iLet Bionic Pancreas System: Guide for Health Care Providers

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Intended Use of This Guide

This information is intended solely for the use of healthcare professionals. Healthcare professionals must always rely on their own professional clinical judgment when deciding whether to use a particular product when treating a particular patient. This document is not medical advice. Beta Bionics recommends that healthcare professionals be familiar with the use of the iLet before prescribing it. Healthcare professionals should refer to the package insert, product label and/or instructions for use before prescribing the iLet. Please contact Beta Bionics Medical Affairs if you have questions about the use of the iLet.

Intended Use of the iLet

The iLet bionic pancreas is intended for use by people with type 1 diabetes mellitus who are 6 years of age or older. The full Indications for Use statement can be found in the User Guide.

How the iLet Algorithms Work

Initialization and Operation Principles

The iLet algorithms require initialization with body weight only and do not require (or allow) input on basal rates, insulin-to-carbohydrate ratios, or insulin sensitivity factors.

The only setting that can be changed is the glucose target, which defaults to "Usual" and can be set to "Lower", or "Higher".

The control algorithms autonomously determine insulin doses every 5 minutes in response to glucose values from a continuous glucose monitor (CGM), insulin dosing history, and user input (e.g., meal announcements and, when CGM glucose values are not available, entered blood-glucose values).

The control algorithms adapt continuously and autonomously to the user's insulin needs.

Design of Insulin Control Algorithms

Insulin doses are governed by three coexisting algorithms.

Basal algorithm: Basal insulin doses are autonomously determined every 5 minutes based on the glucose profile of the previous 24 hours, the current glucose level, and the glucose trend. Basal insulin dosing may be entirely suspended for low or rapidly declining glucose levels.

Bolus algorithm: Bolus insulin doses provide insulin that is required above and beyond basal insulin. They are autonomously determined every 5 minutes based on the glucose profile of the previous 24 hours, the current glucose level, the glucose trend, and the insulin on board. They are computed using a model-predictive control (MPC) algorithm that has been augmented to take the insulin-on-board into account.

Meal dose algorithm: Meal doses are automatically determined in response to user meal announcements, separately for breakfast, lunch, and dinner.

Glucose Target

Both basal and bolus algorithms aim to steer the glucose level to the current glucose target level ("Usual", "Lower", or "Higher"). The current target may be either the default target or a "Sleep" target, which may be different. The "Sleep" target may be set for any start and end time.

The "Usual" glucose target is 120 mg/dl, The "Lower" glucose target is 110 mg/dl, and the "Higher" glucose target is 130 mg/dl. These are the targets towards which the algorithms aim to steer the glucose level, but the average glucose level that is achieved will almost always be higher than the glucose target (rare exceptions may occur in individuals who have very low insulin needs and/or eat very low carbohydrate diets).

Changing of the glucose target is not expected to change the mean glucose by the difference between the old and new targets. For example, changing the target from "Usual" to "Lower" is not expected to reduce the mean glucose by 10 mg/dl. The difference in mean glucose between two targets will vary by individual and by the mean glucose before the target adjustment. Based on clinical studies conducted to date, the average difference in mean glucose achieved between two adjacent targets is expected to be approximately 7 mg/dl.

Given these performance characteristics of the control algorithms, knowing the numerical value of the glucose targets is not relevant to the user. Therefore, they are not a routine part of the training provided to the user.

For a mild glucose rise above the target level, it is primarily the basal algorithm that will respond, whereas for a rapid glucose rise or a significant rise of the glucose level above the glucose target, the bolus algorithm will additionally respond.

For glucose levels below the target level, the bolus algorithm will not be active, and the basal algorithm will reduce basal dosing, up to and including entirely suspending insulin delivery. There is no limit on the duration of an insulin suspension if the CGM value remains in the hypoglycemic range.

Meal doses are issued by the meal dose algorithm in response to meal announcements, independent of the glucose level and the glucose target.

Dose Limits

At each individual 5-minute step, the sum of the basal and bolus insulin is limited to a maximum of 3 units in response to CGM glucose data. In response to an entered blood glucose value when CGM data is not available, the sum of the basal and bolus insulin at each 5-minute step is limited to a maximum of 6 units. This higher limit was chosen because blood glucose values are expected to be entered less frequently.

The iLet basal algorithm does not use any basal rate settings; it autonomously sets and uses a dynamic basal rate. This autonomously set basal rate is limited to 0.045 units per hour per kg of body mass (e.g., for a body mass of 60 kg the limit is 2.7 units per hour or 0.23 units per 5-minute step). The maximum allowable body mass is 255 kg (561 pounds). Therefore, the maximum possible basal rate is 11.5 units per hour. The hourly basal rate has no lower limit (e.g., it can be 0 units per hour).

If the 5-minute basal dose is less than the minimum dose capability of the device (e.g., less than 0.045 units), the intended 5-minute basal dose is stored and summed over consecutive 5-minute steps until the accrued amount reaches at least 0.045 units.

Meal doses are capped at 24 units.

Dose Adaptation

The autonomous basal and bolus dosing adapts continuously to update the aggressiveness or conservativeness of insulin dosing.

If the apparent need for insulin decreases, the insulin dosing aggressiveness will gradually decrease, and the control algorithms will respond to a given glucose level or excursion with relatively smaller doses. A decrease in the apparent need for insulin may be caused by physiological factors (e.g., a change in health condition resulting in increased insulin sensitivity, an increase in physical activity, or the effect of non-insulin medications), an increase in endogenous insulin production, or administration of exogenous insulin (e.g., adding or increasing the dose of long-acting insulin).

If the apparent need for insulin increases, the insulin dosing aggressiveness will gradually increase, and the control algorithms will respond to a given glucose level or excursion with relatively larger doses. An increase in the apparent need for insulin may be caused by physiological factors (e.g., a change in health condition resulting in decreased insulin sensitivity, a reduction in physical activity, the effect of non-insulin medications, or intercurrent illness), a reduction in endogenous insulin production, or a reduction of exogenous insulin (e.g., discontinuing or decreasing the dose of long-acting insulin).

The adaptation of meal doses is entirely separate from adaptation of basal and bolus insulin doses and is intended to track and continually update user insulin requirement around the three meal types. A change in the aggressiveness of basal and bolus insulin dosing will not modify meal doses, but the meal dose algorithm will independently adjust meal dosing in response to the user's needs.

Adaptation Approach

Basal adaptation: Basal insulin doses are based in part on an adapted nominal (baseline) basal dose for each 5-minute step over the 24-hour day (288 steps). The basal dose that is ultimately delivered at each 5-minute step is adjusted from the nominal (baseline) basal dose according to the current glucose level and its trend. Insulin delivery may be suspended in response to low or rapidly falling glucose levels.

The adapted nominal (baseline) basal doses (one for each of the 288 5-minute steps over 24 hours) determine the basal doses that are delivered when the CGM is offline. The basal doses delivered when the CGM is offline can be further adjusted in response to entered blood glucose values. The basal dose may be increased for one 5-minute step in response to a high blood-glucose value that is entered, and basal insulin may be suspended for up to an hour in response to a low blood-glucose value that is entered. Basal insulin may also be suspended in response to entered blood-glucose values that are not low if multiple entered values show that the glucose levels is rapidly falling.

Correction bolus adaptation: Bolus insulin doses are determined autonomously every 5 minutes in response to the current glucose level, the glucose level trend, the adapted aggressiveness, and the insulin on board. Accounting for the insulin on board allows the algorithm to deliver more insulin when needed or refrain from delivering excess insulin that could "stack" and lead to hypoglycemia.

Insulin on board is estimated using a model of insulin absorption into blood and clearance from the blood that considers all correction boluses and meal boluses. Insulin on board is computed at every 5-minute step based on an assumed peak time of insulin in the blood after administration (tmax) of 65 min. This setting was chosen based on the average tmax for people with type 1 diabetes and was validated in pre-pivotal clinical studies. The tmax setting cannot be adjusted.

Meal dose adaptation: Meal doses are adapted over time separately for each meal type ("Breakfast", "Lunch", and "Dinner") based on the 4-hour post-prandial insulin bolus dosing (the sum of meal bolus and correction during this period) that was needed after prior announcements of each meal type. The meal dose controller aims to provide 75% of the insulin that will be needed for an announced meal. The insulin dose for a "Less" meal is 50% of that for a "Usual for me" meal, and the insulin dose for a "More" meal is 150% of that for a "Usual for me" meal. Any additional insulin needed for the meal will be provided by the corrections controller.

Basing the meal dose adaptation on the post-prandial insulin correction bolus dosing ties it to the post-prandial glucose excursions and in turn to the apparent insulin sensitivity of the user around the three different meal types.

Meal dose adaptation only occurs if certain conditions are met around the time of the meal announcement, including:

- Any additional meal announcements after the first announcement for a meal must have occurred within 1 hour of the initial meal announcement, and no further meal announcements were made in the remaining 3h period from the initial meal announcement. This constraint is intended to avoid mixing insulin dosing for one meal with insulin dosing for another meal. If one or more additional meal announcements for a meal occurred within 1 hour of the initial meal announcement, the announcements will be combined, and adaptation will occur on the sum of the announcements. This allows for separate announcements for the same meal (e.g., for appetizer and main course, or for main course and dessert) to be combined by the algorithm.

- No announcements of a different meal types occurred anywhere within the 4-hour adaptation window, even within the first hour after the initial meal announcement (e.g., announcement of a "Lunch" meal within 4 hours of a "Breakfast" meal). This constraint is intended to avoid mixing of insulin dosing for one meal type with insulin dosing for another meal type.

- The glucose levels at the time of the initial meal announcement and the glucose level 4 hours after the time of the initial meal announcement were both equal to or less than 200 mg/dl when the glucose target is "Usual". The glucose threshold is equal to or less than 190 mg/dl when the glucose target is "Lower" and is 210 mg/dl when the glucose target is "Higher". These thresholds are set at 80 mg/dl above the glucose target. This constraint is intended to avoid meal dose adaptation in the setting of a failed infusion set when some or all the insulin doses upon which adaptation would occur may not have been received by the user. It would not be appropriate to adapt the algorithm based on insulin that was not received by the user.

Response to Hypoglycemia

The insulin dosing aggressiveness will be reduced in response to hypoglycemia.

After a CGM value that is less than 60 mg/dl, the bolus algorithm is completely inhibited from dosing insulin to correct hyperglycemia for one hour, and any potential correction doses are reduced to a lesser degree for another 30 minutes. This is to prevent brief, sharp increases in the CGM value resulting from oral carbohydrate treatment from leading to additional insulin dosing, which could lead to a "roller coaster" phenomenon. It is still important for users not to overtreat hypoglycemia with oral carbohydrates.

CGM-Online periods

When CGM readings are available (CGM-online periods) the control algorithms automatically calculate and issue autonomous basal insulin doses (adjusting or suspending them based on CGM glucose values), autonomous bolus doses (adjusting them based on CGM glucose values), and meal doses (the size of which is autonomously determined by the meal dose algorithm) in response to user meal announcements.

During CGM-online periods, basal rates and bolus dosing aggressiveness adapt continually, and meal doses adapt separately for breakfast, lunch, and dinner.

BG-Run Mode

When CGM readings are not available, the control algorithm works in BG-run Mode. In this mode, the iLet automatically calculates and issues basal insulin doses based on basal doses that were saved over the last 7 days when the CGM was online. Basal insulin may be suspended in response to entered blood glucose values that are low.

In BG-run Mode, the iLet may deliver correction bolus doses in response to user-entered high blood-glucose values. Whether a correction bolus is given or not, and the size of any bolus given, will depend on the entered blood-glucose value, the glucose trend (if there are other recently entered blood-glucose values), and the amount of insulin on board.

In BG-run Mode, the iLet will deliver meal doses in response to user meal announcements based on the doses for each meal type and size that were adapted when CGM data were available (e.g., during the recent CGM-online period).

In BG-run Mode, entered blood glucose values can transiently increase (for one 5-minute step only) the basal dose. Entered blood glucose values can also transiently decrease basal dosing, or even suspend basal dosing in response to a low blood glucose or a blood glucose trend that indicates a very rapid descent. In the case of a low blood glucose entry, insulin will be suspended for up to an hour unless another blood glucose is entered indicating a rise in the glucose level.

While local changes in basal and bolus dosing may occur in responses to entered blood-glucose values, these isolated local responses do not impact or cause adaptation in the basal rates, bolus aggressiveness, or meal bolus doses that were stored when CGM data were available, unless at least 70 blood glucose values are entered over a 24-hour period. Therefore, adaptation will generally not occur in BG-run Mode because the user-entered blood glucose data will be too sparse.

Transitioning from an MDI Regimen to the iLet

When transitioning from an MDI regimen using long-acting insulin, the iLet cannot know about the insulin-on-board, and there is the possibility of insulin stacking. However, insulin stacking is of less concern when the external insulin of which the iLet is unaware is long-acting insulin, and the iLet will refrain from dosing insulin if no insulin appears to be needed.

In the Pivotal Trial, there was no specific guidance regarding modifying the long-acting insulin dosing for individuals transitioning to the iLet from an MDI regimen using long-acting insulin.

Some investigators made no modification to the long-acting insulin dose prior to starting therapy with the iLet, relying on the conservative initial dosing and the autonomous adaptation by the iLet.

Some investigators reduced doses of long-acting insulin the night before a scheduled iLet start the following morning, held the morning dose of long-acting insulin the same day as a scheduled iLet start, and reduced the morning long-acting insulin dose before a scheduled iLet start the same afternoon. Some investigators further tailored their plan depending on the half-life of the long-acting insulin (e.g., less adjustment for Levemir than for Lantus; less adjustment for Lantus than for Tresiba and Toujeo).

Reducing the last dose of long-acting insulin may be important if the total daily dose of insulin is very small, or if the dose of long-acting insulin represents a large proportion of the total daily dose.

Starting with the "Higher" target may be appropriate when the user is transitioning from MDI using a long-acting insulin. See **Initial Glucose Target Selection**.

Glucose Target

Initial Glucose Target Selection

The initial target for most users should be set as "Usual".

The initial target should not be set to "Lower". The "Lower" target can be considered after approximately one week of use if, after the iLet has had time to adapt, the average glucose is higher than desired and time in hypoglycemia is low (e.g., percent of time below 54 mg/dl is well below 1% and percent of time less than 70 mg/dl is below 4%).

Starting with the "Higher" target may be appropriate when the user is transitioning from MDI using a long-acting insulin or if the user has a very high mean glucose (e.g., greater than 280 mg/dl) or HbA1c (e.g., greater than 10%) at baseline. Participants with a very high mean glucose or HbA1c may have subjective symptoms of hypoglycemia even when their glucose is in the normal range until they become accustomed to spending more time in the normal glucose range.

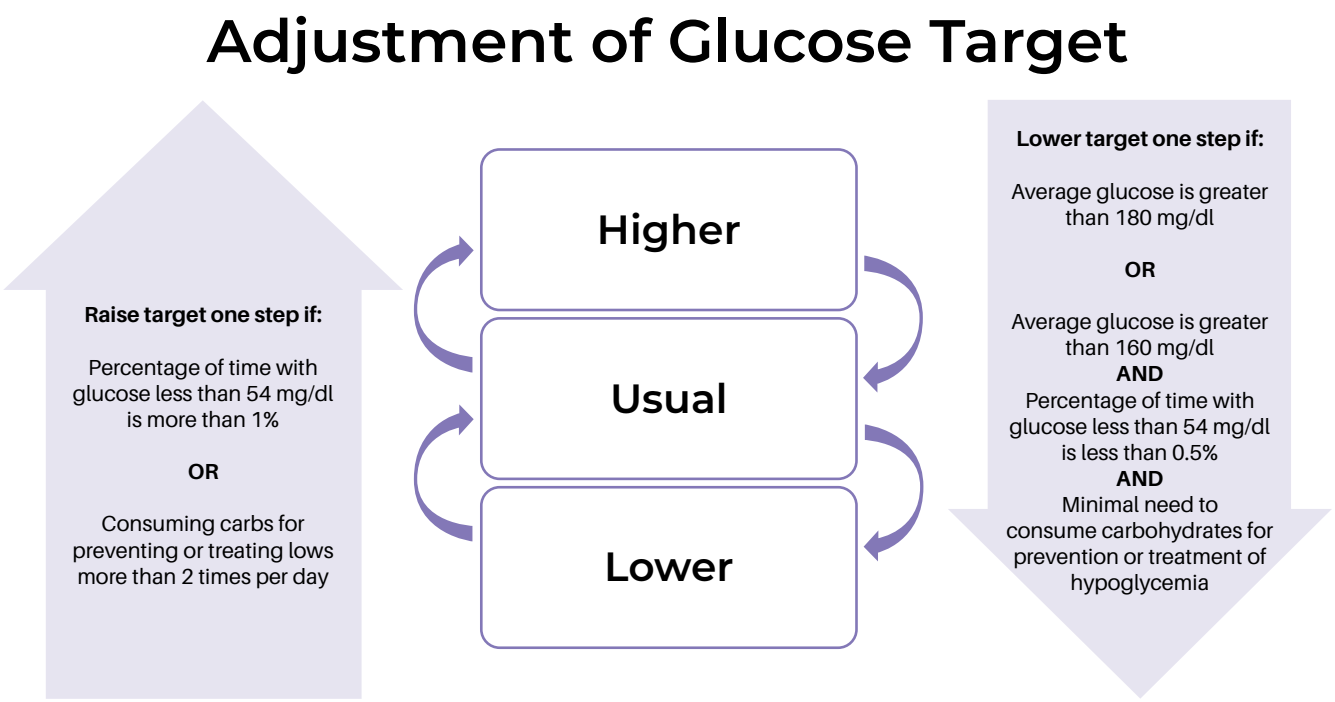
If the starting target is set at "Higher" because the user is transitioning from an MDI regimen using long-acting insulin, or because the user has a very high mean glucose or HbA1c at baseline, the target should be re-visited, ideally within a few days and certainly within 2 weeks. In most cases, unless there is significant hypoglycemia (e.g., time less than 54 mg/dl greater than 1%), the target should be adjusted to "Usual".

Starting with the "Higher" target may be appropriate if the user has a very low insulin total daily dose for their body weight (e.g., less than 0.3 units per kg per day). In this case, the "Higher" target may be appropriate for the long term if their mean glucose is meeting goal for therapy.

Adjustment of the Glucose Target

It is generally recommended to wait at least one week after iLet initialization before adjusting the target downwards to "Lower". However, if the initial glucose target was set to "Higher" because the user was transitioning from a multiple daily injection regimen using long-acting insulin, it should generally be adjusted to "Usual" after a few days of use.

Consider adjusting the glucose target at follow-up visits according to the following recommendations:



In addition to the default target, it is possible to set a "Sleep" target. The "Sleep" target may be set for any start and end time. This makes it possible to lower or raise the target during one period of time without changing the target during another period of time. For example, if the target is set at all times to Usual and the intention is to lower the glucose target from 6:00 AM to midnight, the default target could be changed to "Lower" while at the same time setting the "Sleep" target could be set to "Usual" from midnight to 6:00 AM.

It is not recommended that a "Sleep" target be set until some information about glycemic outcomes with a single target for the entire day has been collected.

Meal Doses

Explaining Meal Announcements to Users

The meal type should be selected based on what the user considers to be breakfast, lunch, or dinner. This can be based on the type of food, the time of day, or another system that works for the user.

The meal size should be based on the amount of carbohydrates in the meal, not the total size of the meal or the amount of protein, fiber, or fat.

The meal size should be chosen compared to the usual amount of carbohydrates the user eats for the chosen meal type. They should be choosing "Usual for me" most of the time.

"Less" should be chosen if the meal has around half the carbohydrates of a "Usual for me" meal. "More" should be chosen if the meal has around 50% more carbohydrates than a "Usual for me" meal. The sizes chosen should be relative to other meals eaten by that user for that type of meal. There should be no consideration of how large the meals are compared to those eaten by other people, or how large they are compared to other meal types.

For example, if a user typically eats a half of an English muffin with jam for breakfast and a large plate of pasta for dinner, those are both "Usual for me" meals for "Breakfast" and "Dinner" respectively.

Snacks should be announced as meals if they have similar carbohydrate content to one of the meal types. For example, if the user had the other half of an English muffin with jam as a late-morning snack, they should announce it as a "Usual for me" breakfast.

Determining if iLet Meal Doses Have Adapted

There are two ways to determine if meal doses have adapted:

On the iLet: If the meal dose for a meal type has not adapted, the "Less" option will not be available for that meal. Therefore, if the "Less" option is available, that meal type has adapted at least once. Even if the "Less" option is available, it is still possible that adaptation is not up to date for the current meal sizes. See **Helping the iLet successfully adapt meal doses**.

In the reports on the smartphone app or on the Beta Bionics iLet reports portal (www.report.betabionics.com): If the report shows that at least one "Less" meal has been delivered for a meal type, that meal type as adapted at least once. However, it is possible for a meal type to have adapted and the "Less" option to be available but never used.

Helping the iLet Successfully Adapt Meal Doses

If one or more meal announcements have not adapted, there are steps the user can take to facilitate adaptation:

- Avoid meals with larger than the "Usual for me" amounts of carbohydrates for a few days to allow initial adaption. If the CGM glucose is more than 80 mg/dl higher than the target (e.g. greater than 200 mg/dl when using the "Usual" target) at the end of the 4-hour adaptation the algorithm will not use that meal for adaptation. See **Meal dose adaptation.**

- Wait at least 4 hours between meals and snacks for a few days – this is the interval over which the meal dose algorithm adapts. If a new meal is announced (whether for a meal or snack) more than 1 hour after but within the 4-hour interval following a first meal announcement, it will cancel adaption for the first meal announcement.

- Avoid unannounced snacks between meals for a few days. If the CGM glucose at the time of the meal announcement is more than than 80 mg/dl higher than the target (e.g. greater than 200 mg/dl when using the "Usual" target) then the algorithm will not use that meal for adaptation. See **Meal dose adaptation.**

- Be consistent with the amount of carbohydrates in "Usual for me", "More, and "Less" meals.

- Never announce meals to treat hyperglycemia when not actually eating. This may train the iLet to give less insulin for the next meal.

- If more carbohydrates are eaten in a meal than accounted for by the initial announcement, announce another meal for the difference within 30 minutes of starting to eat that additional amount. If the initial and additional announcements are within 1 hour, the iLet will combine the two announcements and adapt the meal dose for the total meal size. If it has been more than 30 minutes since the user began eating the additional carbohydrates, they should not announce for the additional carbohydrates.

- Users should not try to "'trick" the iLet but should accurately announce meals of the correct relative size for them.

    - Announcing meals that are larger than the actual amount of carbohydrates to be consumed to get more insulin will have the opposite effect once adaptation occurs. Incorrectly announcing meals as larger than they are will train the iLet to give less insulin for the next meal.

    - Announcing meals that are smaller than the actual amount of carbohydrates to be consumed to get less insulin will have the opposite effect once adaptation occurs. Incorrectly announcing meals as smaller than they are will train the iLet to give more insulin for the next meal.

    - Announcing a meal without eating will cause the meal dose to adapt downward rapidly.

- To encourage meal doses to adapt downwards if the initial weight-based doses are causing hypoglycemia (uncommon, since the initial weight-based meal doses are conservative), it is important not to overtreat any hypoglycemia that occurs in the 4-hour post-prandial period.

Rebound hyperglycemia will cause the iLet to dose insulin, and this will work against downward adaptation. Treating with a small amount of carbohydrate before hypoglycemia occurs to flatten the CGM value curve and obtain a "soft landing" is the ideal way to allow the meal doses to adapt downwards.

Dealing with Meal Announcements After Initial Adaptation Has Occurred

There is no limit on the number of meals that can be announced per day. Once the meal doses have adapted, the best glucose control will be achieved by announcing all meals and snacks that have at least a "Less" amount of carbohydrates. Announcing meals more often than every 4 hours will prevent adaptation, but once initial adaptation has occurred, lack of adaptation in response to many meals should not be a problem as long as occasional updates to the adaptation occur.

Most meals should be announced as "Usual for me".

Announcing a "More" meal will lead to a meal bolus 1.5 times the dose (50% greater than) the dose for a "Usual for me" meal.

Announcing a "Less" meal will lead to a meal bolus 0.5 times the dose (50% smaller than) the dose for a "Usual for me" meal.

Meal announcements can be combined for larger meals. For instance, announcing a "Usual for me" meal and a "Less" meal will give the same amount of insulin as announcing a "More" meal. Announcing two "More" meals will result in delivery of 3 times the dose for a "Usual for me" meal.

If one or more additional meal announcement for a meal occurred within 1 hour of the initial meal announcement, the announcements will be combined, and adaptation will occur on the sum of the announcements. This allows for separate announcements for the same meal. As an example, an unusually large dinner for a special occasion might combine a "Less" announcement for the appetizer course, a "Usual for me" announcement for the main course that is indeed usual for the user, and another "Usual for me" announcement for a dessert that contains a similar amount of carbohydrates as the main course. The total amount of insulin given by the iLet as meal doses would be 2.5 times the insulin for a single "Usual for me" dinner.

Hyperglycemia

Hyperglycemia Soon After Starting a New iLet

Check fluid path including infusion set and the connection of the tubing to the iLet Connect.

Make sure the connection of the tubing to the iLet Connect is firmly tightened and not leaking.

If there is any concern about whether the infusion set is working properly, it should be changed. **When in doubt, change it out!**

Check the body weight that was entered into the iLet. If incorrect, supervise entry of correct body weight. If the entered body weight is far below the actual body weight, the algorithm may limit the amount of insulin the iLet can deliver to a level that is not sufficient to control hyperglycemia. Weight-based limits cannot be overridden through adaptation. On the other hand, raising the weight will not increase insulin dosing if weight-based limits have not been reached through adaptation.

Determine whether the user is announcing all meals and snacks containing meal-like quantities of carbohydrates to the iLet. Information about the average number of meal announcements per day and the meal types and sizes announced can be found on the Beta Bionics iLet reports portal (www.report.betabionics.com).

Determine if the iLet has adapted to meal announcements. See **Determining if iLet meal doses have adapted.**

If one or more meal announcements have not adapted, there are steps the user can take to facilitate adaptation. See **Helping the iLet successfully adapt meal doses.**

Consider whether a change in the glucose target to a lower value during all or part of the day is warranted. If the initial glucose target was "Higher", consider lowering it to "Usual". The glucose target can be lowered (e.g., by one step from "Higher" to "Usual" or from "Usual" to "Lower") for a part of the day (e.g., the daytime) or the entire day.

For example, if the initial glucose target was "Usual", meal announcements have adapted, and the amount of hypoglycemia is below recommended targets (e.g., percentage of time <54 mg/dl is less than 1%), consider reducing the target for all or part of the day to "Lower". In this scenario, it is suggested to consider lowering only the daytime target to "Lower" initially. This can be done by using the "Sleep" target. See **Adjustment of Glucose Target**.

Hyperglycemia When Glucose Control Has Been Generally Good

Investigate whether the user has taken carbohydrates without a meal announcement.

Investigate whether the user has recently taken an unusually large amount of carbohydrates (larger than typical for the kind and size of meal they announced) and whether their diet has changed.

Confirm that the iLet is online and delivering insulin. Confirm that the iLet has not lost power and has insulin in the cartridge. The Bell icon on the home screen can be used to review alarms. The Cartridge icon on the home screen can be used to determine the amount of insulin in the cartridge.

Check the infusion set. There may be no obvious sign of an infusion set gone bad. **When in doubt, change it out!** Infusion sets are often found to be kinked even if there was no occlusion alarm or smell of insulin near the infusion site, and replacement of the infusion set will result in resolution of hyperglycemia.

Check the connection between the iLet Connect and the tubing for signs of leakage or bubbles. Tighten this connection firmly.

Was the iLet Connect installed correctly? The cartridge should be inserted into iLet before the iLet Connect is engaged. This makes sure that the needle is correctly aligned with the septum of the cartridge. If there are signs of leakage around the iLet Connect, change the cartridge, making sure to use a new cartridge and iLet Connect. Make sure to put the cartridge into the iLet first and then inset the iLet Connect.

The iLet insulin cartridge, iLet connect, and tubing should always be replaced together. None of these components should be reused, and they should not be separated once connected.

Was there a large bubble in the iLet Connect or tubing so that the iLet was delivering air instead of insulin? Use Fill Tubing Only via the Cartridge icon to prime the bubble out and ensure consistent insulin delivery. Make sure the user disconnects from their infusion site before priming the tubing.

If an insulin injection is prescribed for elevated ketones the iLet should be disconnected for 90 minutes because there is no way to inform the iLet control algorithm about insulin that it did not deliver. If the iLet is not disconnected for sufficient time after the insulin injection, stacking of insulin will occur and may cause severe hypoglycemia.

Consider whether the insulin has lost bioactivity, for instance from exposure to excessive heat.

Determine if the user has recently raised the glucose target, for instance from "Usual" to "Higher" or from "Lower" to "Usual".

Consider whether the user has been given a new medication that has increased their insulin requirement (e.g., a glucocorticoid). It may take the iLet 24-48 hours to adapt to a change in insulin requirement.

Consider whether the user is ill or under stress such that their insulin requirement has increased. It may take the iLet 24-48 hours to adapt to a change in insulin requirement.

Consider whether there has been a change in the user's insulin requirement that justifies a change in their glucose target to a lower value during all or part of the day. The glucose target can be lowered (e.g., by one step from "Higher" to "Usual" or from "Usual" to "Lower") for a part of the day (e.g., the daytime) or the entire day.

Assess the amount of hypoglycemia and ask the user about use of carbohydrates to prevent or treat hypoglycemia. Consider whether the amount of hypoglycemia has increased due to lifestyle factors and whether the user is overtreating hypoglycemia and causing an increased rate of hyperglycemia.

Average Glucose Higher Than Desired

The iLet control algorithm is designed to drive the mean glucose towards the target without creating excessive hypoglycemia. In practice, this means that the group of individuals with a baseline A1c less than 7% (mean glucose of less than 154 mg/dl) in the Pivotal Trial experienced no significant change in their A1c and mean glucose. Some of these individuals with a baseline A1c less than 7% (mean glucose of less than 154 mg/dl) experienced an increase in their A1c and mean glucose. Individuals with an A1c much lower than 7% or a mean glucose much lower than 154 mg/dl were very likely to experience an increase in their A1c, especially if they were having lots of hypoglycemia at that low A1c.

If a lower A1c is desired, consider lowering the glucose target by one step, but follow up soon after the change to evaluate the effect on hypoglycemia and the need to take carbohydrates to prevent or treat hypoglycemia.

Clinical experience suggests that lifestyle can make a large difference in the mean glucose achieved on the iLet. Individuals who eat fewer carbohydrates in their diet, especially fewer simple carbohydrates, have a lower mean glucose on the iLet than individuals eating higher carbohydrate

diets. If an iLet user decides to make a large change in their dietary habits, the iLet will take some time to adapt to the new meal sizes. If the amount of carbohydrates in a "Usual for me" meal is reduced suddenly and dramatically, the user should be warned to have carbohydrates on hand to prevent or treat hypoglycemia in the late post-prandial period until the iLet adapts to the new meal sizes.

Hypoglycemia

Carbohydrates for the Prevention and Treatment of Hypoglycemia

To avoid reactive hyperglycemia, the amount of carbohydrates to be taken in response to hypoglycemia may need to be reduced compared to the amount used when there is no automation of insulin delivery. The iLet algorithms will already have suspended insulin delivery by the time a hypoglycemic event occurs, so there may be less insulin on board than would be the case without dose automation.

Frequent Hypoglycemia

If the user has frequent hypoglycemia or has more than 1% of the time with a CGM value of less than 54 mg/dl, consider raising the glucose target for all or part of the day by one step (e.g., from "Lower" to "Usual" or from "Usual" to "Higher").

If raising the glucose target was not effective or counterproductive, consider whether a change in the glucose target to a lower value (e.g., from "Higher" to "Usual" or from "Usual" to "Lower") during the daytime is warranted. This counter-intuitive step may be appropriate if the individual is experiencing high post-prandial values despite appropriate adaption of the meal doses. In this case, the lower target will allow the corrections algorithm to add more supplemental insulin earlier in the post-prandial period, which may reduce the amount of insulin on board in the late post-prandial period. Lowering the glucose target during the day may reduce the "roller-coaster" blood glucose phenomenon. The target can be lowered only during the daytime by lowering the primary target (e.g., to "Lower") and then using the "Sleep" target to maintain a higher target (e.g., "Usual") overnight. See **Adjustment of Glucose Target.**

Sick Day Management

The iLet adapts autonomously and continuously to the user's insulin needs. Therefore, in most cases there is no need to make any adjustment to the iLet. If the user experiences increased hypoglycemia during an illness, consider temporarily raising the glucose target during the period of illness (e.g., from "Lower" to "Usual" or from "Usual" to "Higher"). If this is done, the glucose target should be returned to the pre-illness setting after the user recovers.

Elevated Ketones

The Ketone Action Plan

The following Ketone Action Plan was used during the Bionic Pancreas Pivotal Study. Participants in the study were advised to use the Ketone Action plan if their glucose was greater than 300 mg/dl for 90 minutes or greater than 400 mg/dl for any duration. Participants were provided with a fingerstick blood ketone meter and strips.

Elevated ketones were used as an indicator that an insulin infusion set had failed. If ketones were in Zone 1 (blood ketones less than 0.6 mmol/l, corresponding to a negative urine ketone test) they were advised to wait for the iLet to correct the hyperglycemia.

If ketones were in Zone 2 (blood ketones 0.6-2.5 mmol/l, corresponding to trace-moderate on a urine ketone test), and there was no other reason the iLet was not delivering insulin, they were advised to change their infusion set as this was considered evidence of an infusion set failure. They were then advised to wait for the iLet to correct the hyperglycemia and clear the ketones and re-evaluate in 1.5 hours. Failure to clear the ketones within 1.5 hours moved them to Zone 3.

If ketones were in Zone 3 (blood ketones greater than 2.5 mmol/l, corresponding to large on a urine ketone test), participants were advised to disconnect from the iLet for 90 minutes and to give a correction dose of insulin by injection.

The size of the correction dose of insulin in the Pivotal Trial was based on a correction factor derived from the 1800 rule: 1800÷total daily dose (J. Walsh and R. Roberts, Pumping Insulin, CA, San Diego, Torrey Pines Press, 2006). During the Pivotal Trial the recommended correction was 1.25X the calculated correction dose.

The total daily dose can be found in the History screen of the iLet. The total daily dose can also be found in the reports that can be generated by the Beta Bionics smartphone app. Finally, the total daily

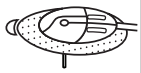
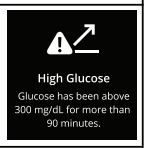
dose can be found on the Beta Bionics iLet reports portal website (www.report.betabionics.com).

The HCP prescribing the iLet is asked to either accept this Ketone Action Plan (either as it stands or with the HCP's preferred modifications) or prescribe their own ketone action plan at the time the iLet is prescribed. This is because the iLet is the first automated insulin delivery system that determines every insulin dose autonomously. Consequently, users may well become less accustomed to choosing their own insulin doses.

Users of the iLet will be trained to contact their HCP for guidance if they find they are in Zone 3 of the Ketone Action Plan. They will be further advised to go to the emergency department if they are unable to contact their HCP.

Ketone Action Plan

LA000059 A

Test your BG and ketones if:	
you are nauseous, vomiting or have diarrhea.	
you think your infusion set is not working.	
your CGM glucose has been above 300 mg/dL for 90 minutes.	
your CGM glucose is above 400 mg/dL.	

Always keep these supplies with you:

- Glucose meter and strips
- Urine ketone strips OR blood ketone meter and strips
- Extra CGM sensor
- Extra infusion set and cartridge
- Insulin vial and syringe, or insulin pen and pen needle

ZONE 1 	**Urine Ketones:** Negative **OR** **Blood Ketones:** less than 0.6 mmol/L	**Check to make sure:** • your iLet is charged, has insulin, and is displaying CGM values. • your infusion set is in place and not leaking. **Continue to monitor your BG:** • If your BG is still high after 90 minutes, check ketones again.
ZONE 2 	**Urine Ketones:** Trace - Moderate **OR** **Blood Ketones:** 0.6 - 2.5 mmol/L	**1. CHANGE** your iLet infusion set. **2. DRINK** extra fluids. **3. RECHECK** BG and ketones in 90 minutes. • If BG is less than 180 mg/dL and ketones are in **ZONE 1,** you do not need to do anything else. • If BG is more than 180 mg/dL and ketones are not in **ZONE 1, GO TO ZONE 3.**
ZONE 3 	**Urine Ketones:** Large **OR** **Blood Ketones:** 2.5 mmol/L or higher	**CALL YOUR HEALTHCARE PROVIDER IMMEDIATELY!** **If your healthcare provider has told you to take an insulin injection, it is important to follow these steps:** 1. **DISCONNECT** from the iLet at the time of injection. 2. Give the injection of rapid acting insulin as instructed by your healthcare provider. 3. **DRINK** extra fluids. 4. **RECHECK** BG and ketones in 90 minutes. • If BG is less than 180 mg/dL and ketones are in **ZONE 1, CHANGE** your iLet infusion set and RECONNECT to the iLet. • If your BG is more than 180 mg/dL and ketones are not in **ZONE 1, CALL YOUR HEALTHCARE PROVIDER, GO TO THE EMERGENCY ROOM, OR CALL 911.**

Ketosis Without Hyperglycemia

Individuals on a very low carbohydrate ketogenic diet may have elevated ketones without hyperglycemia. Likewise, fasting and exercise may also be associated with ketone production. Notably, the Ketone Action Plan suggest that ketones be checked in the setting of hyperglycemia or symptoms of illness. For individuals without hyperglycemia or symptoms of illness, elevated ketones may not be a sign of a failed infusion set, and following the Ketone Action Plan may not be appropriate.

Glucose Management for Individuals Eating Very Few Carbohydrates

Individuals eating very few carbohydrates in a meal or snack (e.g., less than 15 g of carbohydrate for an adult) do not need to announce that meal or snack to the iLet.

If an individual usually eats very low carbohydrate meals, but on occasion eats meals with much more carbohydrate, they should use the "Usual for me", "Less", and "More" structure of the meal announcements only for meals with significant amounts of carbohydrate. They should not announce meals that are very low carbohydrate at all and use the meal announcements only when eating meals that contain significant carbohydrates, and divide only those meals into three sizes, consistent with what is usual for them when eating carbohydrates.

Individuals eating very low carbohydrate diets may have significant ketosis even without problems with insulin delivery. See **Ketosis Without Hyperglycemia.**

BG-Run Mode

Entry into BG-run Mode

Losing CGM values will put the iLet into BG-run Mode. In this mode the iLet can continue to determine all insulin doses as long as BG values are entered frequently.

Reasons for losing CGM values may include: a failed or expired sensor, CGM reporting an error or "???", Bluetooth communication issues between the transmitter and the iLet, or a failed or expired transmitter. When in BG-run Mode, the iLet will only resume the usual mode of insulin dosing when CGM values are available. Therefore, troubleshooting the CGM and making CGM values available to the iLet as soon as possible should be a priority.

To avoid entering BG-run Mode, users should order replacement CGM supplies from Dexcom if sensors fail or fall off or if a transmitter fails early. This can be done online at: https://dexcom.custhelp.com/app/webform. If users are unable to use the website, they should call Dexcom's customer support at 1-888-738-3646.

Users should obtain the required paperwork and order supplies as soon as possible to avoid running out.

Operation of BG-run Mode

If the iLet enters BG-run Mode:

0-7 days after starting the iLet:

- The iLet will alarm to request a BG entry every 1 hour until CGM is restored.
- If no BG is entered within 1 hour of the alert, insulin delivery will stop. User MUST enter a BG, resume CGM, or switch to backup insulin delivery.
- After 48 consecutive hours with no CGM, BG-run mode will end, and all insulin delivery will stop. User MUST resume CGM or switch to back up insulin delivery.
- The start of an insulin suspension will not occur between 12 am and 4 am unless the allowed consecutive 48-hour duration has elapsed. During the 48-hour allowed period, if suspension was indicated between 12 and 4 am, suspension will occur immediately at 4 am.

More than 7 days after starting the iLet:

- The iLet will alarm to request a BG entry every 4 hours until CGM is restored.
- If no BG is entered within 4 hours of the alert, insulin delivery will stop. User MUST enter a BG, resume CGM, or switch to back up insulin delivery.
- After 72 consecutive hours with no CGM, BG-run mode will end, and all insulin delivery will stop. User MUST resume CGM or switch to backup insulin delivery.
- Insulin suspension can occur at any time during the day or night.

Entering BGs in response to alarms is required for insulin delivery to continue. The alarm will sound every 5 minutes. Acknowledging the alarm will snooze it for 30 minutes. Entering a BG value after the alarm will silence the alarm.

The timing of the BG entry will not change when the next BG entry alarm will go off. BGs entered before the alarm will not silence the alarm in advance. The sooner a BG is entered in response to any alarm, the fewer alarms the user will receive.

The Dosing Stops Soon alert will appear when CGM is offline for an extended time. The alert screen will display two timers: The time remaining to enter a BG to avoid insulin suspension and the time remaining to connect to a CGM to avoid insulin suspension. The two timers will be the same in the last few hours of BG-run mode. Entering a BG during this time will not extend the total duration of BG-run mode.

The Dosing Stopped alert will appear when insulin is suspended. The alert screen will display a timer since insulin was suspended. The alert will indicate what is required to resume insulin dosing. A CGM value will always resume insulin dosing. A BG will resume insulin dosing if BG-run Mode has not expired.

Exiting from BG-run Mode

A CGM value will always resume insulin dosing. A BG will resume insulin dosing if BG-run Mode has not expired. If the BG-run Mode has expired (48 or 72 hours have passed), entering a BG will not resume insulin dosing. In this case, the user will need to connect to a CGM or switch to their backup therapy.

Users must have a backup plan in case they are unable to get replacement sensors. See **Backup Insulin Therapy.** If possible, it is preferable to transition to the backup insulin therapy plan in the morning or the evening, at a usual time for taking long-acting insulin.

User should disconnect from the iLet whenever they switch to backup insulin therapy plan.

Glucose Management If the iLet Is Not Functioning

If the iLet is not functioning and is under warranty it will be replaced by Beta Bionics. A backup insulin regimen is needed until the replacement arrives.

Backup Insulin Therapy

The iLet continuously updates the Insulin History screen. This information is relayed through the smartphone app to the cloud where it can be reviewed on the Beta Bionics iLet reports portal (www.report.betabionics.com).

The Insulin History provides the following information:

- Insulin doses given for the "Usual for me" size of the "Breakfast", "Lunch", and "Dinner" meal types.
- Total daily basal dose
- Total daily dose

The total daily basal dose can be used to inform the choice of a daily long-acting insulin dose if using multiple daily injections, or a basal rate if using an insulin pump as a backup device.

The insulin doses for the "Usual for me" meal can be delivered via injection or pump for "Usual for me"-sized meals. The insulin dose for a "Less" meal is 50% of the dose for a "Usual for me" meal. The insulin dose for a "More" meal is 150% of the dose for a "Usual for me" meal.

A correction factor can be determined from the total daily dose using the following formula: 1800÷total daily dose (J. Walsh and R. Roberts, Pumping Insulin, CA, San Diego, Torrey Pines Press, 2006).

If possible, it is preferable to transition to the backup insulin therapy plan in the morning or the evening, at a usual time for taking long-acting insulin.

Insulin Infusion Sets

Choosing an Insulin Infusion Set

Failure of infusion sets is a risk for every insulin infusion system. In the pivotal study, which used the Inset 1 (plastic cannula inserted perpendicular to the skin surface), the rate of insulin set failures was ~1.3% per day. This rate was nearly identical to the rate of infusion set failures in the Control-IQ pivotal study, as show below in Table S25 from the Supplement to Russell, et al. New England Journal of Medicine 2022; 387:1161-1172.

Table S25. Presumed Infusion Set Failures with Comparison to Published Data for the Tandem t:slim X2 insulin pump with Control-IQ Technology

# of presumed infusion set failures within 72 hrs/# of infusion sets worn

Age Group 6-13		Age Group 14-17		Age Group ≥18	
BP	Control-IQ	BP	Control-IQ	BP	Control-IQ
88/1544 (5.7%)	115/2105 (5.5%)	60/808 (7.4%)	189/2731 (6.9%)	55/2407 (2.3%)	143/6216 (2.3%)

In the Table, BP columns refer to the Bionic Pancreas Pivotal study. The Control-IQ columns refer to data from a published analysis assessing the frequency of potential infusion set failures in clinical trials in which patients used the Tandem t:slim X2 insulin pump with Control-IQ Technology, with a variety of infusion sets (Kanapka LG, Lum JW, Beck RW. Insulin Pump Infusion Set Failures Associated with Prolonged Hyperglycemia: Frequency and Relationship to Age and Type of Infusion Set During 22,741 Infusion Set Wears. Diabetes Technol Ther 2022;24:396-402).

Since only infusion sets with a 90-degree insertion were used with the BP in the Bionic Pancreas Pivotal study, for this comparison, the Control-IQ data were limited to 90-degree insertion infusion sets. Data are stratified by age group since failure rates varied by age. The denominator in each cell is the number of infusion sets worn and the numerator is the number of infusion sets which were removed prior to 72 hours preceded by prolonged hyperglycemia. Prolonged hyperglycemia was defined as (1)

CGM >300 mg/dL immediately before infusion set removal, (2) CGM continuously >250 mg/dL in the 2-hour period before the infusion set removal, and (3) CGM >300 mg/dL for at least 90 minutes of the 2-hour period before the infusion set removal.

Research suggests that infusion sets with steel cannulas are less vulnerable to early failures as shown below in Figure 1 of Buckingham, et al. Diabetes Technology and Therapeutics 2014; 16:15-19. The figure shows survival curves for catheters with Teflon cannulas (QS) and for catheters with steel cannulas (ST). Infusion sets with steel cannulas are also reported to be more comfortable to insert than infusion sets with plastic cannulas. Consider the use of an infusion set with a steel cannula for individuals a higher risk of infusion set failure, those with a history of infusion set failures, those for whom an infusion set failure might be detected late, or those for whom the consequences of a failure would be more severe (e.g., children).

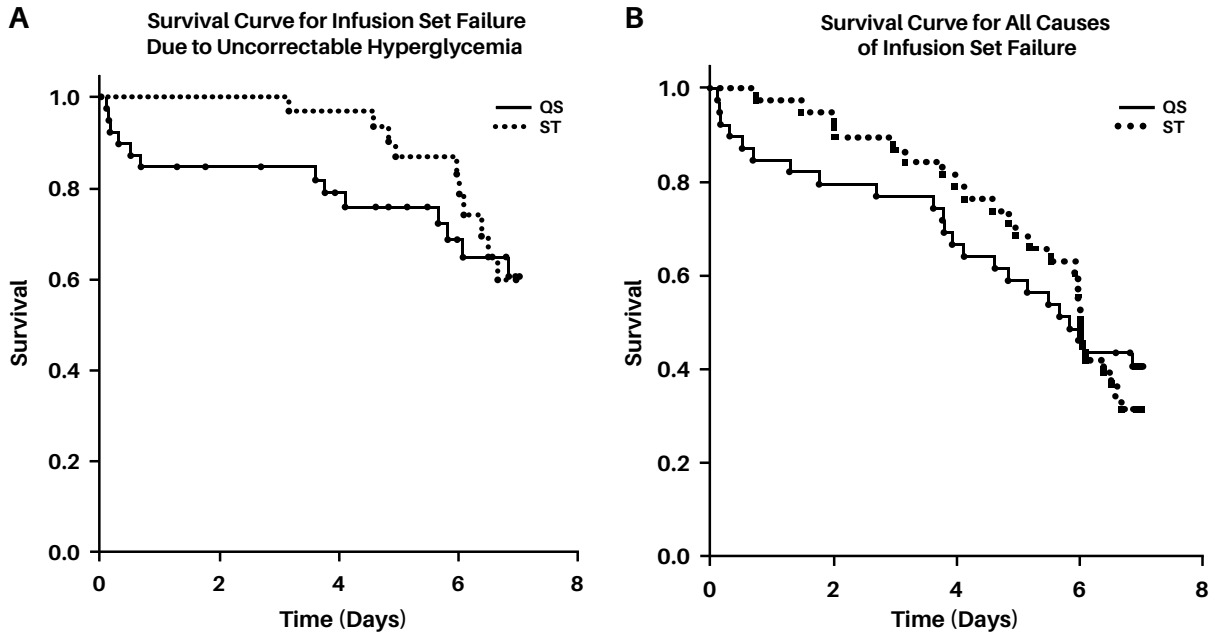


FIG. 1. Survival curves for infusion sets: (**A**) infusion set failure due to uncorrectable hyperglycemia (when the end point was hyperglycemia [>250 mg/dL] and the meter blood glucose level did not decrease by at least 50 mg/dL an hour after a correction bolus and/or blood ketone levels were greater than 0.6 mmol/L) and (**B**) for all causes of infusion set failure (uncorrectable hyperglycemia with or without ketonemia, pain, infusion set fell out [loss of adhesion], pulled out accidentally, erythema and induration, and infection). The solid line is the Teflon catheter (Quick-Set [QS]), and the dotted line is the steel needle catheter (Sure-T [ST]).

It is important to note that iLet infusion sets with steel catheters are approved for one-two days of use, while the iLet infusion sets with Teflon catheters are approved for two-three days of use.

At the present time, only infusion sets with 6 mm cannulas are available for the iLet.

Filling the Infusion Set Cannula

The last step of the workflow to change an infusion set is to "Fill Cannula". The user must select the kind of insulin set they are using. If a Teflon infusion set has been selected, "Fill Cannula" will deliver the appropriate volume of insulin to fill the cannula and reset the reminder to replace the infusion set to count down from three days. For a steel infusion set, "Fill Cannula" will not deliver any insulin (the steel cannula is filled during priming) but will reset the reminder to replace the infusion set to count down from two days.

Alarms

To avoid alarm fatigue, the iLet alarms were designed with the intent that they would all be immediately actionable by the user.

All insulin doses are determined autonomously by the iLet algorithms. Therefore, most hyperglycemia alarms would not be actionable. An alarm that suggests the need to consider insulin infusion set failure is immediately actionable and is included in the suite of alarms. Alarms for hypoglycemia and impending hypoglycemia are immediately actionable, and there are several alarms of this type to meet users' individual needs and preferences. Alarms related to the ability of the iLet to administer insulin are immediately actionable.

High Alarm

This alarm sounds when the CGM value has been greater than 300 mg/dl for 90 minutes. It is likely that there is a problem with the infusion set, or that insulin is not being delivered for some other reason if this alarm is triggered. However, this alarm may sound without an insulin delivery problem before the iLet has adapted, if there is a sudden increase in insulin requirement, or if a very high carb and high fat meal is consumed, or if a meal is consumed without a meal announcement. When this alarm sounds the user should follow the Ketone Action Plan (see Elevated Ketones). This alarm should never be turned off.

Urgent Low Alarm

This alarm sounds when the CGM value is less than 54 mg/dl. This alarm cannot be turned off.

Urgent Low Soon Alarm

This alarm sounds when the CGM value is predicted to be less than 54 mg/dL within 20 minutes. It is suggested that this alarm not be turned off because it will allow the user to treat impending hypoglycemia with a CGM value less than 54 mg/dl before it occurs.

Glucose Falling Quickly

This alarm sounds when the CGM value is less than 100 mg/dL and is falling at a rate of greater than or equal to 2 mg/dL/min (said another way, when the CGM value is predicted to be less than 70 mg/dl within 15 minutes). This alarm will allow users to treat impending hypoglycemia with a CGM value less than 70 mg/dl before it occurs. Automatic suspension of insulin delivery by the iLet may avert hypoglycemia even after this alarms sounds. In consultation with their HCP, users may choose to turn off this alarm to reduce the number of alarms they receive.

Occlusion Alarm

When this alarm occurs insulin dosing is suspended. This alarm must be acknowledged for insulin dosing to resume. In most cases, this alarm means that the infusion set needs to be replaced, but it could also mean that insulin flow through the infusion set tubing was blocked.

Infusion Set Replacement Alarm

The alarm to replace infusion sets is set for three days for Teflon infusion sets and two days for steel infusion sets. It is resent by completing the "Fill Cannula" step during infusion set replacement workflow.

Low Insulin and Insulin Out Alarms

Low insulin alarms will sound when 20 units remain and when 5 units remain. An insulin out alarm will sound when no insulin remains.

Low Battery Alarms

Low battery alarms will sound when approximately 5% of battery power remains and when approximately 2.5% of battery power remains. The battery power is depleted at a rate of approximately 1% per hour under ordinary conditions.

Calibration of the Dexcom G6 CGM

If a blood glucose value is entered into the iLet when CGM data is available, the blood glucose value will be used to calibrate the Dexcom G6 CGM.

Guidelines from Dexcom should be used when determining whether a calibration of the Dexcom G6 should be performed.

If a blood glucose value is entered into the iLet when CGM data is not available, no calibration will be performed. The blood glucose value will be used to determine insulin dosing by the iLet in BG-run iLet mode.

Choice of Insulin for Use with the iLet

Insulins Indicated for Use with the iLet

The iLet ACE Pump and iLet Dosing Decision Software are designed to use rapid-acting U-100 insulin. The following U-100 rapid acting insulin analogs have been tested and found to be safe for use in the iLet device:

- NovoLog (insulin aspart) and Humalog (insulin lispro)

Other Insulins

Humalog (insulin lispro) U200: The iLet has not been tested with Humalog (insulin lispro) U200 and is not indicated for use with Humalog (insulin lispro) U200.

There is no mechanism by which to inform the iLet control algorithms that a more concentrated insulin has been loaded.

If U200 insulin is loaded into a new iLet or an iLet that has been factory reset, the initial weight-based dosing will deliver twice as much insulin per pound of body weight as if U100 insulin were used. **This is expected to be associated with an increased risk of hypoglycemia.**

If U200 insulin is loaded into an iLet that has adapted using U100 insulin, twice as much insulin as the amount determined by the algorithms will be delivered. **This is expected to be associated with a very high risk of hypoglycemia including severe hypoglycemia.**

RHI (regular human insulin) U100: The iLet has not been tested with RHI U100 and is not indicated for use with regular human insulin U100.

RHI U100 has markedly slower absorption kinetics than Humalog (insulin lispro) U100 and Novolog (insulin aspart) U100. There is no mechanism by which to inform the iLet control algorithms that an insulin with slower absorption kinetics has been loaded.

The iLet control algorithms assume a speed of insulin absorption consistent with rapid-acting insulins, such as Humalog (insulin lispro) and Novolog (insulin aspart). If a slower-acting insulin, such as RHI U100 is used, the insulin-on-board calculations by the iLet control algorithm will be incorrect and there is a greatly increased risk of stacking insulin. **This is expected to be associated with a very high risk of hypoglycemia including severe hypoglycemia.**

RHI (regular human insulin) U500: The iLet has not been tested with RHI U500 and is not indicated for use with RHI U500.

There is no mechanism by which to inform the iLet control algorithms that a more concentrated insulin has been loaded.

If U500 insulin is loaded into a new iLet or an iLet that has been factory reset, the initial weight-based dosing will deliver five times as much insulin per pound of body weight as if U100 insulin were used. **This is expected to be associated with a very high risk of hypoglycemia including severe hypoglycemia.**

If U500 insulin is loaded into an iLet that has adapted using U100 insulin, five times as much insulin as the amount determined by the algorithms will be delivered. **This is expected to be associated with a very high risk of hypoglycemia including severe hypoglycemia.**

RHI U500 has dramatically slower absorption kinetics than Humalog (insulin lispro) U100 and Novolog (insulin aspart) U100. There is no mechanism to inform the iLet control algorithm that an insulin with slower absorption kinetics has been loaded. The iLet control algorithms assume a speed of insulin absorption consistent with fast-acting insulins such as Humalog (insulin lispro) and Novolog (insulin aspart). If a slower-acting insulin such as RHI U500 (which is absorbed even more slowly than RHI U100) is used, the insulin-on-board calculations by the iLet control algorithm will be incorrect and there is a greatly increased risk of stacking insulin. **This is expected to be associated with a very high risk of hypoglycemia including severe hypoglycemia.**

Use of the iLet for Users with a Very Low Insulin Requirement

The minimum dose of insulin than can be delivered by the iLet in any step is 0.045 units.

If the amount of insulin to be delivered as a basal rate is less than 0.045 units per 5-minute step (e.g., less than 13 units of total basal insulin per day) then the iLet will not deliver basal insulin at every 5-minute step and will skip some steps even if the glucose is very close to the target.

The iLet will accumulate insulin to be delivered "in memory" until the minimum dose that can be delivered accumulates.

Use of the iLet for Users With High Insulin Requirements

During the Insulin-only Bionic Pancreas Pivotal Trial, a very small number of participants required more insulin than the iLet control algorithm would deliver, or they were using more than one insulin cartridge per day (i.e., more than ~160 u of insulin daily). In these cases, consideration was given to adding long-acting insulin, such as insulin glargine (Lantus) or insulin degludec (Tresiba), to iLet therapy to provide part of the insulin requirement.

Based on this limited experience, it is recommended that addition of long-acting insulin be considered if the total daily insulin dose delivered by the iLet is ≥160 units daily or if the following conditions had been met and the mean glucose on the iLet over several days is >180 mg/dl:

- The user is consistently announcing meals, and the majority of the meals are being announced as "Usual for me".
- The meal doses for all meal types (e.g., "Breakfast", "Lunch", and "Dinner") has successfully adapted.
- The glucose target has been progressively reduced to "Lower" using the provided guidance.

The goal for the recommended approach to long-acting insulin dose adjustment is to provide only a fraction of the basal insulin need. If too much long-acting insulin is added, suspension of insulin delivery by the iLet control algorithm may not be effective in preventing hypoglycemia.

An appropriate range for the long-acting insulin dose may be chosen by determining the Total Daily Basal administered by the iLet (available in the History menu under "Insulin History" on the iLet, and also in the Bionic Report on the web portal) and selecting a dose of long-acting insulin that is **no more than one-half of the "Total Daily Basal" administered by the iLet**.

If the dose of long-acting insulin is adjusted after initiation, it is recommended that the amount of long-acting insulin never exceed one-half of the **total amount of basal insulin from all sources**, which is the sum of any long-acting insulin given daily and the updated "Total Daily Basal" administered by the iLet.

Use of the iLet as a Partially "Untethered" Pump

Some HCPs may prescribe long-acting insulin as an adjunct to the use of a pump or an automated insulin delivery system even when the insulin requirement is not large. This may be done for athletes who wish to disconnect for extended periods of time during exercise, or for users considered to be at very high risk for failed infusions sets.

This use case has not been evaluated for the iLet, but if an HCP chooses to add long-acting for these or similar reasons it is recommended that the dose of long-acting insulin should represent only a fraction of the basal insulin need. If too much long-acting insulin is added, suspension of insulin delivery by the

iLet control algorithm may not be effective in preventing hypoglycemia.

Therefore, it is recommended that the dose of long-acting insulin should be **no more than one-half of the "Total Daily Basal"** administered by the iLet. For this use case, the amount of long-acting insulin will usually be considerably lower than one-half, e.g. 10-30% of the "Total Daily Basal".

If the dose of long-acting insulin is adjusted after initiation, it is recommended that the amount of long-acting insulin never exceed one-half of the **total amount of basal insulin from all sources**, which is the sum of any long-acting insulin given daily and the updated "Total Daily Basal" administered by the iLet.

Limited Access

It is possible to enable the Limited Access setting of the iLet, which will require a numerical passcode to enter a meal announcement or change any settings. This feature is meant to allow parents, guardians, or caregivers to prevent children from inappropriately entering meal announcements or changing settings. This feature may also be useful for adults with cognitive impairment. The Limited Access code is set when activating the feature. The Limited Access feature can be found in Settings menu in the Other sub-menu.

When Limited Access is on, the iLet will give basal and correction bolus insulin as usual, but entry of a meal announcement or changing any settings Will require entry of the Limited Access code.

Factory Reset

If a Factory Reset is performed, all the adaptation of the iLet algorithm will be lost. The user's weight will have to be entered to restart the iLet, and adaptation to the user will restart without any memory of previous use.

If a user has performed actions leading to inappropriate adaptation, it may be appropriate to perform a Factory Rest and start fresh. As an example, imagine a user who was nervous about the insulin to be delivered by the iLet and has been entering meals that should have been announced as "Usual for me" instead as "Less" meals to reduce the amount of insulin they will receive. If they switch to announcing these meals as "Usual for me", the iLet will deliver approximately twice as much insulin as they have been receiving in response to the firstof these announcements. The iLet will adapt the dose downward, but there is a risk of hypoglycemia until the adaption occurs.

In this scenario, the user could keep oral carbohydrates on hand and watch carefully for hypoglycemia after the first few meals announced in the new way until the meal dosing algorithm adapts. On the other hand, an HCP may decide that in this scenario it is best to perform a factory reset and start adaptation over again, this time announcing meals in the appropriate category from the beginning. If this is done, the HCP or a Certified iLet Trainer should make sure the user's weight is entered accurately into the iLet during the startup process and provide appropriate re-education.

Speed of Insulin Delivery

The iLet delivers insulin boluses at an even rate of one unit every three seconds. Therefore, a dose of 10 units will take 30 seconds to deliver. The speed of insulin delivery cannot be adjusted.

Software Updates

Updates to the iLet software can be downloaded to the Beta Bionics smartphone app over cellular or WiFi and delivered to the iLet via the Bluetooth link.

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