

2.01.43	Chronic Intermittent Intravenous Insulin Therapy		
Original Policy Date:	February 14, 2001	Effective Date:	April 1, 2021
Section:	2.0 Medicine	Page:	Page 1 of 9

Policy Statement

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

NOTE: Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

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 (CIIT):

- **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 (CIIT). The following series of CPT codes and HCPCS J codes are used to describe the various components of CIIT. Some codes, such as the code for glucose testing, may be used more than once during a single session of CIIT.

CPT Codes

- **82948:** Glucose; blood, reagent strip
- **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)

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

Related Policies

- N/A

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 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: IZG.

Rationale

Background

Glucose Homeostasis

Insulin-mediated glucose homeostasis involves 3 primary functions that 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 the 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).

Patients with type 1 diabetes require insulin therapy. Insulin therapy for patients with type 1 diabetes usually consists of multiple daily subcutaneous injections with both basal and mealtime insulin or continuous subcutaneous insulin infusions given through an insulin pump.¹ Insulin therapy has improved over the last several decades with newer insulin products providing improved pharmacokinetic parameters to closer mimic physiologic insulin. Intravenous insulin is used in the acute inpatient setting to manage hyperglycemic emergencies (e.g., diabetic ketoacidosis).

Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function - including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and

confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Chronic Intermittent Intravenous Insulin Therapy for Type 1 Diabetes

Clinical Context and Therapy Purpose

The purpose of chronic intermittent intravenous insulin therapy (CIIT) in patients who have type 1 diabetes mellitus is to provide a treatment option that is an alternative to or an improvement on existing insulin therapies.

The question addressed in this evidence review is: Does the use of CIIT used to treat patients with type 1 diabetes mellitus improve net health outcomes?

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is patients with type 1 diabetes mellitus who need improved glycemic control.

Interventions

The therapy being considered is CIIT. Several forms of CIIT, in which insulin is delivered intravenously or into the peritoneal space, have been evaluated.

CIIT—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.² CIIT is principally designed to normalize the hepatic metabolism of glucose. Currently, no studies have been identified that have investigated the proposed mechanism of action of CIIT in humans.

Aoki et al. (1993) 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.³ The authors stated: “We reasoned that if the liver of an 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.

Patients receive CIIT in weekly clinic-based treatment sessions.

Comparators

The following therapies and practices are currently being used to make decisions about treatment to maintain normoglycemia in patients with type 1 diabetes mellitus: guideline-directed diabetic medical therapy including subcutaneous insulin as well as diabetes self-management with glucose monitoring, diet, and exercise regimens.

Outcomes

The general outcomes of interest are symptomatic hyperglycemia and hypoglycemia, disease status changes such as the development of end-organ damage, and treatment-related morbidity.

Patients with type 1 diabetes mellitus require lifelong medical monitoring of glycemic control and end-organ status. Informal publication has indicated that patients have been treated with CIIT for as long as 12 years.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

Glycemic Control

In 1993, Aoki et al. published a case series of 20 patients with “brittle” type 1 diabetes.³ 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 A_{1c} (HbA_{1c}) levels, the lack of a control group limits the interpretation of the results. For example, the intense follow-up of the patients could have impacted results, regardless of any possible effects of the CIIT.^{3,4}

In 1995, Aoki et al. also examined the effect of CIIT with hypertensive medications in 26 patients with type 1 diabetes and associated hypertension and nephropathy.⁵ The 26 patients were randomized to a control group or 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 HbA_{1c} 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 CIIT procedures were not performed. Therefore, those patients receiving CIIT received more intense follow-up during this period. During the treatment phase, patients reported a significant decrease in the 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 CIIT is uncertain.

Section Summary: Glycemic Control

One nonblinded RCT and a case series reporting on the effect of CIIT on glycemic control in type 1 diabetes were identified. Both studies reported improvements: one in HbA_{1c} levels compared with baseline, and the other in a 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.

Reductions in Diabetic End-Organ Damage

Weinrauch et al. (2010) published an RCT of the effects of CIIT on progression of nephropathy and retinopathy in 65 subjects with type 1 diabetes.⁶ Patients were randomized to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29; control group) or standard therapy plus weekly CIIT (n=36; treatment group). Baseline demographic characteristics were similar

between the 2 groups, as were the age of onset, duration of diabetes, control of HbA_{1c} levels, and renal function (average creatinine, 1.59 mg/dL; average creatinine clearance, 60.6 mL/min). Primary endpoints were a 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 uncertain.

Dailey et al. (2000) reported on a prospective, multicenter, controlled study evaluating the effects of CIIT on the progression of diabetic nephropathy.⁷ The authors 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 CIIT plus intensive therapy. Both groups reported a significant decrease in HbA_{1c} 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 endpoint of time to progression of renal failure are needed.

Section Summary: Reductions in Diabetic End-Organ Damage

Two controlled studies focusing on the efficacy of CIIT for reducing diabetic end-organ complications were identified. Both reported significant improvements in intermediate measures of glycemic control in each group from pre- to post-intervention 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 CIIT, the evidence includes 2 randomized controlled trials (RCTs) and several uncontrolled studies. Relevant outcomes are symptoms, change in disease status, and treatment-related morbidity. A limited number of uncontrolled studies have suggested that CIIT might improve glycemic control. The 2 RCTs have reported that CIIT 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 trials is uncertain. Additionally, most published evidence appeared between 1993 and 2010 and, as a result, does not account for improvements in diabetes care. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Supplemental Information

Practice Guidelines and Position Statements

The purpose of the remaining sections in Supplemental Information is to provide reference material regarding existing practice guidelines and position statements, U.S. Preventive Services Task Force Recommendations and Medicare National Coverage Decisions and registered, ongoing clinical trials. Inclusion in the Supplemental Information does not imply endorsement and information may not necessarily be used in formulating the evidence review conclusions.

Guidelines or position statements will be considered for inclusion in Supplemental Information if they were issued by, or jointly by, a U.S. professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

The 2021 American Diabetes Association “Standards of Medical Care in Diabetes” includes the American Diabetes Association’s current clinical practice recommendations and is intended to provide the components of diabetes care, general treatment goals and guidelines, and tools to evaluate the quality of care.¹

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The 2009 Centers for Medicare & Medicaid Services issued a decision memo on the use of outpatient intravenous insulin therapy, which stated⁸:

“Effective ... 2009, the Centers for Medicare and Medicaid Services (CMS) determines that the evidence is adequate to conclude that OIVIT does not improve health outcomes in Medicare beneficiaries. Therefore, CMS determines that OIVIT is not reasonable and necessary.... 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 search for active or recruiting clinical trials in December 2020 did not yield results for trials that might influence this review.

References

1. American Diabetes Association. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Medical Care in Diabetes-2021. *Diabetes Care*. Jan 2021; 44(Suppl 1): S111-S124. PMID 33298420
2. Mirbolooki MR, Taylor GE, Knutzen VK, et al. Pulsatile intravenous insulin therapy: the best practice to reverse diabetes complications?. *Med Hypotheses*. Sep 2009; 73(3): 363-9. PMID 19446964
3. Aoki TT, Benbarka MM, Okimura MC, et al. Long-term intermittent intravenous insulin therapy and type 1 diabetes mellitus. *Lancet*. Aug 28 1993; 342(8870): 515-8. PMID 8102666
4. Aoki TT, Grecu EO, Arcangeli MA. Chronic intermittent intravenous insulin therapy corrects orthostatic hypotension of diabetes. *Am J Med*. Dec 1995; 99(6): 683-4. PMID 7503093
5. Aoki TT, Grecu EO, Prendergast JJ, et al. Effect of chronic intermittent intravenous insulin therapy on antihypertensive medication requirements in IDDM subjects with hypertension and nephropathy. *Diabetes Care*. Sep 1995; 18(9): 1260-5. PMID 8612440
6. Weinrauch LA, Sun J, Gleason RE, et al. Pulsatile intermittent intravenous insulin therapy for attenuation of retinopathy and nephropathy in type 1 diabetes mellitus. *Metabolism*. Oct 2010; 59(10): 1429-34. PMID 20189608
7. Dailey GE, Boden GH, Creech RH, et al. Effects of pulsatile intravenous insulin therapy on the progression of diabetic nephropathy. *Metabolism*. Nov 2000; 49(11): 1491-5. PMID 11092517
8. Centers for Medicaid & Medicare Services. National Coverage Determination (NCD) for Outpatient Intravenous Insulin Treatment (40.7). 2009; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=334>. Accessed January 4, 2021.
9. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.01.43 (February 2021).

Documentation for Clinical Review

- No records required

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy. Inclusion or exclusion of codes does not constitute or imply member coverage or provider reimbursement.

Type	Code	Description
CPT®	82948	Glucose; blood, reagent strip
	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)
HCPCS	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
	J1817	Insulin for administration through DME (i.e., insulin pump) per 50 units
	J7050	Infusion, normal saline solution, 250 cc

Policy History

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

Effective Date	Action
02/14/2001	BCBSA Medical Policy adoption
01/07/2011	Policy title change from Pulsatile Intravenous Insulin Therapy (PIVIT) for Type 1 Diabetes Mellitus (a.k.a. PIVIT or CIIT) Policy revision without position change
09/30/2014	Policy title change from Chronic Intermittent Intravenous Insulin Therapy (CIIT) Policy revision without position change
04/01/2016	Policy revision without position change
04/01/2017	Policy revision without position change
04/01/2018	Policy revision without position change
04/01/2019	Policy revision without position change
04/01/2020	Annual review. No change to policy statement. Literature review updated.
04/01/2021	Annual review. No change to policy statement. Literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

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 at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 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.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	AFTER
Chronic Intermittent Intravenous Insulin Therapy 2.01.43 Policy Statement: Chronic intermittent intravenous insulin therapy is considered investigational .	Chronic Intermittent Intravenous Insulin Therapy 2.01.43 Policy Statement: Chronic intermittent intravenous insulin therapy is considered investigational .