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Intermittent Intravenous Insulin Therapy

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None

Disclaimer

Carefully check state regulations and/or the member contract.
Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Coverage

Intermittent intravenous insulin therapy, also known by other names, including but not limited to pulsatile intravenous insulin therapy (PIVIT), pulse insulin therapy, chronic intermittent intravenous insulin therapy (CIIIT), outpatient intravenous insulin treatment/therapy (OIVIT), hepatic activation therapy, metabolic activation therapy, and Trina Health®'s Artificial Pancreas Treatment®/Microburst Insulin® infusion, **is considered experimental, investigational and/or unproven** for all indications.

NOTE: 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).

Policy Guidelines

The HCPCS code G9147 is specific to outpatient intravenous insulin treatment (OIVIT).

Description

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

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.

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: lZG.

Rationale

This policy was originally created in 2005 and has been updated regularly with searches of the PubMed database. The most recent literature review is through September 19, 2024.

Medical policies assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 to 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 a technology, 2 domains are examined: the relevance, and the quality and credibility. To be relevant, studies must represent one 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.

Intermittent Intravenous Insulin Therapy for Type 1 Diabetes

Clinical Context and Therapy Purpose

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

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

Populations

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

Interventions

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

Intermittent intravenous insulin therapy, also known by other names, including but not limited to pulsatile intravenous insulin therapy (PIVIT), pulse insulin therapy, chronic intermittent intravenous insulin therapy (CIIIT), outpatient intravenous insulin treatment/therapy (OIVIT), hepatic activation therapy, metabolic activation therapy, and Trina Health®'s Artificial Pancreas Treatment®/Microburst Insulin® infusion—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) Intermittent intravenous insulin therapy principally designed to normalize the hepatic metabolism of glucose. Currently, no studies have been identified that have investigated the proposed mechanism of action of CIIIT 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.

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.

Individuals with Type 1 diabetes mellitus require lifelong medical monitoring of glycemic control and end-organ status. Informal publication has indicated that individuals have been treated with intermittent intravenous insulin therapy 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.

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. 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_{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 CIIIT. (3, 4)

In 1995, Aoki et al. also examined the effect of CIIIT 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 (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_{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 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 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 CIIIT is uncertain.

Reductions in Diabetic End-Organ Damage

Weinrauch et al. (2010) published an RCT of the effects of pulsatile insulin infusion 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 infusion (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 [CrCl], 60.6 mL/min). Racial and ethnic demographics were not described. 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 CrCl 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 pulsatile intravenous insulin therapy 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. Racial and ethnic demographics of study patients were not described. 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: 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_{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. 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 intermittent intravenous insulin therapy, 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 intermittent intravenous insulin therapy might improve glycemic control. The 2 RCTs have reported that intermittent intravenous insulin therapy 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 the technology results in an improvement in the net health outcome.

Practice Guidelines and Position Statements

American Diabetes Association

The 2024 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) The guidelines make no mention of intermittent intravenous insulin therapy.

American Association of Clinical Endocrinology

In 2022, the American Association of Clinical Endocrinology updated its 2015 clinical practice guideline for developing a diabetes mellitus comprehensive care plan. (8) The guideline includes

evidence-based recommendations for the comprehensive care of people with both type 1 and type 2 diabetes; recommendations are divided up into 4 sections: screening, diagnosis, targets, and monitoring; comorbidities and complications; management; education and new topics regarding diabetes. There is no mention of CIIIT.

Ongoing and Unpublished Clinical Trials

A search for active or recruiting clinical trials in September 2024 did not yield results for trials that might influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	None
HCPCS Codes	G9147

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <http://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
11/15/2024	Document updated with literature review. Coverage unchanged. References 3, 8, 9 added; some updated; others removed.
11/15/2023	Reviewed. No changes.
05/01/2022	Document updated with literature review. Coverage unchanged. The following references were added/updated: 1, 8.
07/01/2021	Reviewed. No changes.
05/15/2020	Document updated with literature review. Coverage unchanged. Reference 6 added.
04/15/2019	Reviewed. No changes.
12/15/2018	Document updated with literature review. Coverage has changed to the following: Intermittent intravenous insulin therapy, also known by other names, including but not limited to pulsatile intravenous insulin therapy (PIVIT), pulse insulin therapy, chronic intermittent intravenous insulin therapy (CIIIT), outpatient intravenous insulin treatment/therapy (OIVIT), hepatic activation therapy, metabolic activation therapy, and Trina Health®'s Artificial Pancreas Treatment®/Microburst Insulin® infusion is considered experimental, investigational and/or unproven for all indications. Title has changed from Chronic Intermittent Intravenous Insulin Therapy (CIIIT). Reference 10 added.

06/01/2017	Document updated with literature review. Coverage unchanged.
05/15/2016	Reviewed. No changes.
08/15/2015	Document updated with literature review. Coverage unchanged.
09/15/2014	Reviewed. No changes.
06/15/2013	Document updated with literature review. Coverage unchanged.
08/01/2011	Document updated with literature review. Coverage unchanged. CPT/HCPCS codes added.
09/01/2007	Revised/Updated Entire Document
05/01/2005	New Medical Document