patient withdrew from the study. At the time of this analysis the duration of intermittent treatment ranged from 7 to 71 months (mean of 41 [SE 5] months). Glycohemoglobin (HbA1C) concentrations declined from 8.5 (0.4) % at the end of the stabilization phase to 7.0 (0.2) % at the analysis point (p = 0.0003). During the same time the frequencies of major and minor hypoglycemic events also fell significantly (major 3.0 [1.1] to 0.1 [0], minor 13.0 [2.6] to 2.4 [0.8] per month; both p < 0.0001). Because the use of

saline rather than insulin pulses would have led to unacceptable hyperglycemia, these investigators opted for a historical control design.

Gill and Williams (1993) noted that the most important drawback regarding the afore-mentioned study was the lack of a control treatment or control group rendering it impossible to ascribe any observed improvements to CIIIT. Moreover, since this regimen of IT was hospital-based and administered by high-level staff, subjects had support and care much in excess of routine diabetic clinical care; this in itself is likely to be beneficial on diabetic control, independent of any specific treatment given. Gill and Williams stated that improvements appeared to have occurred in the first few months of the study, and that there was no significant further drop in HbA1C after this time. This could be a consequence of the intensive interest and management received by these subjects, rather than a specific effect of CIIIT.

In a prospective, randomized, cross-over clinical trial, Aoki and colleagues (1995a) evaluated anti-hypertensive effects of CIIIT on IDDM subjects with hypertension and DN by monitoring the amount of anti-hypertensive medication (AHM) needed to maintain BP less than or equal to 140/90 mm Hg. After a stabilization period, 26 hypertensive IDDM subjects were randomly assigned to a control or treatment phase for 3 months and then cross-overed into the opposite phase for another 3 months. Addition of CIIIT during the treatment phase was the only procedural difference between the control and treatment phases. The AHM dosage requirements for maintenance of the baseline BP levels decreased significantly (46 %; $p < 0.0001$) and linearly over time ($p < 0.0058$) during the treatment phase, while remaining essentially unchanged during the control phase. The authors concluded that these findings suggested that CIIIT markedly improves BP control, as evidenced by the significantly reduced AHM dosage requirements in subjects with IDDM and hypertension, possibly through an improvement in vascular reactivity.

In a 18-month multi-center, prospective, controlled study, Dailey et al (2000) evaluated the effects of PIVIT on the progression of DN in patients with type 1 DM. Of the 49 patients studied, 26 formed the control group (C), which continued on IT, while 23 formed the treatment group (T) and underwent, in addition to IT, weekly PIVIT. Blood pressure in all patients was maintained below 140/90 mm Hg on AHM, preferentially using angiotensin-converting enzyme (ACE) inhibitors. All subjects were seen in the clinic for 18 months, had monthly HbA1C; and every 3 months, 24-hour urinary protein excretion and creatinine clearance (CrCl) were measured. The HbA1C levels declined from 8.61 % +/- 0.33 % to 7.68 % +/- 0.31 % ($p = 0.0028$) in the T group and from 9.13 % +/- 0.36 % to 8.19 % +/- 0.33 % ($p = 0.0015$) in the C group during the study period. Creatinine clearance declined significantly in both groups, as expected, but the rate of CrCl decline in the T group (2.21 +/- 1.62 ml/min/year) was significantly less than in the C group (7.69 +/- 1.88 ml/min/year, $p = 0.0343$). The authors concluded that when PIVIT was added to IT in type 1 DM patients with DN, it appeared to markedly reduce the progression of DN. The effect appeared to be independent of ACE inhibitor therapy, BP, or glycemic control.

While the studies by Aoki et al (1993, 1995a, 1995b, and 1995c) as well as Dailey et al (2000) reported that CIIIT appeared to improve all problems associated with diabetes therapy, the results of a study by Heinemann et al (1989) were negative, and glucose tolerance of the patients was worse following CIIIT. These researchers examined the effects of insulin pulsing (10 i.v. pulses of human insulin of 0.035 U per kg body weight were given, each of 20-second duration, with intervals of 6 minutes, three times per day covered with adequate administration of glucose) on 2 successive days on glucose-tolerance in 9 well-controlled type 1 DM patients on continuous subcutaneous insulin infusion therapy (aged 26 (7) years, mean (SD); duration of diabetes 10 (7) years; body mass index 23.4 (2.3) kg per m2; HbA1c 6.0 (0.6) %). On the days before and after the insulin pulsing, the patients were subjected to metabolic assessments by an oral glucose tolerance test (1 g glucose per kg body weight) 30 minutes after the subcutaneous injection of 0.15 U per kg body weight regular human insulin and a subsequent bicycle-ergometer test. During these metabolic assessments, plasma free insulin concentrations, plasma glucagon and the non-protein respiratory quotient remained unaffected by the insulin pulsing. However, glucose tolerance deteriorated significantly (maximal glucose concentration 120 minutes after glucose load was 10.0 mmol/L before and 13.9 mmol/L after insulin pulsing, $p < 0.01$). The authors concluded that the pattern of insulin pulsing used in this study did not ameliorate oral glucose homeostasis in well-controlled type 1 DM patients.

In an analysis of CIIIT, Heinemann (2001) noted that most of the studies were uncontrolled, none was double-blinded, and some were under-powered. The author also stated that in studies comparing the effects of pulsatile and continuous intravenous insulin infusion, no overwhelming evidence was found for acute beneficial effects of pulsatile insulin infusion. Heinemann also questioned the measurement of respiratory quotient as an index of hepatic glucose production because respiratory quotient is known to be only of limited validity. The author concluded that "only when a controlled, double-blind, randomized study with a sufficient number of diabetic patients demonstrates that the CIIIT leads to beneficial results would I believe in this form of insulin therapy".

DeWitt and Hirsch (2003) reviewed the literature regarding insulin use in patients with type 1 and type 2 DM. A total of 28 studies for type 1 DM, 18 for type 2 DM, and 48 for insulin-oral combination met the selection criteria. In patients with type 1 DM, physiological replacement, with bed-time basal insulin and a meal-time rapid-acting insulin analog, results in fewer episodes of hypoglycemia than conventional regimens. Rapid-acting insulin analogs are preferred over regular insulin in patients with type 1 DM since they improve HbA1C and reduce episodes of hypoglycemia. In patients with type 2 DM, adding bed-time neutral protamine Hagedom (isophane) insulin to oral IT significantly improves glycemic control, especially when started early in the course of disease. Bed-time use of insulin glargine results in fewer episodes of night-time hypoglycemia than neutral protamine Hagedorn regimens. For patients with more severe insulin deficiency, a physiological insulin regimen should allow lower glycemic targets in the majority of patients. Adverse events associated with IT include hypoglycemia, weight gain, and worsening diabetic retinopathy if HbA1C levels decrease rapidly. The authors concluded that many options for IT are now

available. Physiological IT with insulin analogs is now relatively simple to use and is associated with fewer episodes of hypoglycemia. There is no mentioning of the use of CIIIT in this review.

Bolli (2006) reviewed data from long-term intervention studies regarding therapy in type 1 DM and discussed strategies for preventing hypoglycemia and safely achieving glycemic goals in this patient population. The author noted that twice-daily injection of pre-mixed or self-mixed insulin is the most common IT; however, this therapeutic strategy is also a major contributor to hypoglycemia and, eventually, hypoglycemia unawareness. Hypoglycemia unawareness in patients with type 1 DM has been found to be largely reversible. Moreover, intensive IT may prevent hypoglycemia and maintain glycemic targets. The most physiological regimen of IT available is continuous subcutaneous insulin infusion with an insulin pump; however, insulin glargine is a useful alternative to pump therapy. The author concluded that use of today's rapid- and long-acting insulin analogs in intensive management protocols not only improves glycemic control but also lowers the risk of hypoglycemia. Again, the use of CIIIT was not discussed in this review

Furthermore, available guidelines and position statements from several specialty societies on the management of patients with DM did not discuss the use of CIIIT:

- The American Association of Clinical Endocrinologists/American College of Endocrinology's guideline for the management of DM (2002).
- The National Collaborating Center for Chronic Conditions' clinical guideline on the diagnosis and management of adults with type 1 DM (2004).
- The American Diabetes Association (ADA)'s position statement on care of children and adolescents with type 1 DM (Silverstein et al, 2005).
- The ADA's position statement on nutrition recommendations and interventions for DM (ADA, 2007).

In a pilot study, Weinrauch et al (2007) examined the effect of PIVIT on cardiovascular mechanisms that might contribute to attenuation of renal compromise in IDDM patients with proteinuria. The control group (n = 8) received subcutaneous insulin (3 to 4 injections per day). The experimental group (n = 10) received three 1-hour courses of PIVIT on a single day per week in addition to subcutaneous insulin. Laboratory measurements included 2-dimensional Doppler echocardiography, 24-hour ambulatory monitoring with heart rate variation analysis, platelet aggregation and adhesion, plasma fibrinogen, factor VII, von Willebrand factor, fibrinolytic activity, plasminogen activator inhibitor, and viscosity measured at baseline and 12 months. Blood pressure control was maintained preferentially with angiotensin-converting enzyme inhibitors. Ratio of carbon dioxide production to oxygen utilization was measured with each infusion and showed rapid increase from 0.8 to 0.9 (p = 0.005) at weekly treatments through 12 months. These investigators observed an annualized decrease in creatinine clearance of 9.6 ml/min for controls versus 3.0 ml/min for PIVIT-treated patients. Annualized fall in blood hemoglobin was 1.9 versus 0.8 g/dL, respectively (p = 0.013). There were no differences between the control and PIVIT group with respect to glycohemoglobin, advanced glycated end products, cholesterol, or triglycerides. No differences between the study groups for hemodynamic or hemostatic factors were evident. Blood pressures were not significantly different at baseline or 12 months. The authors concluded that although preservation of renal function with attenuation of loss of blood hemoglobin during 12 months of PIVIT was associated with improvement in the efficiency of fuel oxidation as measured by respiratory quotient, this occurred without differences in metabolic/hemostatic factors, cardiac autonomic function, cardiac wall, or chamber size. The hypothesis that preservation of renal function in IDDM patients with proteinuria by weekly PIVIT involves mechanisms from the autonomic nervous system, cardiac size, and function, or elements of hemostasis was not confirmed.

A decision memo for outpatient intravenous insulin treatment (OIVIT) from the Centers for Medicare & Medicaid Services (2009) stated that the evidence does not show that the use of OIVIT is reasonable and necessary to treat diabetes or any other medical condition. It also noted that the evidence does not demonstrate that the diagnostic tests respiratory quotient, urine urea nitrogen, diagnostic blood glucose or potassium testing performed in the context of OIVIT provide results that can be reasonably used by a physician in managing a patient with diabetes.

Weinrauch et al (2010) examined if deterioration of renal and retinal function in patients with type 1 DM could be blunted by multiple daily insulin doses with or without the addition of weekly PIVIT. A total of 65 patients were evaluated prospectively in 7 centers; 36 participants were randomly allocated to the infusion group and 29 to the standard therapy group. Mean serum creatinine was 1.6 mg/dL in both groups. Subjects were excluded if clearance was less than 30 ml/min. There were no significant differences between the groups with respect to age, duration of diabetes, sex distribution, glycohemoglobin, BP, ACE inhibitor use, proteinuria, or baseline diabetic retinopathy (DR) severity level (all eyes exhibited DR; 8 were deemed technically not amenable to evaluation). Progression of DR was noted in 31.6 % of 57 patients (32.3 % treated, 30.8 % control; p = 1.0) with both eyes evaluable. For patients with 12 or more months of follow-up, 27.9 % of 43 patients demonstrated progression of DR (32.0 % treated, 22.2 % control; p = 0.57). There were no significant differences between study groups with respect to progression or marked progression, nor was there any influence of duration of follow-up. Progression of DR was noted in 18.8 % of 122 eyes that could be adequately evaluated (17.9 % of 67 treated, 20 % of 55 controls; p = 0.39). Serum creatinine increased to 1.7 mg/dL in the treatment group and to 1.9 mg/dL in the control group (p = 0.03). Statistically significant preservation of renal function by PIVIT was not matched by a statistically significant prevention of DR progression compared with standard diabetes care. The authors noted that inadequate statistical power or duration of the study, or lack of further benefit of PIVIT on the retina in the presence of ACE inhibition may be responsible.

Insulin potentiation therapy (IPT) is based on the assumption that intravenous insulin increases the effect of medications so that lower doses of these medications can be used. Advocates of IPT suggest that insulin "opens the pores" of cells throughout the body allowing certain drugs to enter more easily. While treatment of cancer is the main focus of IPT, this approach has also been employed for other diseases.

Lasalvia-Prisco et al (2004) noted that it has been reported that insulin increases the cytotoxic effect (in-vitro) of methotrexate by as much as 10,000-fold. In a prospective, randomized clinical trial, these researchers examined the clinical value of insulin as a potentiator of methotrexate. A total of 30 women with metastatic breast cancer resistant to fluorouracil + adriamycin + cyclophosphamide and also resistant to hormone therapy with measurable lesions were included in this study. Three groups each of 10 patients received two 21-day courses of the following treatments: insulin + methotrexate, methotrexate, and insulin, respectively. In each patient, the size of the target tumor was measured before and after treatment according to the RECIST (Response Evaluation Criteria In Solid Tumors). The changes in the size of the target tumor in the 3 groups were compared statistically. Under the trial conditions, the methotrexate-treated group and the insulin-treated group responded most frequently with progressive disease. The group treated with insulin + methotrexate responded most frequently with stable disease. The median increase in tumor size was significantly lower with insulin + methotrexate than with each drug used separately. These findings confirmed in-vivo the results of previous in-vitro studies showing clinical evidence that insulin potentiates methotrexate under conditions where insulin alone does not promote an increase in tumor growth. Therefore, the chemotherapy anti-tumoral activity must have been enhanced by the biochemical events elicited in tumor cells by insulin. The authors concluded that in multidrug-resistant metastatic breast cancer, methotrexate + insulin produced a significant anti-tumoral response that was not seen with either methotrexate or insulin used separately. These findings need to be validated by well-designed studies with larger sample size and longer follow-up.

The American Cancer Society (2008) noted that 1 very small published study on IPT was done in Uruguay. It included 30 women with breast cancer that was resistant to mainstream therapies. Of these women, 10 received insulin, 10 took methotrexate, and 10 received IPT using both drugs. After 8 weeks, researchers reported that the women in the IPT group had smaller increases in tumor size than either of the other groups. Even though they used lower doses of methotrexate than usual, there were some side effects (mouth sores) noted in the IPT group. This study did not look at survival, quality of life, well-being, or lasting effects. No long-term improvements were shown by this study. Most of the information about IPT comes from individual reports. Even among those, however, there is no evidence that individuals who reported being helped by IPT were followed for long enough to learn whether the treatment worked. Despite supporters' claims that IPT has been well-researched, no scientific studies that show safety and effectiveness have been published in available peer-reviewed journals. These claims cannot be verified. Furthermore, there are concerns about using lower doses of chemotherapy drugs. When chemotherapy drugs are tested in clinical trials, their effects are carefully monitored to learn which dose will best balance the need to kill cancer cells with the goal of keeping side effects at a tolerable level. There is no evidence that chemotherapy at a fraction of the recommended and tested dose can produce the same effect as the full dose if used with insulin.

Damyanov et al (2012) evaluated the results and quality of life of patients with resistant of castration-resistant tumors previously treated with IPT combined with hormone therapy. A total of 16 patients with metastasis prostate tumors after bilateral castration, androgenic blockade, and progression of the disease were observed during the study. The patients were divided into 2 groups:

1. group A consisting of 8 patients treated with low-dose chemotherapy epirubicin, vinblastine, and cyclophosphamide combined with luteinizing hormone releasing hormone (LHRH) agonist; and
2. group B consisting of another 8 patients treated with low-dose chemotherapy docetaxel combined with LHRH agonist.

The overall (groups A and B) results concerning prostate specific antigens after the sixth IPT showed partial effect in 8 out of 16 (50 %) patients, stabilization in 4 out of 16 (25 %), and progression in 4 out of 16 (25 %). The median survival for all treated patients is 11.7 months (range of 3 to 30 months). During the treatment no significant side effects were observed, and no lethal cases occurred. The authors concluded that despite the small number of the treated patients with castration-resistant prostate tumors, the preliminary results were promising; giving hope and expectations for future serious multi-center research over the possibilities for routine implementation of low-dose IPT.

Physiologic Insulin Re-Sensitization (PIR) Infusions

Greenway et al (2022) noted that prevalence of type 2 DM (T2DM) increased from 2.5 % of the U.S. population in 1990 to 10.5 % in 2018 resulting in a major public health problem, due to increases in long-term complications of DM, including neuropathy, retinopathy, nephropathy, skin ulcers, amputations, as well as atherosclerotic cardiovascular disease. In this review, these investigators examined the scientific basis that supports the use of physiologic insulin re-sensitization (PIR). Insulin resistance is the primary cause of T2DM. Insulin resistance results in increasing insulin secretion, leading to beta-cell exhaustion or burnout, which triggers a cascade resulting in islet cell destruction and the long-term complications of T2DM. Concurrent with insulin resistance, the regular bursts of insulin from the pancreas become irregular. This has been treated by the precise administration of insulin more physiologically. These researchers stated that there is evidence that this treatment modality could reverse the diabetes-associated complications of neuropathy, diabetic ulcers, nephropathy, and retinopathy, and that it lowered HbA1c. The authors concluded that PIR has a persuasive scientific basis, significant treatment potential, and likely cost benefits. Moreover, these researchers stated that this approach needs further research to examine the treatment's effect on a broad array of diabetes complications. These studies should include examining the cost of the treatment versus the costs avoided by it. If

randomized controlled trials (RCTs) could replicate the outcomes of case-reports and studies examined in this review, administration of insulin in a physiologic manner represents a promising approach to reduce or avoid the looming increases in disease, disability, death, and cost that will occur as the 88 million pre-diabetics progress to confirmed T2DM in the U.S.

Lewis et al (2023) stated that physiologic insulin secretion consists of an oscillating pattern of secretion followed by distinct trough periods that stimulate ligand and receptor activation. Apart from the large post-prandial bolus release of insulin, β cells also secrete small amounts of insulin every 4 to 8 mins independent of a meal. Insulin resistance is associated with a disruption in the normal cyclical pattern of insulin secretion. In the case of T2DM, β-cell mass is reduced due to apoptosis and β cells secrete insulin asynchronously. When ligand/receptors are constantly exposed to insulin, a negative feedback loop down-regulates insulin receptor availability to insulin, creating a relative hyper-insulinemia. The relative excess of insulin results in insulin resistance (IR) due to decreased receptor availability. Over time, progressive insulin resistance compromises carbohydrate metabolism, and may progress to T2DM. These researchers discussed IR pathophysiology and the use of dynamic exogenous insulin administration in a fashion consistent with more normal insulin secretion periodicity to reverse IR. These researchers stated that administration of insulin in such a physiologic manner appeared to improve insulin sensitivity, lower HgbA1c, and, in some instances, has been associated with the reversal of end-organ damage that results in complications of diabetes. The authors stated that there is emerging evidence supporting the benefits of intravenous (IV) insulin administration that mimics the physiologic pancreatic insulin secretion pattern. These researchers outlined the rationale for how the physiologic secretion of insulin orchestrated glucose metabolism, and how mimicking this secretion profile may serve to improve glycemic control, lower cellular inflammation, and potentially improve outcomes in patients with diabetes.

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The above policy is based on the following references:

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Policy History

- Last Review 10/24/2024

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  Next Review: 08/28/2025

- Review History

- Definitions

Additional Information

- Clinical Policy Bulletin Notes