

Insulin Infusion Pumps, Automated Insulin Delivery and Artificial Pancreas Device Systems

Effective: January 1, 2021

Next Review: October 2021

Last Review: November 2020

IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

An external insulin infusion pump is typically used to deliver insulin into patients with diabetes mellitus. Automated insulin delivery systems (including but not limited to artificial pancreas devices) monitor glucose levels and automatically adjust the delivery of insulin to help achieve tight glucose control.

MEDICAL POLICY CRITERIA

Note: This policy is does not address stand-alone continuous glucose monitors (CGM) which may be considered medically necessary.

- I. An *automated insulin delivery system* (including artificial pancreas devices) may be considered **medically necessary** for diabetes mellitus when either of the following Criteria are met:
 - A. The patient has type 1 diabetes mellitus and all of the following Criteria (1. – 3.) are met:

1. The device is approved by the Food and Drug Administration (FDA) and the patient meets the FDA approved age requirements for the device (see Policy Guidelines); and
 2. Glycated hemoglobin level (Hemoglobin A1c or HbA1c) between 5.8% and 10.0%; and
 3. Used insulin pump therapy for more than 3 months.
- B. The patient has gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia).
- II. An *external insulin infusion pump* may be considered **medically necessary** for diabetes mellitus when either of the following Criteria are met:
- A. The patient has type 1 or 2 diabetes mellitus when all of the following Criteria (1. and 2.) are met:
1. The patient has been performing insulin injections every day with self-adjustments of insulin dose for at least 3 months prior to initiation of the insulin pump and either of the following Criteria are met:
 - a. A healthcare provider documents that the patient has a frequency of glucose self-testing an average of at least 3 times per day during the 2 months prior to initiation of the insulin pump; or
 - b. A healthcare provider documents the use of a continuous glucose monitor.
 2. The patient meets one or more of the following Criteria:
 - a. Glycated hemoglobin level (HbA1c) greater than 7%; or
 - b. History of recurring hypoglycemia; or
 - c. Wide fluctuations in blood glucose before mealtime; or
 - d. Dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dL; or
 - e. History of severe glycemic excursions.
- B. The patient has gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia).
- III. A replacement for all or part of the *external insulin pump* or FDA-approved *automated insulin delivery system* (including artificial pancreas device systems) may be considered **medically necessary** when both of the following Criteria (A. and B.) are met:
- A. The pump is no longer able to perform its basic function due to one or more of the following:
1. Device is out of the warranty period; or
 2. Damage or wear; or

- 3. The device can no longer meet the patient's medical needs due to a significant change in the patient's medical condition (e.g., larger insulin reservoir needed).
- B. The current device cannot be repaired or adapted adequately to meet the patient's medical needs.
- IV. The use of an *external insulin infusion pump* is considered **not medically necessary** when Criterion II. is not met.
- V. A replacement for all or part of the *external insulin pump* or FDA-approved *automated insulin delivery system* (including artificial pancreas device systems) that does not meet Criterion III. is considered **not medically necessary**.
- VI. The use of an *automated insulin delivery system* (including artificial pancreas device systems) is considered **investigational** when Criterion I. is not met including but not limited to a device that is not approved by the FDA.

NOTE: A summary of the supporting rationale for the policy criteria is at the end of the policy.

POLICY GUIDELINES

FDA-Approved Automated Insulin Delivery Systems (Artificial Pancreas Device Systems)

Device	Age Indication	Manufacturer
MiniMed™ 530G System ^a (open-loop, LGS)	≥16 years	Medtronic
MiniMed™ 630G System with SmartGuard™ ^b (open-loop, LGS):		Medtronic
○ MiniMed™ 630G with Guardian™ Sensor 3	≥14 years	
○ MiniMed™ 630G with Enlite™ Sensor	≥16 years	
MiniMed™ 670G System ^c (hybrid closed-loop, LGS or PLGM)	≥7 years	Medtronic
MiniMed™ 770G System ^d (hybrid closed-loop, LGS or PLGM)	≥2 years ^e	Medtronic
t:slim X2 Insulin Pump with Basal-IQ Technology (LGS)	≥6 years	Tandem
t:slim X2 Insulin Pump with Control-IQ Technology (HCL)		

^a MiniMed 530G System consists of the following devices that can be used in combination or individually: MiniMed 530G Insulin Pump, Enlite™ Sensor, Enlite™ Serter, the MiniLink Real-Time System, the Bayer Contour NextLink glucose meter, CareLink® Professional Therapy Management Software for Diabetes, and CareLink® Personal Therapy Management Software for Diabetes (at time of approval).

^b MiniMed 630G System with SmartGuard™ consists of the following devices: MiniMed 630G Insulin Pump, Enlite® Sensor, One-Press Serter, Guardian® Link Transmitter System, CareLink® USB, Bayer's CONTOUR® NEXT LINK 2.4 Wireless Meter, and Bayer's CONTOUR® NEXT Test Strips (at time of approval).

^c MiniMed 670G System consists of the following devices: MiniMed 670G Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), One-Press Serter, and the Contour NEXT Link 2.4 Glucose Meter (at time of approval).

^d MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide Link blood glucose meter, and the Accu-Chek Guide Test Strips. The system requires a prescription. ^eThe 770G System may not be safe for use in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.

LIST OF INFORMATION NEEDED FOR REVIEW

REQUIRED DOCUMENTATION:

The information below **must** be submitted for review to determine whether policy criteria are met. If any of these items are not submitted, it could impact our review and decision outcome.

- Automated insulin delivery system (artificial pancreas device system)
 - History and physical
 - Age of patient
 - Name and type of device requested
 - Documented use of insulin pump for more than 3 months
 - When applicable, documentation of gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia)

- External insulin infusion pumps
 - History and physical
 - Name and type of device requested
 - Medical record documentation stating both of the following:
 - The patient has been performing insulin injections every day with self-adjustments of insulin dose for at least 3 months prior to initiation of the insulin pump; and
 - There is documented frequency of glucose self-testing an average of at least 3 times per day during the 2 months prior to initiation of the insulin pump OR a healthcare provider documents the use of a continuous glucose monitor with documentation of one or more of the following: glycated hemoglobin level (HbA1c) greater than 7%; history of recurring hypoglycemia; wide fluctuations in blood glucose before mealtime; dawn phenomenon with fasting blood sugars frequently exceeding 200 mg/dL; and/or history of severe glycemic excursions
 - When applicable, documentation of gestational diabetes or preconception/pregnancy related suboptimal glycemic control (e.g., erratic blood sugars, ketoacidosis, or symptomatic hypoglycemia)

- Replacement and upgrades
 - History and physical
 - Name and type of device requested
 - Documentation of specifically why pump is no longer able to perform its basic function
 - Documentation that the current device cannot be repaired or adapted adequately to meet the patient's needs

CROSS REFERENCES

[Medication Policy Manual](#), Note: Do a find (Ctrl+F) and enter name in the find bar to locate the appropriate policy.

BACKGROUND

Maintenance of a target blood glucose and target glycated hemoglobin (H_gA_{1c} < 7%), a marker which is used as a proxy for average blood glucose, is now considered standard of care for diabetic patients. Also known as tight diabetic control, this strategy is intended to prevent severe hypoglycemic events and lower the risk of cardiovascular disease mortality associated with uncontrolled glycemia.^[1] In order to achieve tight glucose control, several devices may be used individually or in combination which includes but is not limited to continuous glucose monitors, insulin pumps, and more recently artificial pancreas device systems. The Food and Drug Administration (FDA) describes the basic design of an artificial pancreas device system (APDS) as a CGM linked to an insulin pump with the capability to automatically stop, reduce, or increase insulin infusion based on specified thresholds of measured interstitial glucose. The APDS components are designed to communicate with each other to automate the process of maintaining blood glucose concentrations at or near a specified range or target and to minimize the incidence and severity of hypoglycemic and hyperglycemic events. An APDS control algorithm is embedded in software in an external processor or controller that receives information from the CGM and performs a series of mathematical calculations. Based on these calculations, the controller sends dosing instructions to the infusion pump.

Different APDS types are currently available for clinical use. Sensor augmented pump therapy (SAPT) with low glucose suspend (LGS) (suspend on low) may reduce the likelihood or severity of a hypoglycemic event by suspending insulin delivery temporarily when the sensor value reaches (reactive) a predetermined lower threshold of measured interstitial glucose. Low glucose suspension (LGS) automatically suspends basal insulin delivery for up to two hours in response to sensor-detected hypoglycemia.

A sensor augmented pump therapy with predictive low glucose management (PLGM) (suspend before low) suspends basal insulin infusion with the prediction of hypoglycemia. Basal insulin infusion is suspended when sensor glucose is at or within 70 mg/dL above the patient-set low limit and is predicted to be 20 mg/dL above this low limit in 30 minutes. In the absence of a patient response, the insulin infusion resumes after a maximum suspend period of two hours. In certain circumstances, auto-resumption parameters may be used.

When a sensor value is above or predicted to remain above the threshold, the infusion pump will not take any action based on CGM readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-range system reduces the likelihood or severity of a hypoglycemic or hyperglycemic event by adjusting insulin dosing only if a person's glucose levels reach or approach predetermined higher and lower thresholds. When a patient's glucose concentration is within the specified range, the infusion pump will not take any action based upon CGM readings. Patients using this system still need to monitor their blood glucose concentration, set appropriate basal rates for their insulin pump, and give premeal bolus insulin to control their glucose levels.

A control-to-target system sets target glucose levels and always tries to maintain these levels. This system is fully automated and requires no interaction from the user (except for calibration of the CGM). There are two subtypes of control-to-target systems: insulin-only and bihormonal (e.g., glucagon). There are no systems administering glucagon marketed in the United States.

An APDS may also be referred to as a “closed-loop” system. A closed-loop system has automated insulin delivery and continuous glucose sensing and insulin delivery without patient intervention. The systems utilize a control algorithm that autonomously and continually increases and decreases the subcutaneous insulin delivery based on real-time sensor glucose levels. There are no completely closed-loop insulin delivery systems marketed in the United States.

A hybrid closed-loop system also uses automated insulin delivery with continuous basal insulin delivery adjustments. However, at mealtime, the patient enters the number of carbohydrates they are eating for the insulin pump to determine the bolus meal dose of insulin. A hybrid system option with the patient administration of a premeal or partial premeal insulin bolus can be used in either control-to-range or control-to-target systems.

REGULATORY STATUS

There are several APDS devices approved by the Food and Drug Administration (FDA). These systems are regulated by the FDA as class III device systems.

The MiniMed® 530G System includes a threshold suspend or LGS feature.^{2]} The threshold suspend tool temporarily suspends insulin delivery when the sensor glucose level is at or below a preset threshold within the 60- to 90-mg/dL range. When the glucose value reaches this threshold, an alarm sounds. If patients respond to the alarm, they can choose to continue or cancel the insulin suspend feature. If patients fail to respond, the pump automatically suspends action for two hours, and then insulin therapy resumes.

The MiniMed® 630G System with SmartGuard™, which is similar to the 530G, includes updates to the system components including waterproofing.^{3]} The threshold suspend feature can be programmed to temporarily suspend delivery of insulin for up to two hours when the sensor glucose value falls below a predefined threshold value. The MiniMed 630G System with SmartGuard™ is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a finger stick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on the values provided by the MiniMed 630G system. The device is not intended to be used directly for preventing or treating hypoglycemia but to suspend insulin delivery when the user is unable to respond to the SmartGuard™ Suspend on Low alarm to take measures to prevent or treat hypoglycemia themselves.

The MiniMed® 670G System is a hybrid closed-loop insulin delivery system consisting of an insulin pump, a glucose meter, and a transmitter, linked by a proprietary algorithm and the SmartGuard Hybrid Closed Loop.^{4]} The system includes an LGS feature that suspends insulin delivery; this feature either suspends delivery on low-glucose levels or suspends delivery before low-glucose levels, and has an optional alarm (manual mode). Additionally, the system allows semiautomatic basal insulin-level adjustment (decrease or increase) to preset targets (automatic mode). As a hybrid system; basal insulin levels are automatically adjusted, but the patient needs to administer premeal insulin boluses. The CGM component of the MiniMed 670G System is not intended to be used directly for making manual insulin therapy adjustments; rather it is to provide an indication of when a glucose measurement should be taken.

On August 31, 2020, the MiniMed® 770G System received Premarket Approval from the FDA.^[5] The 770G System was approved as a supplement to the previously approved MiniMed

670G System. Approval of the MiniMed 770G System expanded the indications for use to users down to two years old and updated the pump communication protocol to Bluetooth. The 770G System is a hybrid closed loop system that measures glucose levels and automatically adjusts insulin delivery by either administering or withholding insulin. The 770G System consists of the MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide Link blood glucose meter, and the Accu-Chek Guide Test Strips. The system requires a prescription. The 770G System was approved for the following indications:

The MiniMed 770G system is intended for continuous delivery of basal insulin (at user selectable rates) and administration of insulin boluses (in user selectable amounts) for the management of type 1 diabetes mellitus in persons two years of age and older requiring insulin as well as for the continuous monitoring and trending of glucose levels in the fluid under the skin. The MiniMed 770G System includes SmartGuard technology, which can be programmed to automatically adjust delivery of basal insulin based on continuous glucose monitoring (CGM) sensor glucose values and can suspend delivery of insulin when the sensor glucose value falls below or is predicted to fall below predefined threshold values.

The Medtronic MiniMed 770G System consists of the following devices: MiniMed 770G Insulin Pump, the Guardian Link (3) Transmitter, the Guardian Sensor (3), one-press serter, the Accu-Chek Guide™ Link blood glucose meter, and the Accu-Chek Guide™ Test Strips. The system requires a prescription.

The Guardian Sensor (3) has not been evaluated and is not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. All therapy adjustments should be based on measurements obtained using a blood glucose meter and not on values provided by the Guardian Sensor (3).

Per the FDA approval, a prominent boxed warning is included in the labeling regarding use of the 770G System in users with a total daily insulin dose of less than 8 units, “Medtronic performed an evaluation of the 770G closed loop system and determined that it may not be safe for use in patients who require less than a total daily insulin dose of 8 units per day because the device requires a minimum of 8 units per day to operate safely.”

On June 21, 2018, the FDA approved the t:slim X2 Insulin Pump with Basal-IQ Technology (PMA P180008) for individuals who are six years of age and older.^[6] The System consists of the t:slim X2 Insulin Pump paired with the Dexcom G5 Mobile CGM (Continuous Glucose Monitor), as well as the Basal-IQ Technology. The t:slim X2 Insulin Pump is intended for the subcutaneous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. The t:slim X2 Insulin Pump can be used solely for continuous insulin delivery and as part of the System as the receiver for a therapeutic CGM. The t:slim X2 Insulin Pump running the Basal-IQ Technology can be used to suspend insulin delivery based on CGM sensor readings. Introduction into clinical care is planned for summer 2019.

In December 2019, FDA approved the t:slim X2 Insulin Pump with Control-IQ Technology through the De Novo process.^[7] The device uses the same pump hardware as the insulin pump component of the systems approved in t:slim X2 Insulin Pump with Basal-IQ Technology (P180008) and P140015. A custom disposable cartridge is motor-driven to deliver patient programmed basal rates and boluses through an infusion set into subcutaneous tissue.

There are many insulin pumps on the market that are approved by the FDA. Insulin infusion pumps that are FDA approved include but are not limited to the Omnipod® System and the Omnipod DASH™ System. FDA 510(k) Product Code: LZG.

EVIDENCE SUMMARY

EXTERNAL INSULIN INFUSION PUMP

Randomized controlled trials (RCTs) have evaluated insulin pumps with various functionalities including a low glucose suspend (LGS) feature.^[8-13] Results of these studies have demonstrated that insulin infusion pumps may, in carefully selected patient populations, control blood glucose to near-normal levels.

ARTIFICIAL PANCREAS DEVICE SYSTEMS

The key clinical outcomes regarding the clinical utility of artificial pancreas device systems (APDSs) relate to their ability to improve morbidity and mortality associated with clinically significant, severe, and acute hypoglycemia or hyperglycemic events.

Low Glucose Suspend Devices

Systematic Review and Technology Assessments

Alotaibi (2020) published the results of a systematic review with meta-analysis on the efficacy and safety of insulin pump therapy with predictive low glucose suspend (PLGS) features in children and adolescents with type 1 diabetes.^[14] RCTs evaluating sensor augmented pump (SAP) with a PLGS feature compared to SAP or insulin pump therapy without SAP in decreasing hypoglycemia in children and adolescents with type 1 diabetes were considered. Although all RCTs with patients aged 2 to 18 years with at least two weeks follow-up were evaluated, only five RCTs with total sample size of 493 children aged 6 to 18 years met inclusion criteria. The risk of bias within studies was low for allocation concealment and random sequence generation was low for most studies. Blinding was not always feasible given the nature of the intervention; three of the studies were open-label, whereas in two of the studies, participants were blinded to the intervention, and in one study the outcome assessors also were blinded to the intervention. Risk of publication bias could not be assessed due to the small number of studies evaluated. Intention-to-treat analysis was used in all studies to account for loss of follow-up. Results indicate there is high quality evidence that PLGS is superior to SAP in decreasing percent of time spent in hypoglycemia (sensor glucose [SG] <3.9 mmol/L [<70 mg/dL]/24 h) and nocturnal hypoglycemia (SG <3.9 mmol [<70 mg/dL]/L/night) with an absolute mean difference of 17.4 min/d (95% CI: -19.2, -15.5) and 26.3 min/night (95% CI: -35.5, -16.7), respectively. Percent time spent in hyperglycemia or episodes of diabetic ketoacidosis were not found to be different between groups. The only study with a duration long enough to assess health related quality of life showed no significant difference from baseline to study completion. The authors concluded that among children and adolescents with type 1 diabetes treated with insulin pump therapy, the utilization of PLGS is superior to SAP in decreasing mild to moderate daytime and nocturnal hypoglycemia without increasing the risk of hyperglycemia, but note that future studies evaluating long-term safety and cost-effectiveness are warranted.

A TEC Assessment (2013) reviewed studies that reported on the use of APDSs in patients with type 1 or type 2 diabetes taking insulin who were 16 years and older.^[15] It included studies that

compared an APDS containing an LGS feature with the best alternative treatment in the above population, had at least 15 patients per arm, and reported on hypoglycemic episodes. A single trial met the inclusion criteria, and the TEC Assessment indicated that, although the trial results were generally favorable, the study was flawed, and further research is needed. Reviewers concluded that there was insufficient evidence to draw conclusions about the impact of an APDS, with an LGS feature, on health outcomes.

Randomized Controlled Trials

Beardsall (2020) published the results of a randomized, open-label, parallel controlled trial in 20 pre-term infants receiving CGM alone supported by a paper algorithm compared to CGM with an additional intervention period of closed-loop CGM. The closed-loop system was comprised of (i) an Enlite CGM sensor, (ii) a laptop computer running a model predictive control algorithm and (iii) two Alaris syringe pumps. All 20 babies remained in the study throughout the intervention period from 48 to 72 hours and the mean (SD) length of glucose data collected in each study arm was 137 (16.4) hours and 136 (8.7) hours for CGM and CGM plus closed loop, respectively. During the intervention period, the median (IQR) time spent in the target range (sensor glucose [SG] 4.0–8.0 mmol/L) was significantly higher in babies in the closed-loop group 91% (78, 99) compared with controls 26% (6-64); $p < 0.001$. In addition, the time spent in the wider target range of 2.6–10.0 mmol/L was higher in the closed-loop group: median 100% compared with control group, median 84%. Lower SG was observed in the closed-loop group median (IQR) 6.2 (6.1-7.1) mmol/L compared with the control group 8.6 (7.4-11.1) mmol/L ($p = 0.002$). Time spent with SG levels < 2.6 mmol/L and glucose variability as measured by the SD of SG were similar between groups. In the postintervention period (post-72 hours), there was qualitatively increased time in both glucose target ranges (4.0–8.0 and 2.6–10.0 mmol/L) in the closed-loop group compared with the control group, but these differences did not reach statistical significance. In the closed-loop study group, two babies had documented episodes of hypoglycemia with blood glucose (BG) < 2.6 mmol/L, both associated with a change of maintenance fluids. In the control study group, no babies had a documented BG value < 2.6 mmol/L. One baby in the control group had an episode lasting 205 min when the SG fell to < 2.6 mmol/L (BG was not checked at this time). Limitations to this study include small sample size, lack of blinding, and short study duration. While Medtronic provided the continuous glucose monitoring systems and sensors, the company had no role in study design, data acquisition, preparation of the manuscript, or decision to publish the study.

Breton (2020) published the results of a multi-site RCT comparing a closed-loop system of insulin delivery (closed-loop group, $n = 78$) and a sensor-augmented insulin pump (control group, $n = 23$) in children 6 to 13 years of age who had type 1 diabetes.^[16] The primary outcome was the percentage of time that glucose levels were in the target range of 70 to 180 mg per deciliter, as measured by CGM. The mean (\pm SD) percentage of time that the glucose level was in the target range over the 16 weeks of treatment increased from $53 \pm 17\%$ at baseline to $67 \pm 10\%$ in the closed-loop group and from $51 \pm 16\%$ to $55 \pm 13\%$ in the control group (mean adjusted difference, 11 percentage points [equivalent to 2.6 hours per day]; 95% confidence interval, 7 to 14; $p < 0.001$). The median percentage of time that the system was in the closed-loop mode was 93% (interquartile range, 91 to 95) for patients in the closed-loop group. No episodes of diabetic ketoacidosis or severe hypoglycemia were noted in either study group.

The single trial assessed in the TEC Assessment was the in-home arm of the Automation to Simulate Pancreatic Insulin Response (ASPIRE) trial, reported by Bergenstal (2013).^[12] This industry-sponsored trial used the Paradigm Veo insulin pump. A total of 247 patients were

randomized to an experimental group, in which a continuous glucose monitor with the LGS feature was used (n=121), or a control group, which used the continuous glucose monitor but not the LGS feature (n=126). Key eligibility criteria were 16-to-70 years old, type 1 diabetes, and HbA1c levels between 5.8% and 10.0%. In addition, patients had to have more than 6 months of experience with insulin pump therapy and at least 2 nocturnal hypoglycemic events (≤ 65 mg/dL) lasting more than 20 minutes during a 2-week run-in phase. The randomized intervention phase lasted three months. Patients in the LGS group were required to use the feature at least between 10 PM and 8 AM. The threshold value was initially set at 70 mg/dL and could be adjusted to between 70 mg/dL and 90 mg/dL. Seven patients withdrew early from the trial; all 247 were included in the intention-to-treat analysis. The primary efficacy outcome was the area under the curve (AUC) for nocturnal hypoglycemia events. This was calculated by multiplying the magnitude (in milligrams per deciliter) and duration (in minutes) of each qualified hypoglycemic event. The primary safety outcome was change in HbA1c levels.

The primary end point, mean (standard deviation [SD]) AUC for nocturnal hypoglycemic events, was 980 (1200) mg/dL/min in the LGS group and 1568 (1995) mg/dL/min in the control group. The difference between groups was statistically significant ($p < 0.001$), favoring the intervention group.

Similarly, the mean AUC for combined daytime and nighttime hypoglycemic events (a secondary outcome) significantly favored the intervention group ($p < 0.001$). Mean (SD) AUC values were 798 (965) mg/dL/min in the intervention group and 1164 (1590) mg/dL/min in the control group. Moreover, the intervention group experienced fewer hypoglycemic episodes (mean, 3.3 per patient-week; SD=2.0) than the control group (mean, 4.7 per patient-week; SD=2.7; $p < 0.001$). For patients in the LGS group, the mean number of times the feature was triggered per patient was 2.08 per 24-hour period and 0.77 each night (10 PM-8 AM). The median duration of nighttime threshold suspend events was 11.9 minutes; 43% of events lasted for less than five minutes, and 19.6% lasted more than two hours. In both groups, the mean sensor glucose value at the beginning of nocturnal events was 62.6 mg/dL. After four hours, the mean value was 162.3 mg/dL in the LGS group and 140.0 mg/dL in the control group.

Regarding safety outcomes and adverse events, change in HbA1c level was minimal, and there was no statistically significant difference between groups. Mean HbA1c levels decreased from 7.26 to 7.24 mg/dL in the LGS group and from 7.21 to 7.14 mg/dL in the control group. During the study period, there were no severe hypoglycemic events in the LGS group and four events in the control group (range of nadir glucose sensor values in these events, 40-76 mg/dL). There were no deaths or serious device-related adverse events.

Before reporting on in-home findings, the ASPIRE researchers (Garg [2012]) published data from the in-clinic arm of the study.^[17] This randomized crossover trial included 50 patients with type 1 diabetes who had at least three months of experience with an insulin pump system. After a 2-week run-in period to verify and optimize basal rates, patients underwent two in-clinic exercise sessions to induce hypoglycemia. The LGS feature on the insulin pump was turned on in one session and off in the other session, in random order. When on, the LGS feature was set to suspend insulin delivery for two hours when levels reached 70 mg/dL or less. The goal of the study was to evaluate whether the severity and duration of hypoglycemia were reduced when the LGS feature was used. The study protocol called for patients to start exercise with glucose levels between 100 mg/dL and 140 mg/dL and to use a treadmill or stationary bicycle until their plasma glucose levels were 85 mg/dL or less. The study outcome (duration of

hypoglycemia) was defined as the period of time glucose values were lower than 70 mg/dL and above 50 mg/dL, and hypoglycemia severity was defined as the lowest observed glucose value. A successful session was defined as an observation period of 3 to 4 hours and with glucose levels above 50 mg/dL. Patients who did not attain success could repeat the experiment up to three times.

The 50 patients attempted 134 exercise sessions; 98 of them were successful. Duration of hypoglycemia was significantly shorter during the LGS-on sessions (mean, 138.5 minutes; SD=68) than the LGS-off sessions (mean, 170.7 minutes; SD=91; $p=0.006$). Hypoglycemia severity was significantly reduced in the LGS-on group. The mean (SD) lowest glucose level was 59.5 (72) mg/dL in the LGS-on group and 57.6 (5.7) mg/dL in the LGS-off group ($p=0.015$). Potential limitations of the Garg study included evaluation of the LGS feature in a research setting and short assessment period.

A second RCT evaluated the in-home use of the Paradigm Veo System.^[18] The trial by Ly (2013) in Australia was excluded from the 2013 TEC Assessment due to the inclusion of children and adults and lack of analyses stratified by age group (the artificial pancreas system approved in the United States at the time of the review was only intended for individuals ≥ 16 years). The Ly trial included 95 patients with type 1 diabetes between 4 and 50 years of age (mean age, 18.6 years; $>30\%$ of sample <18 years old) who had used an insulin pump for at least 6 months. In addition, participants had to have an HbA1c level of 8.5% or less and have impaired awareness of hypoglycemia (defined as a score of at least four on the modified Clarke questionnaire). Patients were randomized to six months of in-home use of the Paradigm Veo System with automated insulin suspension when the glucose sensor reached a preset threshold of 60 mg/dL or to continued use of an insulin pump without the LGS feature. The primary study outcome was the combined incidence of severe hypoglycemic events (defined as hypoglycemic seizure or coma) and moderate hypoglycemic events (defined as an event requiring assistance from another person). As noted, findings were not reported separately for children and adults.

The baseline rate of severe and moderate hypoglycemia was significantly higher in the LGS group (129.6 events per 100 patient-months) than in the pump-only group (20.7 events per 100 patient-months). After 6 months of treatment, and controlling for the baseline hypoglycemia rate, the incidence rate per 100 patient-months was 34.2 (95% confidence interval [CI], 22.0 to 53.3) in the pump-only group and 9.6 (95% CI, 5.2 to 17.4) in the LGS group. The incidence rate ratio was 3.6 (95% CI, 1.7 to 7.5), which was statistically significant favoring the LGS group. Although results were not reported separately for children and adults, the trialists conducted a sensitivity analysis in patients younger than 12 years (15 patients in each treatment group). The high baseline hypoglycemia rates could be explained in part by two outliers (children ages 9 and 10 years). When both children were excluded from the analysis, the primary outcome was no longer statistically significant. The incidence rate ratio for moderate and severe events excluding the two children was 1.7 (95% CI, 0.7 to 4.3). Mean HbA1c levels (a secondary outcome) did not differ between groups at baseline or at 6 months. Change in HbA1c levels during the treatment period was -0.06% (95% CI, -0.2% to 0.09%) in the pump-only group and -0.1% (95% CI, -0.3% to 0.03%) in the LGS group; the difference between groups was not statistically significant.

Prospective Studies

Gómez (2017) published the results of a cohort of 111 type 1 diabetic individuals with documented hypoglycemia and hypoglycemia unawareness who received a sensor-augmented insulin pump with LGS therapy.^[19] Participants used a combination system with the Medtronic Paradigm 722 or Paradigm Veo pump connected to the MiniMed CGM device. At a mean follow-up of 47 months (SD=22.7), total daily insulin dose was reduced (mean difference, -0.22 U/kg; 95% CI, -0.18 to -0.26 U/kg; $p < 0.001$). HbA1c levels were reduced from a baseline value of 8.8% (SD=1.9%) to 7.5% (SD=1.0%) at five months (mean difference, -1.3%; 95% CI, -1.09% to -1.50%; $p < 0.001$) and 7.1% (SD=0.8%; mean difference, -1.7%; 95% CI, -1.59% to -1.90%; $p < 0.001$). At baseline, 80% of subjects had had at least one episode of hypoglycemic awareness compared with 10.8% at last follow-up ($p < 0.001$). Episodes of severe hypoglycemia decreased from 66.6% to 2.7% ($p < 0.001$).

Retrospective Studies

Agrawal (2015) retrospectively analyzed use of the threshold suspend feature associated with the Paradigm Veo System in 20,973 patients, most of whom were treated outside of the United States.^[20] This noncontrolled descriptive analysis provided information on the safety of the device when used in a practice setting. The threshold suspend feature was enabled for 100% of the time by 14,673 (70%) patients, 0% of the time by 2249 (11%) patients, and the remainder used it intermittently. The mean (SD) setting used to trigger suspension of insulin was a sensor glucose level of 62.8 (5.8) mg/dL. On days when the threshold suspend feature was enabled, there was a mean of 0.82 suspend events per patient day. Of these, 56% lasted for 0 to 5 minutes, and 10% lasted the full two hours. (Data on the length of the other 34% of events were not reported.) On days when the threshold suspend feature was on, sensor glucose values were 50 mg/dL or less 0.64% of the time compared with 2.1% of sensor glucose values 50 mg/dL or less on days when the feature was off. Reduction in hypoglycemia was greatest at night. Sensor glucose percentages equivalent to 17 minutes per night occurred when the threshold suspend feature was off vs glucose percentages equivalent to five minutes per night when the threshold suspend feature was on. Data on the use of the device has suggested fewer and shorter hypoglycemic episodes. The length and severity of hypoglycemic episodes were not fully discussed in this article.

Section Summary

For individuals who have type 1 diabetes who receive an artificial pancreas device system with a low glucose suspend feature, the evidence includes three randomized controlled trials (RCTs) conducted patients six years and older. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. All of these RCTs reported primary outcomes were favorable for the group using an artificial pancreas system; however, findings from one trial were limited by nonstandard reporting of hypoglycemic episodes, and findings from the other trial were no longer statistically significant when two outliers (children) were excluded from analysis. The RCT limited to adults showed an improvement in the primary outcome (AUC for nocturnal hypoglycemic events). AUC is not used for assessment in clinical practice, but the current technology does allow user and provider review of similar trend data with a CGM.

Results from the ASPIRE study suggested that there were increased risks of hyperglycemia and potential DKA in subjects using the threshold suspend feature. This finding may be related to whether or not actions are taken by the user to assess glycemic status, etiology of the low glucose (activity, diet or medication) and to resume insulin infusion. Both retrospective and

prospective observational studies have reported reductions in rates and severity of hypoglycemic episodes in automated insulin delivery system users.

In addition, one small study reported favorable outcomes for closed-loop systems in pre-term infants, however, this study is limited by very small sample size, lack of blinding, and short study duration.

The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant. Limitations of the published evidence preclude determining the effects of the technology on overall glycemic control as assessed by HbA1c and other parameters and thus, net health outcomes.

Hybrid Closed-loop Insulin Delivery Systems

Systematic Review

Karageorgiou (2019) published a systematic review and network meta-analysis evaluating the efficacy of closed-loop systems in glycemic control for non-adults with type 1 diabetes mellitus.^[21] The meta-analysis included 25 studies (N=504). The closed-loop system group spent a significantly higher percentage of time in a target glycemic range and the mean glucose was also decreased in the closed-loop system group (MD: 3.01%, 95% CI [1.68-4.34%]). Overall the closed-loop system showed better outcomes compared to standard insulin pumps for non-adults.

Prospective Studies

Bergental (2016) published a prospective single-arm study on the safety of the hybrid closed-loop system in patients with type 1 diabetes.^[22] It included 124 patients ages 14-to-75 years old who had type 1 diabetes for at least two years, had HbA1c levels less than 10.0%, and who had used an insulin pump for at least six months. There was an initial run-in period at baseline for patients to learn how to use the device followed by a 3-month period of device use. The study period included a 6-day hotel stay with a 1-day period of frequent sampling of venous blood glucose levels to verify device accuracy. The primary safety end points were the incidence of severe hypoglycemia and diabetic ketoacidosis and the incidence of device-related and serious adverse events.

There were no episodes of severe hypoglycemia or ketoacidosis during the study. A total of 28 device-related adverse events occurred, all of which could be resolved at home. There were four serious adverse events, one case each of appendicitis, bacterial arthritis, worsening rheumatoid arthritis, and *Clostridium difficile* diarrhea. There were also a number of predefined descriptive end points (but no statistically powered efficacy end points). The device was in the closed-loop mode for a median of 97% of the study period. Mean (SD) HbA1c levels were 7.4% (0.9%) at baseline and 6.9% (0.6%) at the end of the study, and the percentage of sensor glucose values within the target range was 66.7% at baseline and 72.2% at the end of the study.

A multicenter pivotal trial published by Garg (2017) evaluated the safety of Medtronic's hybrid closed-loop system, using methods similar to those of Bergental (NCT02463097) and employing the same device (MiniMed 670G).^[23] Of 129 subjects, 124 completed the trial; 30 were adolescents (age range, 14-21 years) and 94 were adults (age range, 22-75 years), all of whom had type 1 diabetes for at least two years before the study, and used insulin pump therapy for six months or more. A three-month study period was preceded by a run-in period

for subjects to be more familiar with the equipment, and the sensor glucose values were confirmed by an extended hotel stay (6-day/5-night with daily exercise). In both the adolescent and adult cohorts, the trial found improvements during the study phase over the run-in phase, with an increased percentage of glucose values in the favorable range (for adults, a mean improvement of 68.8% to 73.8%; for adolescents, a mean improvement of 60.4% to 67.2%; $p < 0.001$ for both cohorts). Similarly, the authors reported a decrease in the percentage of values outside of the target range (< 70 mg/dL or > 180 mg/dL): for adults, time spent below the target range decreased from 6.4% to 3.4% ($p < 0.001$); time above the range decreased from 24.9% to 22.8% ($p = 0.01$). For both cohorts, HbA1c levels showed a significant reduction between baseline and the end of study: for adults, the mean decreased from 7.3% to 6.8% ($p < 0.001$), while for adolescents, the mean decreased from 7.7% to 7.1% ($p < 0.001$). Secondary outcomes, which included a reduction of nocturnal hyperglycemia and hypoglycemia, increase in mean overall body weight, and a reduction of basal insulin, were favorable for the study phase, compared with the run-in phase; measurements from the hotel stay verified the in-home glucose values. However, there were several limitations in the trial, including its nonrandomized design, the exclusion of individuals who had recently experienced diabetic ketoacidosis or severe hypoglycemia, and the interaction between subjects and site personnel. Additionally, most of the adult cohort were already using CGM, and baseline HbA1c levels were lower than average for both cohorts; both baseline characteristics potentially limit the generalizability of the results.

One type of hybrid insulin delivery system employs a predictive algorithm to keep the patient's glucose levels within a specific range or zone, only increasing or decreasing insulin levels if the device detects that glucose levels are going to fall outside the defined zone. Forlenza (2017) published a randomized controlled crossover trial comparing the efficacy of a zone model predictive control algorithm with that of sensor-augmented pump therapy; the trial included 20 subjects (19 completed), all with type 1 diabetes and having at least three months treatment with a subcutaneous insulin infusion pump.^[24] The six week, in-home study was divided into 2-week blocks, with two randomized groups alternating treatment between an artificial pancreas system (DiAs web monitoring) or sensor-augmented pump therapy (Dexcom Share); subjects in both arms reported glucose values and, if applicable, sensor failure. For several primary end points, which included percentage of time in the target glucose range (70-180 mg/dL) and reduction in hypoglycemia (< 70 mg/dL), the algorithm-controlled artificial pancreas system was found to be superior to the sensor-augmented pump therapy (71.6 vs 65.2%, $p = 0.008$; 1.3 vs 2%, $p = 0.001$, respectively); however, while the mean glucose value was lower in the artificial pancreas system than in the control group, the difference between them was not significant ($p = 0.059$). Measurements of nocturnal hypoglycemia were consistent with day-to-day findings. For the secondary end point (safety of both systems after extended wear), the study found that the mean glucose did not change between the first and seventh day of wear. A limitation of the trial was its use of remote monitoring of subjects; also, the trialists noted that, given the marked difference in outcomes between responders and nonresponders, an error might have occurred in setting basal rates. The remainder of the review is focused on additional studies that recently evaluated HCL systems in children and adolescents with type 1 diabetes.

The RCT by Tauschman (2018) evaluated individuals with uncontrolled type 1 diabetes as reflected in mean Hb1c < 8 %.^[25] Approximately, 50% of the subjects were between 6-21 years of age and 25% are 6-12 years old. Both groups achieved a reduction in HbA1c but were statistically greater in the HCL group compared to the control group. The investigators reported that the HbA1c improvements were not different among children, adolescents, and adults (data

not shown in tables). No severe hypoglycemic events were reported consistent with decrease in time spent with glucose <70mg/dl.

Abraham (2018) reported the results of a six month, multicenter, RCT in children and adolescents with type 1 diabetes comparing use of an insulin pump with suspend before low or predictive low-glucose management (PLGM) with sensor-augmented insulin pump therapy (SAPT) alone.^[26] At six months, significant reductions were seen in day and night hypoglycemia and number of hypoglycemic events <63mg/dl lasting longer than 20 minutes. There were no differences in HbA1c at six months in either group. A follow-up analysis in 140 participants evaluated the effect of percentage time of sensor use on glycemic control in individuals on SAPT with and without PLGM.^[27] The mean \pm SD age of the cohort was 13.4 \pm 2.8 years, duration of diabetes was 7.1 \pm 3.7 years and HbA1c was 7.5 \pm 0.8%. The sensor use was calculated as a percentage; the number of sensor glucose recordings was compared to the number of expected total recordings, which was then categorized into four groups <40%, 40 to <60%, 60 to <80% and \geq 80%. The frequency of sensor use was 7.86% (n = 11) in <40%, 24.29% (n = 34) in 40 to <60%, 36.43% (n = 51) in 60 to <80% and 31.43% (n = 44) in \geq 80%. With every 10% increase in sensor use in participants in the SAPT group, mean reduction of HbA1c was -0.14% [-0.25 to -0.04] (p = 0.007) while in the PLGM group, the mean reduction was -0.04% [-0.15 to 0.06] (p = 0.361). These results indicate that improvement in glycemic control is dependent on frequency of sensor use, with higher sensor uptake corresponding to improved glycemic outcomes.

Forlenza (2019) reported the data and analysis of the supplemental information filed with the FDA to support the expanded indication for the MiniMed 670G system to children 7-13 years of age.^[28] The nonrandomized, single arm multicenter study reported the day and night use of the automated insulin delivery and PLGM for three months in the home setting. There were no serious adverse events and use of the system was associated with reduction in HbA1c and increased time in target glucose range.

Wood (2018) reported an in-clinic evaluation of a 7-13 year-old cohort of the 670G pivotal trial that was designed to evaluate the performance characteristics of the device when activity induced hypoglycemic patterns were used to set individual device parameters for ongoing use by the study participant.^[29] The suspend before low prevention capability was confirmed in 97.5% of patients experiencing a sensor glucose of \leq 55mg/dl.

Messer (2018) reported on a subanalysis of the adolescent and young adult participants in the 670G pivotal trial to better characterize the carbohydrate input and insulin bolus determination features of the device over a three-month period.^[30] Participants successfully utilized the device without significant changes in total daily dose of insulin but improved percentage time in range (70-180 mg/dl).

Section Summary

For individuals who have type 1 diabetes who receive an artificial pancreas device system with a hybrid closed-loop insulin delivery system, the evidence includes a multicenter pivotal trial using devices cleared by the Food and Drug Administration, supplemental data and analysis for expanded indications and more recent studies focused on children and adolescents. Three crossover RCTs using a similar first-generation device approved outside the United States have been reported. Relevant outcomes are symptoms, change in disease status, morbid events, resource utilization, and treatment-related morbidity. Of the three crossover RCTs assessing a related device conducted outside the United States, two found significantly better

outcomes (ie, time spent in nocturnal hypoglycemia and time spent in preferred glycemic range) with the device than with standard care and the other had mixed findings (significant difference in time spent in nocturnal hypoglycemia and no significant difference in time spent in preferred glycemic range). For the US regulatory registration pivotal trial, the primary outcomes were safety and not efficacy. Additional evidence from device performance studies and clinical studies all demonstrate reductions in time spent in various levels of hypoglycemia, improved time in range (70-180mg/dl), rare diabetic ketoacidosis and few device-related adverse events. The evidence is sufficient that the magnitude of reduction for hypoglycemic events in the type 1 diabetes population is likely to be clinically significant. The variation in the definition of primary and secondary outcomes in the study design and conduct of the published evidence are limitations that preclude determining the effects of the technology on net health outcomes. Reduction in the experience of hypoglycemia and inappropriate awareness of hypoglycemia and glycemic excursions were identified as important acute clinical outcomes in children, adolescents and adults and are related to the future risk for end organ complications.

PRACTICE GUIDELINE SUMMARY

AMERICAN DIABETES ASSOCIATION

The American Diabetes Association has released multiple publications on controlling type 1 diabetes as outlined below.

Date	Title	Publication Type	Recommendation	Level of Evidence
2020	Standards of Medical Care in Diabetes	Guideline standard ³¹	Use of technology should be individualized based on a patient’s needs, desires, skill level, and availability of devices. Nonprofit websites can offer advice for providers and patients to determine the suitability of various options.	E
			Insulin pump therapy may be considered as an option for all adults, children, and adolescents with type 1 diabetes who are able to safely manage the device.	A
			Automated insulin delivery systems may be considered in children (B) and adults with type 1 diabetes to improve glycemic control. (A)	B
			Sensor-augmented pump therapy with automatic low glucose suspend may be considered for adults and children with type 1 diabetes to prevent/mitigate episodes of hypoglycemia.	B

AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND THE AMERICAN COLLEGE OF ENDOCRINOLOGY

The American Association of Clinical Endocrinologists and American College of Endocrinology (2018) published a joint position statement on the integration of insulin pumps and continuous glucose monitoring in patients with diabetes.^[32] The statement emphasized the use of continuous glucose monitoring and insulin pump therapy for type 1 diabetes patients who are not in glycemic target ranges despite intensive attempts at self-blood glucose monitoring and multiple insulin injection therapy.

In 2014, the American Association of Clinical Endocrinologists and the American College of Endocrinology published a joint position statement for insulin pump management.^[33] The consensus statement was developed by evaluating the current evidence, and when evidence from randomized controlled trials lacked, by consensus of a task force of experts. The summary of recommendations states that data support CSII for basal-bolus insulin therapy in patients with type 1 diabetes mellitus (T1DM), when selection is based on a comprehensive evaluation of the patient's knowledge of diabetes management principles. Specific patient selection recommendations include the ideal CSII candidate as follows:

- A patient with T1DM or intensively managed insulin-dependent type 2 diabetes mellitus
- Currently performing ≥ 4 insulin injections and ≥ 4 self-monitored blood glucose (SMBG) measurements daily
- Motivated to achieve optimal blood glucose control
- Willing and able to carry out the tasks that are required to use this complex and time-consuming therapy safely and effectively
- Willing to maintain frequent contact with their health care team

SUMMARY

There is enough research to show that the use of an external insulin infusion pump or FDA-approved automated insulin delivery system (artificial pancreas device) improves health outcomes for select patients with diabetes mellitus or preconception/pregnancy related suboptimal glycemic control. Clinical practice guidelines based on research recommend these devices in certain populations and clinical scenarios. Therefore, the use of an external insulin infusion pump or an FDA-approved automated insulin delivery system (artificial pancreas device) may be considered medically necessary when policy criteria are met.

There is not enough research to show that an insulin pump or FDA-approved automated insulin delivery system (artificial pancreas device) improve health outcomes in all other situations. No clinical practice guidelines based on research recommend these devices for patients not addressed in the policy criteria. Therefore, the use of an external insulin infusion pump or FDA-approved automated insulin delivery system (artificial pancreas device) is investigational when the policy criteria are not met.

All or part of an insulin pump or automated insulin delivery system (artificial pancreas device) may warrant replacement or upgrade when the current device is no longer able to perform its basic function and cannot be repaired or adapted adequately to meet the patient's medical needs. Therefore, a replacement or upgrade may be considered medically necessary when

policy criteria are met. A replacement or upgrade is considered not medically necessary when the device is adequately functioning and can meet the patient's medical needs.

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CODES

Codes	Number	Description
CPT	None	
HCPCS	A9999	Miscellaneous DME supply or accessory, not otherwise specified
	E0784	External ambulatory infusion pump, insulin
	E0787	External ambulatory infusion pump, insulin, dosage rate adjustment using therapeutic continuous glucose sensing
	E1399	Durable medical equipment, miscellaneous
	S1034	Artificial pancreas device system (e.g., low glucose suspend [LGS] feature) including continuous glucose monitor, blood glucose device, insulin pump and computer algorithm that communicates with all of the devices
	S1035	Sensor; invasive (e.g., subcutaneous), disposable, for use with artificial pancreas device system
	S1036	Transmitter; external, for use with artificial pancreas device system
S1037	Receiver (monitor); external, for use with artificial pancreas device system	

Date of Origin: September 2000