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## Medical Policy



### Title: **Chronic Intermittent Intravenous Insulin Therapy**

<b>Professional</b>	<b>Institutional</b>
Original Effective Date: December 9, 2016	Original Effective Date: December 9, 2016
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<b>Populations</b>	<b>Interventions</b>	<b>Comparators</b>	<b>Outcomes</b>
Individuals: • With type 1 diabetes	Interventions of interest are: • Chronic intermittent intravenous insulin therapy	Comparators of interest are: • Standard medical management	Relevant outcomes include: • Symptoms • Change in disease status • Treatment-related morbidity

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## **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.

## **OBJECTIVE**

The objective of this evidence review is to evaluate whether the use of chronic intermittent intravenous insulin therapy improves the net health outcome, including glycemic control, and reduces end-organ damage outcomes for patients with type 1 diabetes, compared with standard insulin therapy.

## **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.<sup>1</sup> 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).

## **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

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substantially equivalent to existing devices for the delivery of intravenous medications. FDA product code: IZG.

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## **POLICY**

Chronic intermittent intravenous insulin therapy is considered **experimental / 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).

**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.**

## **RATIONALE**

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through January 4, 2022. December 21, 2020.

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 (CIIIT) 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.

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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.<sup>2</sup> 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.<sup>3</sup> 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.

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### **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.<sup>3</sup> All patients received 4 daily injections of insulin (type of insulin not described); additional oral drug therapy, if any, was not described. Racial and ethnic demographics of study patients were 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<sub>1c</sub> (HbA<sub>1c</sub>) 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.<sup>3,4</sup>

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.<sup>5</sup> The 26 patients were randomized to a control group (Group B) or a treatment group (Group A) for 3 months and then crossed over for an additional 3 months. Racial and ethnic demographics of study patients were noted as follows: Group A (n=13), 85% White, 15% Hispanic/Latino; Group B (n=13), 100% White. At baseline, all patients were being treated with 4 daily insulin injections and had achieved acceptable HbA<sub>1c</sub> 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

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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: Glycemic Control**

One nonblinded RCT and a case series reporting on the effect of CIIIT on glycemic control in type 1 diabetes were identified. Both studies reported improvements: one in HbA<sub>1c</sub> 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 CIIIT on the progression of nephropathy and retinopathy in 65 subjects with type 1 diabetes.<sup>6</sup> Patients were randomized to standard therapy of 3 to 4 daily subcutaneous insulin injections (n=29; control group) or standard therapy plus weekly CIIIT (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<sub>1c</sub> levels, and renal function (average creatinine, 1.59 mg/dL; average creatinine clearance [CrCl], 60.6 mL/min). Racial and ethnic demographics of study patients were not described. Primary endpoints were a progression of diabetic retinopathy and nephropathy. There was no significant difference in the 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 CrCl 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 CIIIT on the progression of diabetic nephropathy.<sup>7</sup> 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 CIIIT plus intensive therapy. Racial and ethnic demographics of study patients were not described. Both groups reported a significant decrease in HbA<sub>1c</sub> 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**

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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 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 CIIIT, 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 CIIIT might improve glycemic control. The 2 RCTs have 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 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**

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### **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.

### **American Diabetes Association**

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.<sup>8</sup> American Diabetes Association. 9. Pharmacologic Ap... | 1): S111-S124. PMID 33298420]. There is no mention of chronic intermittent intravenous insulin therapy (CIIIT).



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

Not applicable.

**Ongoing and Unpublished Clinical Trials**

A search for active or recruiting clinical trials in January 2022December 2020 did not yield results for trials that might influence this review

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## CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. This may not be a comprehensive list of procedure codes applicable to this policy.

Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. 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.

The code(s) listed below are medically necessary ONLY if the procedure is performed according to the "Policy" section of this document.

<b>CPT/HCPCS</b>	
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)
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

## ICD-10 DIAGNOSES

Experimental / Investigational for all diagnoses related to this medical policy.

## REVISIONS

12-09-2016	Policy added to the bcbsks.com web site on 11-09-2016 with an effective date of 12-09-2016.
03-15-2017	Updated Description section.
	Updated Rationale section.
	In Coding section: ▪ Updated coding bullets.
	Updated References section.
03-28-2018	Updated Description section.
	Updated Rationale section.

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<b>REVISIONS</b>	
	Updated References section.
03-27-2019	Updated Description section.
	Updated Rationale section.
	In Coding section: <ul style="list-style-type: none"> <li>▪ Removed CPT codes: 94681, 99070, 99211.</li> </ul>
	Updated References section.
03-1-2021	Updated Description section
	Updated Rationale section
	Updated Reference section
03-23-2022	Updated Description Section
	Updated Rationale Section
	Updated References Section
03-23-2022	Archived

## REFERENCES

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9. 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, 2022.