Chronic intermittent intravenous insulin therapy is considered investigational.

Policy Guidelines:
This policy does not apply to use of intravenous insulin infusions in the inpatient setting (i.e., for the treatment of diabetic ketoacidosis or diabetic hyperosmolar coma).

Coding
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 chronic intermittent intravenous insulin therapy (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.

J Codes
- J7050: Infusion, normal saline solution, 250 cc
- J1817: Insulin for administration through DME (i.e., insulin pump) per 50 units

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

- Implantable Infusion Pump

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)] prohibits 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.

Regulatory Status

Any insulin infusion pump can be used for the purposes of chronic intermittent intravenous insulin therapy. Infusion pumps have been cleared for marketing by the U.S. Food and Drug Administration (FDA) through the 510(k) process. The FDA determined that this device was substantially equivalent to existing devices for the delivery of intravenous medications. FDA product code: lZG.

Rationale

Background

Glucose Homeostasis

Insulin-mediated glucose homeostasis involves 3 primary functions which occur at 3 locations: (1) insulin secretion by the pancreas; (2) glucose uptake, primarily in the muscle, liver, gut, and fat; and (3) hepatic glucose production. In the fasting state, when insulin levels are low, most glucose uptake into cells is non-insulin-mediated. Glucose uptake is then balanced by liver production of glucose. However, after a glucose challenge, insulin binds to specific receptors on the hepatocyte to suppress glucose production. Without this inhibition, marked hyperglycemia may result.

Medications for Glucose Homeostasis in Diabetes

Diabetes is characterized by elevated blood glucose levels due to inadequate or absent insulin production (type 1 diabetes) or due to increased hepatic glucose production, decreased peripheral glucose uptake, and decreased insulin secretion (type 2 diabetes).

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], 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. Standard insulin management involves use of subcutaneous injection to mimic a physiologic insulin profile. Intravenous insulin is used in the acute inpatient setting to manage hyperglycemic emergencies (e.g., diabetic ketoacidosis).
**Chronic Intermittent Insulin Therapy**

Several forms of chronic intermittent insulin therapy, in which insulin is delivered intravenously or into the peritoneal space, have been evaluated.

Chronic intermittent intravenous insulin therapy (CIIIT)—also referred to as outpatient intravenous insulin therapy, pulsatile intravenous insulin therapy, hepatic activation therapy, or metabolic activation therapy—involves delivering insulin intravenously once weekly over several hours in a pulsatile fashion using a specialized pump controlled by a computerized program that adjusts the doses based on frequent blood glucose monitoring. CIIIT is principally designed to normalize the hepatic metabolism of glucose. In 1993, Aoki et al proposed that, in patients with type 1 diabetes, lower levels of insulin in the portal vein are associated with a decreased concentration of the liver enzymes required for hepatic metabolism of glucose. They stated: “We reasoned that if the liver of an IDDM [insulin-dependent diabetes mellitus; i.e., type 1 diabetes] patient could be perfused with near-normal concentrations of insulin during meals, the organ could be reactivated,” and proposed that intermittent intravenous pulsatile infusions of insulin administered once weekly while the patient ingests a carbohydrate meal would 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 because it is delivered to the liver. The goal of this outpatient therapy is improved glucose control through improved hepatic activation.

**Literature Review**

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. Because of the many variables associated with management of diabetes, randomized controlled trials (RCTs) of CIIIT are necessary to permit conclusions about treatment effectiveness.

No studies were identified that investigated the proposed mechanism of action of CIIIT in humans.

**Chronic Intermittent Intravenous Insulin Therapy (CIIIT) and Glycemic Control in Diabetic Patients**

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 time appropriate adjustments in diet, insulin doses, and physical activity were made. While the study reported a decrease in the hemoglobin A1c (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.

Aoki et al (1995) also examined the effect of CIIIT with hypertensive medications in 26 patients with type 1 diabetes and associated hypertension and nephropathy. The 26 patients were randomized to a control group or to a treatment group for 3 months and then crossed over 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, alpha-2 agonists). The study was randomized, but 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.

Section Summary: CIIIT and Glycemic Control in Diabetic Patients

One nonblinded RCT and 1 case series reporting on the effect of CIIIT on glycemic control in type 1 diabetic patients were identified. Both studies reported improvements: one in HbA1c compared with baseline, and the other in dose of antihypertensive medication in the treatment group compared with control. However, the lack of a blinded control comparator group in the RCT limits the conclusions that can be drawn.

CIIIT and Reductions in Diabetic End-Organ Damage

In 2010, Weinrauch et al published an RCT of the effects of CIIIT on progression of nephropathy and retinopathy in 65 subjects with type 1 diabetes.4 Patients were randomized to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29; control group) or to standard therapy plus weekly CIIIT (n=36; treatment group). Baseline demographic characteristics were similar between the 2 groups, as were age of onset, duration of diabetes, control of HbA1c levels, 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 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 smaller in the treatment group (0.09 mg/dL) than in the control group (0.39 mg/dL; p=0.035). While average creatinine clearance fell less in the treatment group (-5.1 mL/min), the difference versus standard therapy was not significant (-9.9 mL/min; p=0.30). Glycemic control did not vary significantly. The clinical significance of the difference in creatinine levels is unknown.

In 2000, Dailey et al reported on a prospective, multicenter, controlled study of the effects of CIIIT on the progression of diabetic nephropathy. They assessed 49 type 1 diabetes patients with nephropathy who were following the Diabetes Control and Complications Trial intensive therapy regimen. Of these, 26 were assigned to the control group, which continued intensive therapy, and 23 were assigned to the treatment group, which underwent weekly CIIIT plus intensive therapy. Both groups reported a significant decrease in HbA1c levels during the 18-month study period. Creatinine clearance declined in both groups as expected, but the rate of decline in the treatment group was significantly less than in the control group. The clinical significance of this finding is uncertain. Larger clinical trials that evaluate the end point of time to progression of renal failure are needed.

Section Summary: CIIIT and Reductions in Diabetic End-Organ Damage

Two controlled studies focusing on the efficacy of CIIIT for reducing diabetic end-organ complications were identified. Both reported significant improvements in intermediate measures of glycemic control in each group from pre- to postintervention, but did not consistently report differences in clinically meaningful outcomes from the beginning of the studies to the end. Similarly, there were no significant differences between treatment groups in the RCT.

Summary of Evidence

For individuals who have type 1 diabetes who receive chronic intermittent intravenous insulin therapy (CIIIT), the evidence includes 2 randomized controlled trials (RCTs) and uncontrolled studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. A limited number of uncontrolled studies have suggested that CIIIT might improve glycemic control. The 2 RCTs reported that CIIIT might moderate the progression of nephropathy or retinopathy. However, the published studies were small and reported improvements on intermediate outcomes only (i.e., changes in laboratory values). The clinical significance of the differences reported in these studies is uncertain. Additionally, most published evidence appeared between 1993 and 2000 and, as a result, does not account for recent improvements in diabetes care. The evidence is insufficient to determine the effects of the technology on health outcomes.
Supplemental Information
Practice Guidelines and Position Statements
Clinical practice guidelines from professional associations, including the American Diabetes Association (updated in 2017) and the American Association of Clinical Endocrinologists and American College of Endocrinology (updated in 2015), have not included chronic intermittent intravenous insulin therapy (CIIT) in guidelines for managing type 1 diabetes.

The American College of Physicians updated its Best Practice Advice in 2014 on inpatient glycemic control, which provided some recommendations on the use of intensive insulin therapy, including:

- “Best Practice Advice 1: Clinicians should target a blood glucose level of 7.8 to 11.1 mmol/L (140-200 mg/dL) if insulin therapy is used in SICU [surgical intensive care unit]/MICU [medical intensive care unit] patients.”
- “Best Practice Advice 2: Clinicians should avoid targets less than 7.8 mmol/L (140 mg/dL) because harms are likely to increase with lower blood glucose targets.”

U.S. Preventive Services Task Force Recommendations
Not applicable.

Medicare National Coverage
In 2009, the Centers for Medicare and Medicaid Services issued a decision memo on use of outpatient intravenous insulin therapy, which stated:

“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 OIVIT [outpatient intravenous insulin therapy; CIIT] 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 non-covered under Medicare when furnished pursuant to an OIVIT regimen....”

Ongoing and Unpublished Clinical Trials
A currently unpublished trial that might influence this review is listed in Table 1.

Table 1. Summary of Key Trials

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
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<tr>
<td>NCT01023165a</td>
<td>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</td>
<td>2000</td>
<td>Nov 2015 (unknown)</td>
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</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.

References


### Documentation 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 may be considered investigational.

<table>
<thead>
<tr>
<th>Type</th>
<th>Code</th>
<th>Description</th>
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<tr>
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<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)</td>
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<td></td>
<td>99070</td>
<td>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)</td>
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<tr>
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<td>99211</td>
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### Chronic Intermittent Intravenous Insulin Therapy

**HCPCS**

<table>
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</tr>
<tr>
<td>J1817</td>
<td>Insulin for administration through DME (i.e., insulin pump) per 50 units</td>
</tr>
<tr>
<td>J7050</td>
<td>Infusion, normal saline solution, 250 cc</td>
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**ICD-10 Procedure**

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<td>3E030VG</td>
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<td>3E033VG</td>
<td>Introduction of Insulin into Peripheral Vein, Percutaneous Approach</td>
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<td>3E040VG</td>
<td>Introduction of Insulin into Central Vein, Open Approach</td>
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<td>3E043VG</td>
<td>Introduction of Insulin into Central Vein, Percutaneous Approach</td>
</tr>
<tr>
<td>3E050VG</td>
<td>Introduction of Insulin into Peripheral Artery, Open Approach</td>
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<td>3E053VG</td>
<td>Introduction of Insulin into Peripheral Artery, Percutaneous Approach</td>
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<td>3E060VG</td>
<td>Introduction of Insulin into Central Artery, Open Approach</td>
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<tr>
<td>3E063VG</td>
<td>Introduction of Insulin into Central Artery, Percutaneous Approach</td>
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**ICD-10 Diagnosis**

| Diagnosis | All Diagnoses |

### Policy History

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

<table>
<thead>
<tr>
<th>Effective Date</th>
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<tr>
<td>02/14/2001</td>
<td>BCBSA Medical Policy adoption</td>
<td>Medical Policy Committee</td>
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<td>01/07/2011</td>
<td>Policy title change from Pulsatile Intravenous Insulin Therapy (PIVIT) for Type 1 Diabetes Mellitus (a.k.a. PIVIT or CIIIT)</td>
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<td></td>
<td>Policy revision without position change</td>
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<td>09/30/2014</td>
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<td>Medical Policy Committee</td>
</tr>
</tbody>
</table>

### 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 (as applicable to your plan)**

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 be directed to the Prior Authorization Department. Please call (800) 541-6652 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.