INTERMITTENT INTRAVENOUS INSULIN THERAPY

Policy Number: 2014T0502H
Effective Date: May 1, 2014

INSTRUCTIONS FOR USE
This Medical Policy provides assistance in interpreting UnitedHealthcare benefit plans. When deciding coverage, the enrollee specific document must be referenced. The terms of an enrollee's document (e.g., Certificate of Coverage (COC) or Summary Plan Description (SPD) and Medicaid State Contracts) may differ greatly from the standard benefit plans upon which this Medical Policy is based. In the event of a conflict, the enrollee's specific benefit document supersedes this Medical Policy. All reviewers must first identify enrollee eligibility, any federal or state regulatory requirements and the enrollee specific plan benefit coverage prior to use of this Medical Policy. Other Policies and Coverage Determination Guidelines may apply. UnitedHealthcare reserves the right, in its sole discretion, to modify its Policies and Guidelines as necessary. This Medical Policy is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. The MCG™ Care Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

BENEFIT CONSIDERATIONS

Essential Health Benefits for Individual and Small Group:
For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”). Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs. However, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans. The determination of which benefits constitute EHBs is made on a state by state basis. As such, when using this guideline, it is important to refer to the enrollee’s specific plan document to determine benefit coverage.
Intermittent intravenous insulin therapy (IIIT) is unproven and not medically necessary for reducing symptoms, improving glycemic control or preventing diabetic sequelae in patients with insulin dependent diabetes. There is insufficient evidence in the clinical literature demonstrating the clinical utility of IIIT. The limited number of published studies lack adequate controls, randomization and blinding. Further studies, with larger sample sizes, are necessary to determine the health benefit of IIIT.

Insulin potentiation therapy is unproven and not medically necessary for the treatment of cancer, infectious diseases, arthritis and other conditions. There is inadequate evidence in the peer-reviewed, published clinical literature demonstrating that this therapy is safe and/or effective.

The codes listed in this policy are for reference purposes only. Listing of a service or device code in this policy does not imply that the service described by this code is a covered or non-covered health service. Coverage is determined by the benefit document. This list of codes may not be all inclusive.

<table>
<thead>
<tr>
<th>HCPCS Code</th>
<th>Description</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>G9147</td>
<td>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.</td>
<td></td>
</tr>
</tbody>
</table>

For approximately 1% of insulin-dependent diabetics, conventional intensive insulin therapy (IIT) by subcutaneous injection or pump does not adequately control the symptoms of diabetes or prevent progression to significant diabetic complications such as nephropathy, neuropathies and hypertension (DCCT, 1993). While the reason for this lack of response to conventional IIT is not well understood, it is known that in nondiabetic subjects, pancreatic cells release insulin in a pulsatile manner in response to ingested glucose and carbohydrates (Lang, 1979). The high pulses of insulin are believed to be necessary to fully activate hepatic enzymes that metabolize glucose, inhibit the liver's endogenous production of glucose and possibly carry out other protective and homeostatic functions (Bratusch-Marrain, 1986). Also, the insulin level in the hepatic portal vein is many times higher than in the peripheral blood, with almost 50% being removed on the first pass through the liver (Waldhausl, 1982). It is hypothesized that for some patients, the failure of subcutaneous insulin infusion to mimic the natural pulsatile pattern and failure to achieve high levels of insulin in the portal vein results in progressive deleterious processes, despite normal levels of insulin in the peripheral blood (Foss, 1982; Aoki, 2001).

Intermittent intravenous insulin therapy (IIIT) does not replace conventional IIT, but rather is an addition to it. IIIT is initially carried out over 2 days, and thereafter is performed 1 day a week (Aoki, 1993). Three times on each day of treatment, an ingested glucose challenge is treated with 7 to 10 intravenous (IV) insulin pulses over 1 hour. Insulin dose is tailored to respond adequately to the glucose challenge. The rationale behind this treatment regimen is that some of the hepatic enzymes have long half-lives, and therefore a once weekly treatment schedule is believed to be adequate for effect (Aoki, 1993).

The pulsatile nature of natural insulin release and the metabolic functions of the liver are not controversial. However, a number of questions remain regarding the efficacy of and necessity for IIIT (Heinemann, 2001). Published trials have been small and have not employed randomization or double blinding, and most have been carried out by the major proponent of the technique who...
Intermittent Intravenous Insulin Therapy runs a center for its application. It is suspected that some of the apparent positive effects of IIIT could result from the higher circulating insulin levels that IIIT causes, as well as heightened attention and vigilance on the part of patients and clinicians involved in a trial. In addition, the clinical significance of some of the effects of IIIT is not clear.

Insulin potentiation therapy (IPT) is based on the assumption that intravenous insulin increases the effect of medications so that lower doses of these medications can be used. Practitioners of this therapy suggest that insulin "opens the pores" of cells throughout the body allowing certain drugs to enter more easily. The treatment of cancer is the main focus, but IPT has been used for other diseases.

According to proponents of this therapy, cancer cells have 20 times more insulin sensitive receptors than normal healthy cells. By introducing insulin into the body before the chemotherapy drugs, the insulin highlights the cancer cells due to their higher insulin receptor content and thereby enhancing the absorption of the chemotherapy. Therefore, a lower dose of chemotherapy is needed and there are fewer dose related side effects (Ayre, 2000).

IPT is performed by injecting intravenous insulin. After the blood glucose falls, chemotherapeutic, antibiotic or other agents are injected. The drugs used are in lower doses than the amounts that have been proven to be effective. Then a strong glucose solution is infused to raise the blood glucose. The practitioners who perform this procedure are trained in two-day courses and then become "licensed" to perform IPT. However, there is no evidence that any regulatory body oversees these licenses (Baratz, 2007).

CLINICAL EVIDENCE

The clinical evidence was reviewed on February 14, 2014 with no additional information identified that would change the unproven and not medical necessary conclusion.

Intermittent Intravenous Insulin Therapy

Weinrauch et al. (2010) conducted a trial of multiple daily insulin doses with or without the addition of weekly pulsatile intravenous insulin infusion therapy (PIVIT) to determine the effect on kidney and retinal function. Patients were randomized to the PIVIT group (n=36) or the standard therapy group (n=29). Serum creatinine increased to 1.7 mg/dL in the treatment group and to 1.9 mg/dL in the control group. Statistically significant preservation of renal function by pulsatile insulin infusion was not matched by a statistically significant prevention of diabetic retinopathy (DR) progression compared with standard diabetes care. The authors concluded that inadequate statistical power, duration of the study or lack of further benefit of pulsatile insulin infusion on the retina in the presence of angiotensin-converting enzyme inhibition may be responsible.

In a pilot study, Weinrauch et al. (2007) evaluated the effect of pulsatile insulin infusion on cardiovascular mechanisms that might contribute to attenuation of renal compromise in type 1 diabetes mellitus patients with proteinuria. The control group (8 patients) received subcutaneous insulin (3-4 injections per day). The intravenous infusion group (10 patients) received three 1-hour courses of pulsed intravenous insulin infusion on a single day per week in addition to subcutaneous insulin. Laboratory measurements included 2-dimensional Doppler echocardiography, 24-hour ambulatory monitoring with heart rate variation analysis, platelet aggregation and adhesion, plasma fibrinogen, factor VII, von Willebrand factor, fibrinolytic activity, plasminogen activator inhibitor and viscosity measured at baseline and 12 months. Blood pressure control was maintained preferentially with angiotensin-converting enzyme inhibitors. Ratio of carbon dioxide production to oxygen utilization was measured with each infusion and showed rapid increase from 0.8 to 0.9 (P = .005) at weekly treatments through 12 months. The authors observed an annualized decrease in creatinine clearance of 9.6 mL/min for controls vs 3.0 mL/min for infusion patients. Annualized fall in blood hemoglobin was 1.9 vs 0.8 g/dL, respectively (P = .013). There were no differences between the control and infusion group with respect to glycohemoglobin, advanced glycated end products, cholesterol or triglycerides. No
differences between the study groups for hemodynamic or hemostatic factors were evident. Blood pressures were not significantly different at baseline or 12 months. The authors concluded that although preservation of renal function with attenuation of loss of blood hemoglobin during 12 months of intravenous insulin infusion was associated with improvement in the efficiency of fuel oxidation as measured by respiratory quotient, this occurred without differences in metabolic/hemostatic factors, cardiac autonomic function, cardiac wall, or chamber size. The hypothesis that preservation of renal function in type 1 diabetes mellitus patients with proteinuria by weekly pulsed insulin infusion involves mechanisms from the autonomic nervous system, cardiac size, and function, or elements of hemostasis was not confirmed.

One early study tracking plasma glucose control as an outcome of IIIT published negative results; insulin pulsing did not improve glycemic control, and glucose tolerance was actually worse after treatment than before (Heinemann, 1989). However, this was a prospective before-and-after trial with no parallel controls and the weakness of the study design, as well as the very small sample size (n=9), preclude conclusions regarding IIIT. A slightly larger trial (n=20) of the same design reported better glycemic control when patients received IIIT, as well as fewer major and minor hypoglycemic episodes. However, the lack of a parallel control group hampers evaluation of the magnitude of treatment effect of IIIT (Aoki, 1993).

Two studies examined both glycemic control and, as an indicator of the progression of diabetic nephropathy, annual rate of decline in creatinine clearance. The first study was a retrospective examination of before-and-after results in 31 diabetics with overt nephropathy (Aoki 1999). At a mean of 37 months following initiation of IIIT, blood glucose control was improved, and the annual rate of decline in creatinine clearance was less than that reported in the literature. These results are supported by a multicenter RCT of 90 type 1 diabetics with overt nephropathy (Dailey, 2000). Glycemic control, as indicated by HbA1c levels, improved similarly in both IIIT and control groups:

- Controls: baseline 9.13%; after 18 months 8.19%
- IIIT Group: baseline 8.61%; after 18 months 7.68%

However, the rate of decline in creatinine clearance was slowed in the IIIT group compared with the control group:
- Controls: 7.69 mL/min/year
- IIIT Group: 2.21 mL/min/year

The authors believed it was not possible to blind patients and clinicians using sham IIIT. However, they attempted to control for changes due to close monitoring and attention by having the control patients come in for examination and IIIT vigilance instruction. A weakness of the study is that the additional insulin used in the IIIT regimen may have resulted in better blood glucose control, independent of method of administration; thus, it is not possible to reliably attribute the positive trial results solely to IIIT. In addition, only 55% of patients originally enrolled in the trial completed 18 months of treatment.

Using a different outcome measure, a randomized crossover trial (n=26) examined the effect of IIIT on hypertension control, as measured by the amount of hypertension medication required to maintain acceptable blood pressure in type 1 diabetics (Aoki, 1995a). The average decline in medication at the end of 3 months of IIIT was 46.5%, a statistically significant reduction. While it is difficult to attribute this decline in medication to anything other than IIIT, there was acceptable blood pressure control both with and without IIIT. Therefore, the clinical significance of this result is unclear. Additional studies that examined the effect of IIIT on diurnal variation in blood pressure (Aoki, 1995b), and orthostatic hypotension (decreased blood pressure immediately after standing up) (Aoki, 1995c) were also performed by the same research group.

Insulin Potentiation Therapy
Despite individual reports, there are no published scientific studies available showing that insulin
potentiation therapy (IPT) is safe or effective in treating cancer in humans. IPT may have serious side effects (American Cancer Society, 2008).

FDA approval for a clinical study was obtained in 2000. To maintain this approval, an Institutional Review Board had to approve the clinical study. The "review board" that approved the study was composed of possibly unqualified practitioners and was ordered to shut down in January 2001 after the FDA concluded that it was run improperly. IPT for cancer treatment remains off-label use.

Only one small non-US randomized controlled study with short term follow-up in breast cancer patients has been published in the peer-reviewed medical literature.

Lasalvia-Prisco et al. (2004) who reported on 30 patients (3 groups of 10) randomized to receive two 21-day courses of insulin with methotrexate (IPT), methotrexate alone, or insulin alone. Patients had metastatic breast cancer that was resistant to fluorouracil, adriamycin, and cyclophosphamide as well as hormone therapy if they had a positive estrogen receptor status. The primary outcome assessed at 8 weeks after initiation of treatment was tumor response using the Response Evaluation Criteria In Solid Tumors (RECIST) system. Using the RECIST disease status, 9 patients in the IPT group were considered stable, and 1 progressive versus 7 progressive and 3 stable in the methotrexate only group and 8 progressive and 2 stable diseases in the insulin-only group. In addition, the IPT group had significantly lower increases in tumor size than the methotrexate-only and the insulin-only treatment groups. Toxicities were low in both the IPT group and the methotrexate only group as the individual methotrexate dosage of 2.5 mg/m² used in the study was lower than optimal. The authors suggest this supports the theory that the antitumoral effects of methotrexate were potentiated by the insulin. While this study may suggest insulin enhances some biochemical event with the administration of chemotherapy in the short term, it does not report on any long term effects or health outcomes. Therefore, further studies are needed to demonstrate any improvements in health outcomes with the use of insulin potentiation therapy.

Additional search terms
Cellular activation therapy, hepatic activation therapy, intercellular activation therapy, metabolic activation therapy, pulsatile intravenous (IV) insulin treatment, pulse insulin therapy and pulsatile therapy.

Professional Societies
Clinical practice guidelines from relevant professional organizations such as the American Diabetes Association and the American Association of Clinical Endocrinologists do not identify intermittent intravenous insulin therapy or insulin potentiation therapy as a treatment for diabetes or other conditions.

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

As a procedure, intermittent intravenous insulin therapy does not require FDA approval; however, drugs and devices used in the procedure have received FDA approval.

Typically, insulin potentiation therapy is described as an off label use of insulin. The FDA regulates the sale of drugs and approves the labeling of drugs for particular uses. However, under some circumstances a drug indicated for one use can be used for another or may be used at dosages higher than those on the label.

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS)

Medicare does not cover outpatient intravenous (IV) insulin therapy (OIVIT). Refer to the National Coverage Determination (NCD) for Outpatient Intravenous Insulin Treatment (40.7). Local Coverage Determinations (LCDs) do not exist at this time. (Accessed February 14, 2014)
REFERENCES


<table>
<thead>
<tr>
<th>Date</th>
<th>Action/Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>05/01/2014</td>
<td>• Reorganized policy content</td>
</tr>
<tr>
<td></td>
<td>• Added benefit considerations language for Essential Health Benefits for Individual and Small Group plans to indicate:</td>
</tr>
<tr>
<td></td>
<td>• For plan years beginning on or after January 1, 2014, the Affordable Care Act of 2010 (ACA) requires fully insured non-grandfathered individual and small group plans (inside and outside of Exchanges) to provide coverage for ten categories of Essential Health Benefits (“EHBs”)</td>
</tr>
<tr>
<td></td>
<td>• Large group plans (both self-funded and fully insured), and small group ASO plans, are not subject to the requirement to offer coverage for EHBs; however, if such plans choose to provide coverage for benefits which are deemed EHBs (such as maternity benefits), the ACA requires all dollar limits on those benefits to be removed on all Grandfathered and Non-Grandfathered plans</td>
</tr>
<tr>
<td></td>
<td>• The determination of which benefits constitute EHBs is made on a state by state basis; as such, when using this guideline, it is important to refer to the enrollee’s specific plan document to determine benefit coverage</td>
</tr>
<tr>
<td></td>
<td>• Updated coverage rationale; added language to indicate the</td>
</tr>
</tbody>
</table>
unproven services are “not medically necessary”
- Archived previous policy version 2013T0502G