EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
DreaMed Advisor Pro

DECISION SUMMARY

A. DEN Number:

DEN170043

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the DreaMed Advisor Pro

C. Manufacturer and Instrument Name:

DreaMed Diabetes, Ltd.: DreaMed Advisor Pro

D. Type of Test or Tests Performed:

Insulin Therapy Adjustment Device

E. System Descriptions:

1. Device Description:

DreaMed Advisor Pro is a software device that is designed to provide insulin therapy adjustment recommendations to physicians to assist in the management of diabetes for patients with Type 1 diabetes using an insulin pump and a continuous glucose monitoring (CGM) system.

The DreaMed Advisor Pro gathers and analyzes information inputted through qualified 3rd party Diabetes Management Systems (DMS), which collects biological input information from various diabetes devices. Diabetes device information required and used by DreaMed Advisor Pro includes glucose readings (CGM sensor readings with the option for capillary blood glucose measurements), insulin dosing logs, and meal data during daily routine care.

Following data collection and analysis, the DreaMed Advisor Pro generates results containing summary data and recommendations for adjustments to the patient's insulin therapy parameters, including: basal insulin delivery rate(s), insulin to carbohydrate ratio, and correction factor (insulin sensitivity)(b) (4) DreaMed Advisor Pro may also advise behavioral changes. Results are sent to a qualified 3rd party Diabetes Management Systems, which displays results to physicians and a report provided by DreaMed Diabetes. The physician can approve, reject or change the recommendations and issue the updated treatment plan to the patient.

2. Principles of Operation:

   Algorithmic software device

3. Modes of Operation:

   Does the applicant's device contain the ability to transmit data to a computer, webserver, or mobile device?

   Yes ____X____ or No _____

   Does the applicant's device transmit data to a computer, webserver, or mobile device using wireless transmission?

   Yes ____X____ or No ____X____

4. Specimen Identification:

   Not Applicable

5. Specimen Sampling and Handling:

   Not Applicable

6. Calibration:

   Not Applicable

7. Quality Control:

   Not Applicable

8. Software:

   FDA has reviewed applicant's Hazard Analysis and Software Development processes for this line of product types:

   Yes____X____ or No_____

F. Regulatory Information:

1. Regulation section:

   21 CFR 862.1358

2. Classification:

   Class II

3 Product code:

   QCC

4. Panel:

   Chemistry (75)

G. Indications for Use:

1. Indication(s) for Use:

   DreaMed Advisor Pro is a decision-support software intended for assisting healthcare professionals in the management of patients with Type 1 diabetes who:

   - use insulin pumps as their insulin delivery therapy;
   - monitor their glucose levels using either of the following:
     - CGM, or
     - CGM and self-management blood glucose meter
   - are above the age of 6 and under 65 years old; and
   - use rapid acting U-100 insulin analogs in their pump

   DreaMed Advisor Pro is indicated for use by healthcare professionals when analyzing continuous glucose monitoring (CGM), self-monitoring blood glucose (SMBG) and pump data to generate recommendations for optimizing a patient's insulin pump settings for basal rate, carbohydrate ratio (CR), and correction factor (CF); without considering the full clinical status of a particular patient. DreaMed Advisor Pro does not replace clinical judgment.

2. Special Conditions for Use Statement(s):
   - For prescription use only
   - For in vitro diagnostic use only
   - This device is not intended to to send recommendations directly to patients without initially being reviewed and approved by a healthcare professional (HCP).
   - This device cannot generate recommendations for patients who are unwilling or unable to use a CGM.
   - This device is not intended for use with patients who use automated insulin dosing systems (e.g., "closed-loop", "artificial pancreas").
   - This device is not intended for use with patients who use insulin(s) other than U-100.

The Advisor Pro is designed to consider the pharmacodynamics and pharmacokinetics of U-100 insulin only. Using Advisor Pro with other types of insulin may lead to patient harm.

- This device is not intended for use for patients treated with insulin injections, intravenous (IV) insulin, or a combination of insulin injections and/or IV insulin and insulin pump therapy. Since Advisor Pro analyzes the insulin dosing history from the insulin pump, it will be blind to insulin delivered by injections and/or IV insulin. This could result to a false conclusion about the changes to the patient's insulin pump settings and may lead to patient harm.
- This device is not intended for patients using other concomitant non-insulin glucose lowering therapies. Since the Advisor Pro analyzes the insulin dosing history from the insulin pump, reducing glucose levels by other means will not be taken into consideration by Advisor Pro. This could result to a false conclusion about the changes to the patient's insulin pump settings and may lead to patient harm.
- This device is not intended for use with patients under the age of 6 or above the age of 65.
- This device is not intended for use in pregnant women.
- DreaMed Advisor Pro is not recommended for patients who are taking medications that might affect CGM values, such as acetaminophen. Please refer to the warnings and contraindications of the patient's CGM to determine whether said medications may falsely raise glucose readings of the sensor.

3. Special Instrument Requirement(s):

DreaMed performs integration testing with third party Diabetes Management Systems (DMS) to ensure that the DMS verifies that the medical devices providing data are approved or cleared for use in the geographical area where the HCP and patient are utilizing the system. Integration testing demonstrates that DreaMed has verified the integration between the DMS and DreaMed for the server and for the algorithm. A third party DMS is qualified through the DMS qualification plan and the integration test results.

H. Standard/Guidance Documents Referenced:

1. ISO 14971 Medical devices - Application of Risk Management to Medical Devices.
2. IEC 62366-1:2015 Medical Devices - Part 1: Application of Usability Engineering to Medical Devices
3. IEC62304:2006 Medical Device Software - Software Life Cycle Processes
4. ISO 15223-1 Medical Devices - Symbols To Be Used With Medical Device Labels, Labelling, And Information To Be Supplied - Part 1: General Requirements
5. ISO 14155 Clinical Investigation Of Medical Devices For Human Subjects - Good Clinical Practice

I. Performance Characteristics*:*

1. Analytical Performance:

a. Accuracy:

Not applicable.

b. Precision/Reproducibility:

Not applicable.

c. Linearity:

Not applicable.

d. Carryover:

Not applicable.

e. Interfering Substances:

Not applicable.

2. Clinical Performance:

There were two studies conducted to evaluate the DreaMed Advisor Pro in the clinical use setting. The first study (n=15) compared differences in the use of DreaMed Advisor Pro between expert endocrinologists and the DreaMed Advisor Pro. The second study (n=6) evaluated glycemic information in patients under the care of diabetes healthcare professionals compared to DreaMed Advisor Pro.

The first study was an expert diabetes physician survey, conducted in 3 centers in Germany, Israel and Slovenia, with 3 physicians from each center participating. Uploads of 15 patients (children and adolescents with Type 1 Diabetes utilizing an insulin pump) including data of 3 weeks of CGM, SMBG and insulin pump data were assessed. Each of the 9 experts received 15 anonymized PDF files, and was asked to complete a form describing the proposed recommended changes to insulin dosing including the basal rate, carbohydrate ratio, and correction factors. In addition, each expert was asked to state if any behavioral or lifestyle changes were recommended. The results were compared to the Advisor Pro automated recommendations. The recommendations from the physicians at each site were also compared. The study results suggest that the recommendations of the DreaMed Advisor Pro were generally similar to the recommendations of expert physicians with respect to the basal rate as well as the carbohydrate ratio (CR). The results indicated that there was a difference between the physicians compared to DreaMed Advisor Pro and physician recommendations

for the correction factor (CF). The results also suggest that there was diversity between experts with regards to recommendations to the same data.

The second study was a single center study, conducted at a pediatric hospital in Israel. A set of 6 subjects used the the algorithm and were compared to paired, randomized subjects (n=7) in the control group. Each subject completed two iterations of treatment recommendations, either guided by the Advisor Pro in the intervention group, or the expert physician in the control group. Endpoints were compared between the two groups (the study group guided treatment by the Advisor Pro and the control group guided by the physician) during 6 weeks before intervention and during the study period when the insulin dosing was adjusted. The results of this study suggest that percentage of CGM time within the sensor glucose range of 70-180 mg/dL was increased during the intervention and, percentage of CGM readings below 70 mg/dL was reduced in the Advisor Pro Group compared to the control group. The sponsor reports that no serious adverse events occurred in either group of the study. The other parameters relevant to diabetes management (total daily dose, average daily number of insulin boluses, amount of carbohydrates) did not demonstrate clear differences between the Advisor Pro and the control group.

The findings from these two studies support the safety of use of the DreaMed Advisor Pro. The findings from the expert physician survey suggest that, in general, insulin dosing recommendations made by expert endocrinologists vary to similar degrees between insulin dosing recommendations made by DreaMed Advisor Pro and expert endocrinologists. The second study also supports the safety and clinical validity of the DreaMed Advisor Pro. However, given the small size, limited duration, general study design, and choice of endpoints used in these studies, it is not possible to make definitive conclusions about short- or long-term benefits related to time in range or glycemic control associated with use of the DreaMed Advisor Pro.

DreaMed Diabetes, Ltd. also erformed a task analysis and a use-related risk analysis to identify potential use errors involved with use of DreaMed Advisor Pro and their associated harms and severities. Patients with type 1 diabetes regularly check in with their HCPs and the product is not intended to be used in an emergency situation. Human factors testing was performed to validate that these risks are likely mitigated to an acceptable level.

As a simulated□use study, no actual treatment occurred. Participants were asked to interact with the product as they would in real life, but not actually change their pump settings or make recommendations for real patients since it was simulated. According to the Sponsor, all users in real life would have an opportunity to receive training before first time use of the product. Therefore, all study participants first received representative training on the product. After a break of at least 1 hour to allow for memory decay, participants were observed using the product in a one□on□one moderated simulated□use testing session that lasted up to 30 minutes for lay user participants and up to 60 minutes for HCP participants.

A total of 48 lay user participants (17 adult patients, 16 adult caregivers,15 pediatric patients) and 15 HCPs were included for analysis in the study. An additional two pediatric patients, one adult patient, and three HCPs were disqualified for not meeting the screening criteria or

representing anticipated users. All lay user participants reported being smartphone users and would consider using an app to help manage their (or the person they care for) diabetes. All patients were diagnosed with type 1 diabetes and are currently using an insulin pump.

The design and results of the study were reviewed and found acceptable.

J. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Parts 801 and 809, as applicable and the special controls for this type of device.

K. Identified Risks to Health and Mitigation Measures

Identified Risks to Health	Required Mitigations
Erroneous or extreme changes in insulin dosing recommendations may cause hypoglycemia or hyperglycemia.	General Controls and special controls (1), (2), and (3)
Incorrect interpretation of results may lead to inappropriate clinical decision making.	General Controls and special controls (1), and (3)
Incorrect understanding of appropriate device use may lead to inappropriate treatment decisions.	General Controls and special controls (1), (2), and (3)
Patient harm due to insecure transmission of data.	General Controls and special control (1)
Data corruption may lead to inappropriate treatment recommendations.	General Controls and special control (1)

L. Benefit/Risk Determination

DreaMed Advisor Pro is a software device intended for assisting healthcare professionals in the management of patients with Type 1 diabetes who use insulin pumps as their insulin delivery therapy, monitor their glucose levels (either by using CGM, or CGM and self-management blood glucose meter), and are above the age of 6 and under 65 years old. DreaMed Advisor Pro is indicated for use as an adjunctive device to support healthcare professionals when analyzing CGM, SMBG and insulin pump data to generate recommendations for optimizing a patient's insulin pump settings, without considering the full clinical status of a particular patient. It does not replace clinical judgement. DreaMed Advisor Pro is intended for use only with patients who use rapid acting U-100 insulin analogs in their pump.

The DreaMed Advisor Pro offers benefits of convenience to patients by providing an automated analysis that is systematically conducted, potentially decreasing the burden to healthcare

professionals in insulin pump adjustments, and thus allowing for the opportunity for patients to receive more frequent insulin pump adjustments. The DreaMed Advisor Pro also offers indirect benefits to patients, by offering potential benefits of convenience to healthcare professionals by potentially reducing the time necessary in adjusting insulin pump settings, as well as providing an automated analysis that is conducted systematically. Decreasing the time burden to healthcare professionals in making insulin pump adjustments, would allow for optimizing valuable office visit time with healthcare professionals.

The two studies evaluating clinical use of the device (described above), conducted by the sponsor are not sufficient to demonstrate increased effectiveness with respect to traditionally recognized clinical outcomes, given limitations in study design, sample size, and population(s) studied. However, given the challenges in the current state of insulin pump management, as well the potential convenience and potential for more frequent optimization of insulin pump settings, there are likely benefits to patients in terms of more frequent opportunities to optimize insulin pump parameters.

Potential risks associated with use of the DreaMed Advisor Pro are risks associated with suboptimal insulin dosing recommendations or diabetes management tips, which can be due to the risk of inaccurate CGM, SMBG, insulin delivery information, time mismatch or time zone changes. In addition, there is a risk of healthcare professional overreliance on the DreaMed Advisor Pro recommendations and diabetes management tips, without considering the clinical context.

The potential clinical consequences of these risks are risks relating to acute and chronic consequences of hypoglycemia, hyperglycemia and suboptimal glucose control, which include hypoglycemia, severe hypoglycemia, hyperglycemia, diabetic ketoacidosis (DKA), worsening of glycemic control and diabetic complications. The potential clinical consequences of these known/probable risks are more than minimal. However, given the information provided supporting safe use of this device and the mitigations provided by the special controls established for this device type, along with general controls, the potential risks associated with use of the DreaMed Advisor Pro can be mitigated such that they are are not expected to be greater than the risks associated with insulin pump parameter titration without use of this device.

There are mitigations against potentially inaccurate data (sensor glucose or blood glucose values) being used in the determination of recommendations provided by the DreaMed Advisor Pro. First, this device provides recommendations relating to insulin dosing and diabetes management tips to the healthcare provider, not directly to the patient. The healthcare professional could choose to reject potentially unsafe recommendations based on their training and clinical judgement.

Further, the device algorithm has designated limitations and parameters to changes which seem generally consistent with the scope of recommendations and diabetes management tips generated by the device and implementable in insulin pumps, and seem generally consistent with clinical decision making. Users of this device are required to use CGM, which provides them with additional feedback relating to glucose values, and helps to mitigate risks relating to potentially suboptimal recommendations from this device.

Further, the labeling clearly states that this device is intended to be used to support healthcare professionals when analyzing CGM, SMBG and pump data to generate insulin dosing suggestions, and that it does not replace clinical judgement. The labeling provides transparency to the healthcare professional so that the healthcare professional can be sufficiently aware of the intended use and functionality of the device, limitations of the device, as well as of situations in which the device should not be used. The device also has mechanisms to determine "valid" data, and can "filter" data that is not considered valid. Finally, the healthcare professional has the ability to change or delete any of the recommendations (insulin dosing related or diabetes management tip related) prior to this information being available to their patient.
There are risks relating to cybersecurity as well as risks relating to data corruption specific to use of this device. General and special controls are sufficient to mitigate against these risks.

Overall, the potential benefits of the DreaMed Advisor Pro outweigh the potential risks that are mitigated by the assigned special controls and general controls for the proposed indications for use.

M. Patient Perspectives:

This submission did not include specific information on patient perspectives for this device. Patient perspectives FDA considered for the DreaMed Advisor Pro include information obtained through discussion with patients at public forums regarding their experience with continuous glucose monitoring systems, insulin dosing aids, and insulin pumps in general.

N. Conclusion

The information provided in this *de novo* submission is sufficient to classify this device into class II under regulation 21 CFR 862.1358. FDA believes that the special controls, in combination with the general controls provide a reasonable assurance of the safety and effectiveness of the device type. The device is classified under the following:

Product Code: QCC
Device Type: Insulin Therapy Adjustment Device
Class: II (special controls)
Regulation: 21 CFR 862.1358

(a) *Identification*: An insulin therapy adjustment device is a device intended to incorporate biological inputs, including glucose measurement data from a continuous glucose monitor, to recommend insulin therapy adjustments adjustments as an aid in optimizing insulin therapy regimens for patients with diabetes mellitus.

(b) Classification: Class II (special controls). The special controls for this device are

1. Design verification and validation must include the following:
    - (i) A complete description of the required data inputs, including timeframe over which data inputs must be collected and number of data points required for accurate recommendations.
    - (ii) A complete description of the types of device outputs and insulin therapy adjustment recommendations, including how the recommendations are generated.
    - (iii) Robust data demonstrating the clinical validity of the device outputs and insulin therapy recommendations.
    - (iv) A robust assessment of all input data specifications, including accuracy requirements for continuous glucose monitors and other devices generating data inputs, to ensure accurate and reliable therapy adjustment recommendations. This assessment must include adequate clinical justification for each specification.
    - (v) A detailed strategy to ensure secure and reliable means of data transmission to and from the device, including data integrity checks, accuracy checks, reliability checks, and security measures.
    - (vi) Robust data demonstrating that users can understand and appropriately interpret recommendations generated by the device.
    - (vii) An appropriate mitigation strategy to minimize the occurrence of dosing recommendation errors, and to mitigate the risk to patients of any residual dosing recommendation errors to a clinically acceptable level.
2. The device must not be intended for use in implementing automated insulin dosing.
3. Your 809.10(b) labeling must include:
    - (i) The identification of specific insulin formulations that have been demonstrated to be compatible with use of the device.
    - (ii) A detailed description of the specifications of compatible devices that provide acceptable input data (e.g., continuous glucose monitors, insulin pumps) used to provide accurate and reliable therapy adjustment recommendations.
    - (iii) A detailed description of all types of required data (inputs) and dosing recommendations (outputs) that are provided by the device.
    - (iv) A description of device limitations, and instructions to prevent possible disruption of accurate therapy adjustment recommendations (e.g., time zone changes due to travel).