Chronic intermittent intravenous insulin therapy (CIIIT) is a technique for delivering variable-dosage insulin to diabetic patients with the goal of improved long-term glycemic control. Through an unknown mechanism, it is postulated to induce insulin-dependent hepatic enzymes to suppress glucose production.

**Policy**

Chronic intermittent intravenous insulin therapy is considered **investigational**.

**Policy Guidelines**

The following HCPCS code is specific to chronic intermittent intravenous insulin therapy (CIIIT):  
- **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

There is no specific CPT code describing CIIIT. The following series of CPT codes and HCPCS J codes are used to describe the various components of CIIIT. Some codes, such as the code for glucose testing, may be used more than once during a single session of CIIIT:

**CPT codes**

- **82948**: Glucose; blood, reagent strip
- **94681**: Oxygen uptake, expired gas analysis; including CO₂ output, percentage oxygen extracted
- **96365**: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
• **96366**: Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)

• **99070**: Supplies and materials (except spectacles), provided by the physician or other qualified health care professional over and above those usually included with the office visit or other services rendered (list drugs, trays, supplies, or materials provided)

• **99211**: Office or other outpatient visit for the evaluation and management of an established patient that may not require the presence of a physician or other qualified health care professional. Usually, the presenting problem(s) are minimal. Typically, 5 minutes are spent performing or supervising these services.

**HCPCS J codes**

• **J7050**: Infusion, normal saline solution, 250 cc

• **J1817**: Insulin for administration through DME (i.e., insulin pump) per 50 units

**General Information**

Chronic intermittent intravenous insulin therapy is typically offered in specialized clinics. Locations offering CIIIT include: Sacramento, CA; Boca Raton and Fort Lauderdale, FL; Wichita, KS; Reno, NV; Brooklyn, NY; and Midland, TX. Further information can be found at the Aoki Diabetes Research Institute website (http://www.adri.org).

**Benefit Application**

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program (FEP)) prohibit Plans from denying Food and Drug Administration (FDA) - approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

**Rationale**

**Background**

There are 3 main sites of insulin-mediated glucose homeostasis that must function in a coordinated fashion to maintain euglycemia: (1) insulin secretion by the pancreas; (2) glucose uptake, primarily in the muscle, liver, gut, and fat; and (3) hepatic glucose production. For example, in the fasting state, when insulin levels are low, most glucose uptake is noninsulin mediated. Glucose uptake is then balanced by liver production of glucose, critical to nourish vital organs, such as the brain. However, after a glucose challenge, insulin binds to specific receptors on the hepatocyte to suppress glucose production. Without this inhibition, as can be seen in diabetic patients, marked hyperglycemia may result. Different classes of diabetic drug therapy target different
aspects of glucose metabolism. Various insulin secretagogues (e.g., sulfonylureas) function by increasing the pancreatic secretion of insulin; thiazolidinediones (e.g., pioglitazone [Actos] and rosiglitazone [Avandia]) function in part by increasing glucose uptake in the peripheral (principally skeletal) tissues; and biguanides (e.g., metformin) function by decreasing hepatic glucose production. While patients with type 2 diabetes may be treated with various combinations of all 3 of these classes of drugs, with or without additional insulin, patients with type 1 diabetes, who have no baseline insulin secretion, receive exogenous insulin therapy. Large-scale randomized studies have established that tight glucose control is associated with a decreased incidence of microvascular complications of diabetes (i.e., nephropathy, neuropathy, retinopathy). Currently, the American Diabetes Association recommends a target hemoglobin A1c (HbA1c) concentration of less than 7%.

CIIIT, also referred to as outpatient intravenous insulin therapy (OIVIT); pulsatile intravenous insulin therapy; hepatic activation; or metabolic activation, involves delivering insulin intravenously over a 6- to 7-hour period in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the dosages based on frequent blood glucose monitoring. CIIIT therapy is principally designed to normalize the hepatic metabolism of glucose. In a 1993 article describing the development of the technique, Aoki et al proposed that in patients with insulin-dependent diabetes mellitus (IDDM), lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. (1) The authors state, “We reasoned that if the liver of an IDDM patient could be perfused with near-normal concentrations of insulin during meals, the organ could be reactivated,” and proposed that once weekly 6-hour intravenous pulsatile infusions of insulin while the patient ingests a carbohydrate meal will increase the portal vein concentrations of insulin, ultimately stimulating the synthesis of glucokinase and other insulin-dependent enzymes. The pulses are designed to deliver a higher, more physiologic concentration of insulin to the liver than is delivered by traditional subcutaneous injections. This higher level of insulin is thought to more closely mimic the body’s natural levels of insulin as it is delivered to the liver. It is hoped that this therapy ultimately results in improved glucose control through improved hepatic activation.

CIIIT is typically delivered once weekly as outpatient therapy.

**Regulatory Status**

Any insulin infusion pump can be used for the purposes of CIIIT. Infusion pumps have received U.S. Food and Drug Administration (FDA) marketing clearance through the 510(k) process, as they are determined to be substantially equivalent to predicate devices for the delivery of intravenous medications. FDA product code: lZG.

**Literature Review**

The following is a key summary of the literature to date, which primarily addresses whether chronic intermittent intravenous insulin therapy (CIIIT) improves glycemic control in diabetic patients and whether CIIIT reduces end organ damage associated with diabetes. No studies were identified that investigate the proposed mechanism of action of CIIIT in humans.

**Does CIIIT Improve Glycemic Control in Diabetic Patients?**

Because of the many variables associated with diabetic management, randomized controlled trials (RCTs) are necessary to validate treatment effectiveness. No blinded randomized clinical trials focusing on the efficacy of CIIIT for glucose control were found.
In 1993, Aoki et al published a case series of 20 patients with “brittle” type 1 diabetes. All patients received 4 daily injections of insulin (type of insulin not described); additional oral drug therapy, if any, was not described. Throughout the study, patients remained in close contact with the clinic (at least once a week), during which appropriate adjustments in diet, insulin therapy, and activity were made. While the study reported a decrease in the HbA1c levels, the lack of a control group limits the interpretation of results. For example, the intense follow-up of the patients could have impacted results, regardless of any possible effects of the CIIIT.\(^1,2\)

Aoki et al also examined the effect of CIIIT with hypertensive medications in 26 patients with type 1 diabetes and associated hypertension and nephropathy.\(^3\) The 26 patients were randomly assigned to a control group or treatment group for 3 months and then crossed over to the opposite group for an additional 3 months. At baseline, all patients were being treated with 4 daily insulin injections and had achieved acceptable HbA1c levels of 7.4%. Patients also achieved acceptable baseline blood pressure control (<140/90 mm Hg) with a variety of medications (i.e., angiotensin converting enzyme inhibitors, calcium channel blockers, loop diuretics, and alpha-2 agonists). While the study was randomized, it was not blinded in that sham CIIIT procedures were not performed. Therefore, those patients receiving CIIIT received more intense follow-up during this period. During the treatment phase, patients reported a significant decrease in dosage of antihypertensive medicines. No difference in glycemic control was noted. Because all patients had adequate blood pressure control at baseline, the clinical significance of the decrease in antihypertensive dosage requirement associated with CIIIT is uncertain.

Does CIIIT Reduce Diabetic End-Organ Damage?

Because of the many variables associated with diabetic management, RCTs are necessary to validate treatment effectiveness. Two RCTs focusing on the efficacy of CIIIT for reducing diabetic end organ complications are discussed below.

In 2000, Dailey et al reported on the effect of CIIIT on the progression of diabetic nephropathy.\(^4\) A total of 49 patients with type 1 diabetes were included. Of these, 26 were assigned to the control group, and 23 were assigned to the treatment group that underwent weekly CIIIT. Both groups reported a significant decrease in HbA1c during the 18-month study period. The creatinine clearance declined in both groups as expected, but the rate of decline in the treatment group was significantly less compared with the control group. Again, the clinical significance of this finding is uncertain; larger clinical trials that look at the end point of time to progression of renal failure are needed.

In 2010, Weinrauch et al published a study of the effects of CIIIT on progression of nephropathy and retinopathy in 65 subjects with type 1 diabetes.\(^5\) Patients were randomly allocated to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29) or standard therapy plus weekly CIIIT (n=36). Baseline demographic characteristics were similar between the 2 groups, as were age of onset, duration of diabetes, diabetic control, and renal function (average creatinine, 1.59 mg/dL; average creatinine clearance, 60.6 mL/min). Primary end points were progression of diabetic retinopathy and nephropathy. There was no significant difference in progression of diabetic retinopathy. Progression was noted in 18.8% of 122 eyes that were adequately evaluated (17.9% of 67 treated eyes, 20.0% of 55 controls; \(p=0.39\)). On average, serum creatinine increased in both groups; the increase was less in the treatment group (0.09 mg/dL vs 0.39 mg/dL, respectively; \(p=0.035\)). While average creatinine clearance fell less in the treatment group, the difference was not significant (-5.1 mL/min vs -9.9 mL/min, respectively; \(p=0.30\)). Glycemic control did not vary significantly. The clinical significance
of the difference in creatinine levels is unknown and requires further evaluation in trials involving a larger number of patients.

**Ongoing Clinical Trials**

A search of the online database [ClinicalTrials.gov](http://ClinicalTrials.gov) in June 2014, identified the following studies evaluating the use of CIIIT:

- **Multicenter Trial to Evaluate the Effects of Intensive Bolus Intravenous Insulin Delivery on Metabolic Integrity in Type 1 and Type 2 Diabetics Who Despite Tight Control and Proper Diet Still Suffer From Metabolic Problems** (NCT01023165). This is a nonrandomized Phase 3 trial to evaluate outcomes related to quality of life and diabetic complications in patients with diabetic complications who undergo weekly bolus insulin sessions. Enrollment is planned for 2000 subjects; the planned study completion date is November 2015.

- **A Randomized Controlled Trial to Evaluate Early Intermittent Intensive Insulin Therapy as an Effective Treatment of Type 2 Diabetes: REmission Studies Evaluating Type 2 DM - Intermittent Insulin Therapy (RESET-IT)** (NCT01755468). This is a randomized, open-label trial to compare intermittent insulin therapy with continuous metformin therapy for patients with type 2 diabetes. Enrollment is planned for 148 subjects; the planned study completion date is December 2017.

**Summary**

Chronic intermittent intravenous insulin therapy (CIIIT) is a technique for delivering variable-dosage insulin to diabetic patients with the goal of improved long-term glycemic control. Through an unknown mechanism, it is postulated to induce insulin-dependent hepatic enzymes to suppress glucose production.

It is hypothesized that CIIIT improves hepatic glucose regulation. A limited number of uncontrolled studies suggest that CIIIT may improve glycemic control. Two randomized trials report that CIIIT may moderate the progression of nephropathy. However, the published studies are small and report benefits on intermediate outcomes only (i.e., changes in laboratory values). This evidence does not permit definitive conclusions regarding the health benefits of CIIIT. Therefore, the technique is considered investigational.

**Practice Guidelines and Position Statements**

Clinical practice guidelines from professional associations, including the American Diabetes Association and the American Association of Clinical Endocrinologists, do not include CIIIT within each organization's clinical practice guidelines for diabetes. The American College of Physicians published a clinical practice guideline in 2011 on the use of intensive insulin therapy for the management of glycemic control in hospitalized patients; the recommendations put forth in this guideline were based on earlier systematic reviews on this topic which did not include CIIIT.

**U.S. Preventive Services Task Force Recommendations**

CIIIT is not a preventive service.

**Medicare National Coverage**

“Effective for claims with dates of service on and after December 23, 2009, the Centers for Medicare and Medicaid Services (CMS) determines that the evidence is adequate to conclude that outpatient intravenous insulin therapy (OIVIT, i.e., CIIIT) does not improve health outcomes in Medicare beneficiaries. Therefore, CMS determines that OIVIT is not reasonable and necessary for any indication under section 1862(a)(1)(A) of the Social
Security Act. Services comprising an Outpatient Intravenous Insulin Therapy regimen are nationally noncovered under Medicare when furnished pursuant to an OIVIT regimen (see subsection A. above).”

References


Documentation Required for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to benefit design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement.
IE

The following services are considered investigational and therefore not covered for any indication.

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<th>Description</th>
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Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

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<tr>
<td>2/14/2001</td>
<td>BCBSA Medical Policy adoption</td>
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<td>1/7/2011</td>
<td>Policy title change from Pulsatile Intravenous Insulin Therapy</td>
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### Definitions of Decision Determinations

**Medically Necessary:** A treatment, procedure or drug is medically necessary only when it has been established as safe and effective for the particular symptoms or diagnosis, is not investigational or experimental, is not being provided primarily for the convenience of the patient or the provider, and is provided at the most appropriate level to treat the condition.

**Investigational/Experimental:** A treatment, procedure or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California / Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a Split Evaluation, where a treatment, procedure or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

### Prior Authorization Requirements

This service (or procedure) is considered **medically necessary** in certain instances and **investigational** in others (refer to policy for details).

For instances when the indication is **medically necessary**, clinical evidence is required to determine **medical necessity**.

For instances when the indication is **investigational**, you may submit additional information to the Prior Authorization Department.

Within five days before the actual date of service, the Provider MUST confirm with Blue Shield that the member’s health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member’s eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should also be directed to the Prior Authorization Department. Please call 1-800-541-6652 or visit the Provider Portal www.blueshieldca.com/provider.

The materials provided to you are guidelines used by this plan to authorize, modify, or deny care for persons with similar illness or conditions. Specific care and treatment may vary depending on individual need and the benefits covered under your contract. These Policies are subject to change as new information becomes available.