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## OVERVIEW

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.

## MEDICAL CRITERIA

Not applicable

## PRIOR AUTHORIZATION

Not applicable

## POLICY STATEMENT

### BlueCHiP for Medicare

Chronic intermittent intravenous insulin therapy is considered not covered as the evidence is insufficient to determine the effects of the technology on health outcomes.

### Commercial Products

Chronic intermittent intravenous insulin therapy is considered not medically necessary as the evidence is insufficient to determine the effects of the technology on health outcomes.

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage, or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

## 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 noninsulin-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, 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. CIIT 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.

For individuals who have type 1 diabetes who receive CIIT, the evidence includes two 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 CIIT might improve glycemic control. The 2 RCTs 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 studies is uncertain. Additionally, most published evidence appeared between 1993 and 2010 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.

### **CODING**

The following code is not covered for BlueCHIP for Medicare and not medically necessary for Commercial Products:

**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.

### **RELATED POLICIES**

Not applicable

### **PUBLISHED**

Provider Update, July 2019

Provider Update, September 2018

Provider Update, May 2017

### **REFERENCES**

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