FreeStyle Libre 2 — A New ICGM Device

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ADC-23858 v3.0

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INTRODUCTION

Continuous glucose monitoring (CGM) systems are increasingly becoming an important part of diabetes management, both for people with diabetes that use insulin and those that do not. Over 3 million people with diabetes use sensors for their daily glucose management.[1] CGM systems capture rich data and give clinicians and patients additional information that facilitate more informed treatment decisions.

This synopsis paper is a comparative evaluation of two such CGM systems that are cleared under the new iCGM requirements[2] from the U.S FDA (Food and Drug Administration) the FreeStyle Libre® 2 system and the Dexcom G6® system. These systems perform similarly in many respects. However, end users and healthcare providers deciding between these systems may desire information on how the specifications, performance and product indications of these two systems differ. Included in this paper is an overview of certain factors that end users and healthcare providers may want to consider when deciding which of these systems are appropriate, namely:

1. Both FreeStyle Libre 2 and Dexcom G6 systems meet iCGM performance requirements.

2. The FreeStyle Libre 2 system generates glucose results every minute while the Dexcom G6 generates glucose results every five minutes.

3. MARD of the FreeStyle Libre 2 system is 9.2% compared to 9.9% for the Dexcom G6 in the adult population: the pediatric MARD are 9.7% for the FreeStyle Libre 2 system and 9.6% for the Dexcom G6.

4. Both FreeStyle Libre 2 and Dexcom G6 systems have optional real time low and high glucose alarms, that can be configured. The Dexcom G6 system also has an urgent low alarm that cannot be changed or turned off. The alarm performance for the two systems are comparable at low glucose levels and FreeStyle Libre 2 has slightly better performance at high glucose levels.

5. In a head- to- head study, the FreeStyle Libre 2 system showed significantly better accuracy in the first 12 hours compared to the Dexcom G6 system.

6. All CGM sensors are affected by interfering agents. For example, ingestion of high doses of ascorbic acid supplements (not food source) could cause one to potentially miss a severe low glucose event while using the FreeStyle Libre 2 system. The Dexcom G6 system could be affected by three different interfering agents: repeated use of normal doses of acetaminophen, hydroxyurea (which may cause the sensor to read high even at highest concentrations under therapeutic treatment) and *in-vitro* data suggests uric acid at the normal reference interval may also interfere.

7. The FreeStyle Libre 2 system is a 14-day sensor which is not capable of user reactivation to extend its use life. The Dexcom G6 sensor can be extended by the user. In the extended period, the sensor may not meet the iCGM requirements and therefore may not be suitable for automated insulin dosing decisions.

Data for each of the above are addressed in this paper in turn.

BACKGROUND

Continuous glucose monitoring systems were typically considered as Class III products and approved through a premarket approval (PMA) process. In 1997, the Food and Drug Administration Modernization Act (FDAMA) added the de novo classification pathway under section 513(f)(2) of the FD&C Act, establishing an alternate pathway to classify new devices into Class I or II that had automatically been placed in Class III after receiving a Not Substantially Equivalent (NSE) determination in response to a 510(k) submission. In this process, a sponsor who receives an NSE determination may, within 30 days of receiving notice of the NSE determination, request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act.

In 2012, section 513(f)(2) of the FD&C Act was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA), to provide a second option for de novo classification In this second pathway, a sponsor who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may request FDA to make a risk-based classification of the device under section 513(a)(1) of the Act without first submitting a 510(k). Under this declassification of continuous glucose monitoring systems, FDA introduced performance requirements that the continuous glucose monitoring system should meet and created a Class II under the generic name "Integrated continuous glucose monitoring system".[1]

[1]https://abbott.mediaroom.com/2020-02-20-New-Real-World-Data-Show-that-Abbotts-FreeStyle-Libre-System-Delivers-Positive-Health-Outcomes-for-People-with-Type-1-and-Type-2-Diabetes; https://www.closeconcerns.com/knowledgebase/r/a2b34e9a; https://www.closeconcerns.com/knowledgebase/r/a9118b46?utm_source=Closer+Look+Subscribers+2018&utm_campaign=6b35d8ae75-2020-05-21_MDT_1Q2005_21_2020&utm_medium=email&utm_term=0_c55d924bf1-6b35d8ae75-409215945
[2]https://www.accessdata.fda.gov/cdrh_docs/pdf17/DEN170088.pdf

An integrated continuous glucose monitoring system (iCGM) is intended to automatically measure glucose in bodily fluids continuously or frequently over a specified period. iCGM systems are designed to reliably and securely transmit glucose measurement data to digitally connected devices. iCGM systems can be used alone, or in conjunction with these digitally connected devices for the purpose of managing a disease or condition related to glycemic control.

An integrated continuous glucose monitoring system is subject to the special controls in addition to the general controls of the FD&C Act. These special controls require a robust clinical study demonstrating the performance of the device across the wear duration and the dynamic range. The special controls also require that the data is transferred securely and reliably at clinically meaningful time intervals to integrated devices. Additionally, the device must demonstrate clinically acceptable performance in the presence of clinically relevant levels of potential interfering substances. Further, the device must take appropriate measures so that the disposable sensors cannot be used beyond their claimed wear period.

The Dexcom G6 system was cleared under this classification in 2018. The FreeStyle Libre 2 system received clearance recently (June 2020) under the same performance requirements. Though both products meet the iCGM requirements, the systems have different designs and chemistries and therefore some performance differences are expected. This document compares these two systems from a clinical point of view.

SYSTEM SPECIFICATIONS

The FreeStyle Libre 2 system is a 14-day sensor reporting glucose every minute. The Dexcom G6 system is a 10-day sensor reporting glucose every 5 minutes.

The FreeStyle Libre 2 system contains a sensor and a reader. It has the same form factor (shape, size) as the FreeStyle Libre 14-day system. The FreeStyle Libre 2 system is designed to generate a new glucose result every minute with sensor use life of up to 14 days. The FreeStyle Libre 2 sensor automatically communicates with the FreeStyle Libre 2 reader and can provide glucose alarms when enabled. The FreeStyle Libre 2 system maintains the scan feature of the FreeStyle Libre 14-day system, where the user scans the sensor to obtain the glucose value, trend information and last 8 hours of glucose information. The sensor is for single use only. It is also designed for use with a mobile app, which Abbott is working to bring to the U.S. market.

Figure 1: FreeStyle Libre 2 system

The Dexcom G6 system has a sensor, transmitter and a receiver/ phone app. The sensor is for single use only. However, the transmitter can be reused for up to 3 months. The Dexcom G6 system generates new glucose results every five minutes and the sensor use life is up to 10 days. The Dexcom G6 system requires a reusable transmitter to transmit the glucose result from the disposable sensor to the receiver. The receiver continuously updates the information on the receiver every five minutes. Table 1 compares a few distinct features of these two systems. Other factors that do not contribute to differing performance are not listed.

Table 1 : Comparison of product features

	FreeStyle Libre 2	Dexcom G6
Enzyme	Glucose oxidase	Glucose Oxidase
Wired enzyme	Yes	No
Dependent on oxygen	No	Yes
Measurement voltage	Low	High
Dynamic range, mg/dL	40-400	40-400
Data update frequency, minutes	1	5
Sensor useful life	14 days	10 days
Sensor disposable	Yes	Yes
Needs additional transmitter	No	Yes
Compatibility with smart phone apps	No*	Yes
Real time low and high glucose alarms	Optional	Urgent low alarm fixed; other alarms optional
Alarm frequency, mins	1	5

* It is also designed for use with a mobile app, which Abbott is working to bring to the U.S. market.

The FreeStyle Libre 2 and the Dexcom G6 systems offer different features in how the user accesses glucose measurements. Both devices require some effort by the user, either picking up the reader to review the data that has already been transmitted (Dexcom G6) or bringing the reader near the sensor to obtain glucose result (FreeStyle Libre 2). Both systems provide real-time glucose alarm, when configured, without any user intervention.

ANALYTICAL ACCURACY OF THE SYSTEM

The FreeStyle Libre 2 system has a MARD of 9.2% compared to 9.9% for the Dexcom G6 system in the adult patient population.

Clinical performance of the FreeStyle Libre 2 and Dexcom G6 systems are presented in their respective user guides.[3,4] The data from the instructions for use are presented below. It should be noted that no subjects were excluded from the study demonstrating the performance of the FreeStyle Libre 2 system based on drugs or supplements that the subjects were taking during the study. However, subjects taking acetaminophen (Tylenol) were excluded from the Dexcom G6 accuracy study.[5]

Table 2 summarizes the overall system accuracy of the FreeStyle Libre 2 system. The mean absolute relative difference (MARD) is 9.2% for the adult patient population while the pediatric population (age 6 and older) is 9.7%. For pediatric patients age 4 and 5, it had a MARD of 11.8% against capillary blood glucose reference performed at home, under normal living condition.

Table 3 summarizes the overall system accuracy of Dexcom G6 system. The MARD is 9.9% for the adult patient population while the pediatric population (ages 6 to 17 years) is 9.6%. For pediatric patients age 4 and 5, it had a MARD of 9.9% against capillary blood glucose reference, where the capillary testing was performed in a controlled clinical setting.

Table 2: Summary of the performance of the FreeStyle Libre 2 system for different subject groups

Subject group	Subjects, N	Matched pairs (n)	% within ±20% / ±20mg/dL	% within ±20% / ±20mg/dL on day 1	MARD, %
Overall	273	25281	92.2	86.4	9.3
Adults (ages 18+)	144	18735	92.4	87.5	9.2
Pediatric (ages 6-17)	129	6546	91.6	84.1	9.7
Pediatric (ages 4-5)*	8	341	85.9	87.9	11.8

* Results presented are from CGM- SMBG (Self-Monitoring of Blood glucose) matched paired measurements

Table 3: Summary of the performance of the Dexcom G6 for different subject groups

Subject group	Subjects	Matched pairs (n)	% within ±20% / ±20mg/dL	% within ±20% / ±20mg/dL on day 1	MARD, %
Overall	324	25101	91.7	87.8	9.8
Adults (ages 18+)	159	19329	91.6	87.1	9.9
Pediatric (ages 6-17)	165	5772	92.0	90.2	9.6
Pediatric (ages 2-5)*	8	82	92.7	n/a	9.9

* Results presented are from in-clinic CGM-SMBG matched paired measurements.

[3]FreeStyle Libre 2 Flash Glucose Monitoring System, User Manual
[4]Dexcom G6 Continuous Glucose Monitoring System User Guide
[5]https://clinicaltrials.gov/ct2/show/NCT02880267

PERFORMANCE AGAINST iCGM REQUIREMENTS

FreeStyle Libre 2 and Dexcom G6 systems meet iCGM requirements. The FreeStyle Libre 2 system has clear advantages over the Dexcom G6 system for some of the requirements.

Both FreeStyle Libre 2 and Dexcom G6 systems have demonstrated that they meet iCGM requirements. In this document, only requirements pertaining to the clinical study results (iCGM requirement (v)) are discussed. Table 4 compares the performance of the two systems against the individual performance requirements. Requirements A-G are related to the accuracy of the system compared to laboratory reference. The FreeStyle Libre 2 system performs equivalent to or better than the Dexcom G6 system for all accuracy requirements. Requirements H and I are related to system's noise resulting in reporting a hypoglycemic event as hyperglycemic event or vice versa. Both systems met this requirement. Requirements J & K are related to the sensor indicating a rate of change of glucose opposite to that of the true glucose. Both systems demonstrated that rates of change of glucose presented by the sensor are in reasonable concordance with the true rate of change measured by the reference analyzer.

Special control requirement (vi) requires that data demonstrating similar accuracy and rate of change performance of the iCGM in the pediatric population as compared to that in the adult population. Table 4 also presents the data from the pediatric patient population (ages 6 to 17 years). The FreeStyle Libre 2 system demonstrated better performance in the hypoglycemic range compared to the Dexcom G6 system. At other glucose ranges, the performance of the two systems are comparable.

Table 4: Summary of performance against iCGM requirements for adult patient population for Dexcom G6 and FreeStyle Libre 2 system

iCGM Special Control Performance Requirements	Threshold (lower confidence Interval)	Adult		Pediatric	
		FreeStyle Libre 2	Dexcom G6	FreeStyle Libre 2	Dexcom G6
A: Within 15mg/dL, <70mg/dL	>85%	86.7	85.4	77.2	67.5
B: Within 15%, 70-180mg/dL	>70%	73.1	71.4	74.8	76.6
C: Within 15%, >180mg/dL	>80%	89.4	82.8	84.4	81.7
D: Within 40mg/dL, <70mg/dL	>98%	99.1	98.6	97.5	88.8
E: Within 40%, 70-180mg/dL	>99%	99.4	99.1	98.9	99.2
F: Within 40%, >180mg/dL	>99%	99.9	99.9	99.5	99.8
G: Within 20%	>87%	88.7	88.2	88.1	88.7
H: CGM<70mg/dL & Ref >180mg/dL	0	0	0	0	0
I: CGM>180mg/dL & Ref <70mg/dL	0	0	0	0	0
J: CGM ROC >1mg/dL/min & Ref ROC <-2mg/dL/min	<1%	0.6	0.2	0.5	0.1
K: CGM ROC <-1mg/dL/min & Ref ROC >2mg/dL/min	<1%	0.5	0.0	0.5	0.6

From Table 4, it is evident that the FreeStyle Libre 2 demonstrated performance similar to the Dexcom G6 system with slightly better performance against some of the requirements.

ALARM PERFORMANCE

The FreeStyle Libre 2 system has optional real time high and low glucose alarms that can be configured while the Dexcom G6 system has an urgent low glucose alarm that cannot be changed or turned off, and configurable low and high glucose alarms.

The FreeStyle Libre 2 system has an optional real-time high and low glucose alarms that, when configured, will inform the user when the glucose level crosses the threshold set by the user. The Dexcom G6 system has an urgent low glucose alarm at 55mg/dL that cannot be changed or turned off. A fixed alarm could lead to alarm fatigue, and social stigma associated with alarms in teens and young adults.[6] The remaining Dexcom G6 alarm levels can be changed or turned off.

The ability of the system to alarm appropriately when alerts were set at different thresholds was assessed by comparing sensor results to YSI measurements within a 15-minute time window at low and high glucose threshold levels to determine whether an alert would have been generated. At each threshold, true alarm rate (whether YSI is in agreement with the device when the device alerts) and detection rate (whether the device alerts when YSI is within the threshold) were calculated. The false alarm rate and missed detection rates are calculated as (100%-true alarm rate) and (100%-detection rate).

LOW GLUCOSE ALARMS

Low glucose alarm performance is comparable between the two systems for adult data, while in the pediatric data, The FreeStyle Libre 2 alarms perform better than the Dexcom G6 alarms.

Low Glucose Alarms are designed to alert the user when the glucose concentration goes below a threshold set by the user. The threshold is set by the user for their individual need. The Dexcom G6 system has an urgent low alert level of 55mg/dL, that cannot be changed or turned off and the low glucose can be set between 60 and 90mg/dL. The FreeStyle Libre 2 system low glucose alerts can be set between 60 and 100mg/dL.

The low glucose alarm rates for the FreeStyle Libre 2 system for the adult and pediatric patients are listed in Table 5 and Table 7 respectively. The low glucose alert rates for the Dexcom G6 system for the adult and pediatric patients are listed in Table 6 and Table 8 respectively. Low glucose alert rates of the FreeStyle Libre 2 system are comparable to the Dexcom G6 system at all threshold levels. For the pediatric patients, these results are slightly better for the FreeStyle Libre 2 system.

Table 5: Low Glucose Alarm and Detection Rate Evaluations (Adult data) for FreeStyle Libre 2

Low Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
60	9861	72.6	27.4	1527	75.7	24.3
70	21504	86.0	14.0	3652	89.3	10.7
80	32784	91.3	8.7	4753	97.3	2.7
90	41299	93.6	6.4	5591	98.5	1.5

[6] "Turn it off!": diabetes device alarm fatigue considerations for the present and the future., Shivers et al, J Diabetes Sci Technol 2013;7:789–794.

Table 6: Low Glucose Alarm and Detection Rate Evaluations (Adult data) for Dexcom G6

Low Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
55	1,408	66.6	33.4	642	63.9	36.1
60	2,370	74.6	25.4	1,158	74.1	25.9
70	5,079	85.5	14.5	2,365	86.0	14.0
80	8,187	89.1	10.9	3,372	92.7	7.3
90	11,147	89.4	10.6	4,287	94.6	5.4

Table 7: Low Glucose Alarm and Detection Rate Evaluations (Pediatric data) for FreeStyle Libre 2

Low Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
60	2780	62.9	37.1	373	87.4	12.6
70	6363	80.3	19.7	963	93.5	6.5
80	9747	85.6	14.4	1318	96.4	3.6
90	12550	92.2	7.8	1656	97.3	2.7

Table 8: Low Glucose Alarm and Detection Rate Evaluations (Pediatric data) for Dexcom G6

Low Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
55	358	31.6	68.4	66	68.2	31.8
60	521	44.1	55.9	119	73.1	26.9
70	1,054	68.0	32.0	369	81.6	18.4
80	1,794	80.5	19.5	671	88.1	11.9
90	2,746	86.3	13.7	1,030	92.8	7.2

HIGH GLUCOSE ALARMS

The FreeStyle Libre 2 performed slightly better than the Dexcom G6 in the high glucose alarm performance.

High glucose alarms are designed to alert the user when glucose concentration goes above a threshold set by the user. The threshold is set by the user for their individual need. The FreeStyle Libre 2 high glucose alarms can be set between 120 and 400mg/dL. The Dexcom G6 high glucose alarms can be set between 120 and 300mg/dL.

The high glucose alarm rates for the FreeStyle Libre 2 for the adult and the pediatric patients are listed in Table 9 and Table 11 respectively. The high glucose alarm rates for the Dexcom G6 system for the adult and pediatric patients are listed in Table 10 and Table 12 respectively. High glucose alarm rates of the FreeStyle Libre 2 system are better than the Dexcom G6 system at all threshold levels.

Table 9: High Glucose Alarm and Detection Rate Evaluations (Adult data) for FreeStyle Libre 2

High Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
120	105544	99.1	0.9	11417	98.2	1.8
140	93574	99.1	0.9	10152	98.1	1.9
180	74290	99.2	0.8	8080	97.8	2.2
200	66039	99.2	0.8	7269	97.1	2.9
220	57549	99.0	1.0	6390	96.9	3.1
240	48733	98.4	1.6	5550	95.6	4.4
300	21512	96.3	3.7	2672	90.0	10.0

Table 10: High Glucose Alarm and Detection Rate Evaluations (Adult data) for Dexcom G6

High Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
120	37,061	97.5	2.5	12,664	97.6	2.4
140	32,148	97.2	2.8	11,175	96.8	3.2
180	23,424	96.6	3.4	8,455	95.2	4.8
200	19,586	96.0	4.0	7,265	93.6	6.4
220	15,689	95.6	4.4	6,143	91.2	8.8
240	12,279	94.6	5.4	5,007	88.7	11.3
300	4,211	85.9	14.1	2,095	74.8	25.2

Table 11: High Glucose Alarm and Detection Rate Evaluations (Pediatric data) for FreeStyle Libre 2

High Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
120	34176	98.8	1.2	4441	98.2	1.8
140	30107	98.0	2.0	3945	98.4	1.6
180	22430	98.4	1.6	3125	98.0	2.0
200	19425	98.0	2.0	2791	98.0	2.0
220	16371	98.2	1.8	2492	96.9	3.1
240	13559	98.0	2.0	2172	95.7	4.3
300	6064	90.8	9.2	962	91.0	9.0

Table 12: High Glucose Alarm and Detection Rate Evaluations (Pediatric data) for Dexcom G6

High Glucose Alarm level (mg/dL)	Alarm Rate			Detection Rate		
	Number of Events (n)	True Alarm Rate (%)	False Alarm Rate (%)	Number of Events (n)	Correct Detection Rate (%)	Missed Detection Rate (%)
120	11,683	97.3	2.7	3,930	97.8	2.2
140	10,113	96.2	3.8	3,388	97.7	2.3
180	6,821	93.4	6.6	2,366	94.7	5.3
200	5,190	93.3	6.7	1,874	91.2	8.8
220	4,096	90.4	9.6	1,453	91.7	8.3
240	3,068	86.9	13.1	1,093	90.2	9.8
300	1,010	77.2	22.8	374	84.8	15.2

PERFORMANCE IN THE FIRST 12 HOURS OF SENSOR WEAR

In a head-to-head study, the FreeStyle Libre 2 system performed significantly better than the Dexcom G6 during the first 12 hours of sensor wear (MARD 9.1% vs 18.5% respectively)

Performance data in the instructions for use suggests on the first day of the sensor wear both systems had similar performance. However, typically, performance of the sensor is affected significantly in the first 12 hours compared to second 12 hours of the first day. In order to determine the performance of the systems in the first 12 hours of the sensor wear, an Abbott sponsored study comparing the performance of each system to venous plasma glucose reference measurements was performed. Twenty-five subjects at one clinical site in the United States wore one FreeStyle Libre sensor on the back of the upper arm and one G6 sensor on the abdomen. Both sensors were used with no additional manual calibrations. G6 sensor was inserted one hour prior to FreeStyle Libre sensor to align the warm up period. Subjects underwent venous YSI sampling every 15 minutes for a total of 8 hours. FreeStyle Libre sensor data were analyzed using the FreeStyle

Libre 14-day algorithms (early version of EU Free-Style Libre 2 system) for accuracy assessment. The study showed that 64.3% of the Dexcom G6 results and 84.8% of the FreeStyle Libre results with the FreeStyle Libre 14-day system algorithm were within the 20%/20mg/dL while, 5.3% of the Dexcom G6 results and 1.2% of the FreeStyle Libre 14-day system results were outside of 40%/40mg/dL from the YSI reference. The Dexcom G6 system showed 18.5% MARD while the FreeStyle Libre 14-day system had 13.2% MARD.[7]

The data from this study was reassessed with the new FreeStyle Libre 2 algorithm. The data showed that 91.8% of the FreeStyle Libre 2 results are within the 20%/20 mg/dL and 0.5% of the FreeStyle Libre 2 results are outside of 40%/40 mg/dL from the YSI reference. Figure 2 shows the histograms of mean relative difference (MRD) and MARD of individual sensor from the Dexcom G6 and the FreeStyle Libre 2 systems. The Dexcom G6 system shows 18.5% MARD (6.4% MRD) while the FreeStyle Libre 2 system has 9.1% MARD (7.2% MRD). Sensors from the Dexcom G6 system showed wider spread in both MARD and MRD compared to the FreeStyle Libre 2 system. Figure 3 shows the system agreement plot between the two systems against YSI reference.[8]

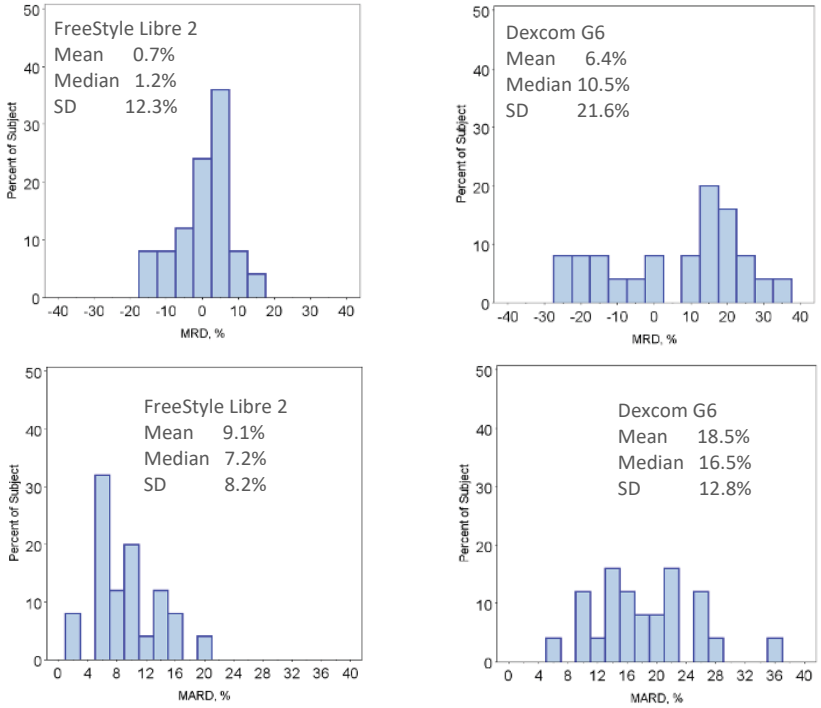


Figure 2: Histograms of individual sensor MRD and MARD of both FreeStyle Libre 2 and Dexcom G6 CGM systems.

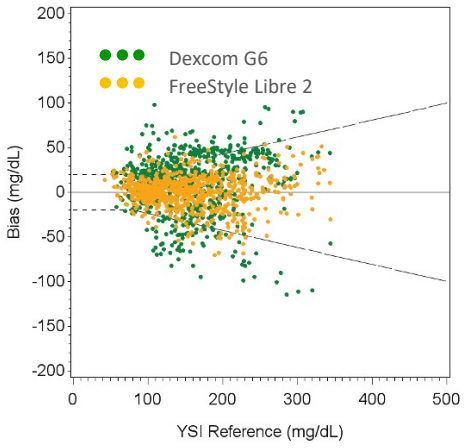


Figure 3: The Bland-Altman difference plot of the two CGM systems versus the YSI reference. Dash lines are the ±20%/±20mg/dL limits

[7]A Head-to-Head Comparison Study of the First-Day Performance of Two Factory-Calibrated CGM Systems; D. Denham, J Diabetes Sci Technol. 2020 Mar;14(2):493-495. doi: 10.1177/1932296819895505. Epub 2020 Jan 8

[8]Data on file at Abbott Diabetes Care

INTERFERENCE FROM COMMON COMPOUNDS

Most CGM sensors are based on enzyme-based chemistry, where an enzyme, typically glucose oxidase, is immobilized at an electrode surface. These sensors are inserted under the skin and measure glucose in the interstitial fluid (ISF). The enzymatic oxidation of the glucose in the presence of dissolved oxygen generates hydrogen peroxide, which is electrochemically measured. The reaction scheme of the measurement technology is provided in Figure 4.

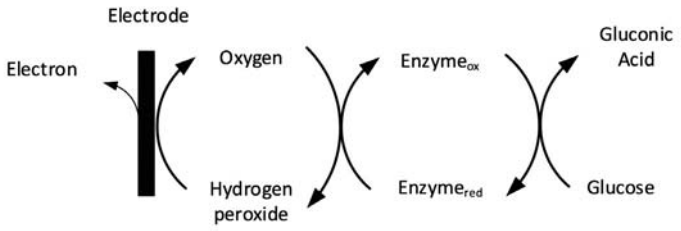


Figure 4: Chemical reactions in a hydrogen peroxide measuring technology

Oxidation of hydrogen peroxide typically requires voltages where other electrochemically active compounds present in the ISF can get oxidized. Sensor fabrication includes a diffusion membrane to control the flow of glucose to the electrode surface and therefore control the dynamic range of the sensor system. These membranes can be designed to block some of these electrochemically active compounds. However, some of the compounds that could potentially interfere are smaller molecules compared to glucose and therefore can freely diffuse to the electrode surface. An additional permselective membrane can be added under the enzyme layer to block compounds that are larger than hydrogen peroxide. Dexcom G6 system uses this measurement technology.

One of the alternate approaches is to use a mediator that has an oxidation voltage that is lower than the common interfering compounds. The mediator is chemically linked to the enzyme through a polymer chain to form the wired enzyme. The reaction scheme for such a method of measurement is provided in Figure 5. This type of sensor fabrication also includes membranes like the ones described above. FreeStyle Libre 2 system uses this wired enzyme technology. The wired enzyme-based chemistry offers better sensor stability in the body and less sensitivity to electrochemically active compounds that may be present in the ISF.

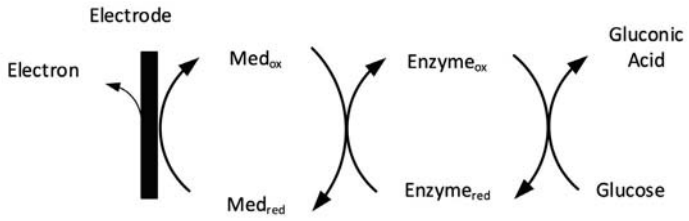


Figure 5: Chemical reactions in a mediated chemistry

As described above, CGM systems may be affected by electrochemically active compounds present in the ISF. The choice of the diffusion membrane and measurement potential can determine the magnitude of the interference. Some of the common electrochemically active compounds that could affect the sensor performance are acetaminophen, ascorbic acid (Vitamin C), salicylic acid (metabolic product of aspirin), ibuprofen, and uric acid. Recently, hydroxyurea has been identified as a potentially interfering agent with the Dexcom G6 system.

Note that both systems use glucose oxidase as the enzyme, which is highly selective and does not react with other common saccharides such as maltose or galactose.

INTERFERENCE PROFILE OF THE FREESTYLE LIBRE 2 SYSTEM

At high doses of ascorbic acid supplements (not food source), the FreeStyle Libre 2 system may give elevated sensor results causing the sensor to potentially miss severe hypoglycemic events

The FreeStyle Libre 2 sensor has been tested for common interfering compounds such as acetaminophen, salicylic acid, ibuprofen, levodopa, methyldopa, dopamine, uric acid and hydroxyurea. At the highest concentrations under therapeutic treatment, these compounds do not show clinically significant interference. However, FreeStyle Libre 2 glucose readings may be falsely elevated at higher doses of ascorbic acid supplements.

Vitamin C is available in many of the fruits and vegetables at levels sufficient for the normal functioning of the human body. Recommended Dietary Allowance (RDA) for vitamin C is provided in Table 13.[9] At normal dietary intake, vitamin C is not expected to affect FreeStyle Libre 2 readings. A typical glass (8 oz) of orange juice has 124 mg of ascorbic acid. Centrum Adult has 60 mg while Centrum Women has 75 mg of ascorbic acid. However, some

[9]Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (http://www.nap.edu/catalog.php?record_id=9810). Washington, DC: National Academy Press, 2000.

people take additional dietary supplements. For example, some supplements, including cold remedies such as Airborne® and Emergen-C® recommend taking up to 3 grams of the supplement per day. It should be noted that ADA advises against routine supplementation with antioxidants, such as vitamins E and C and carotene, due to lack of evidence of efficacy and concern related to long-term safety.[10]

At normal intake levels (not in scurvy), ascorbate has a half-life of approximately 30 minutes.[11] The plasma half-life of ascorbic acid is widely reported to be between 8-40 days during periods of deficient intake, when the renal transporters actively reabsorb the vitamin to prevent acute scurvy. When intake levels are higher, more rapid excretion occurs. Therefore, the bioavailability of ascorbic acid is dependent on the dose. Levine et al. demonstrated that at lower doses (200mg), bioavailability is almost 100% and at higher doses (1250mg), there is a significant reduction in bioavailability.[12] The maximum plasma concentration is achieved at around 90 minutes at a dose of 1250mg. The level of ascorbic acid returns to the physiological circulating levels in approximately 6 hours after taking this high dose of the supplement.

The FreeStyle Libre 2's instructions for use provide the following information to the user. "Taking ascorbic acid (vitamin C) supplements while wearing the Sensor may falsely raise Sensor glucose readings. You can take doses of ascorbic acid up to 500 mg per day and make treatment decisions with the Sensor. Taking more than 500 mg of ascorbic acid per day may affect the Sensor readings which could cause you to potentially miss a severe low glucose event. Ascorbic acid can be found in supplements including multivitamins. Some supplements, including cold remedies such as Air- borne® and Emergen-C®, may contain high doses of 1000 mg of ascorbic acid and should not be taken while using the Sensor. See your healthcare professional to understand how long ascorbic acid is active in your body."

Abbott performed a clinical study to evaluate the effect of ascorbic acid on FreeStyle Libre 2 performance. Data from 57 adult subjects with diabetes was collected over a 13-hour period. Each subject had a one-hour baseline phase where venous blood was collected every 10 minutes. After this first hour, a dose of 1000 mg of ascorbic acid was given with a meal and venous samples were collected every 20 minutes for the next four hours.

Subjects the received a second dose of 1000 mg of ascorbic acid with a meal and the same process was continued for another 4 hours. A third dose of 1000 mg of ascorbic acid was then given, and study subjects were followed for 4 more hours. The maximum average bias from the reference and baseline at each ingestion of ascorbic acid are presented in Table 14.

Table 13: Recommended Dietary Allowances (RDAs) for Vitamin C

Age	Male	Female	Pregnancy	Lactation
0–6 months	40 mg*	40 mg*		
7–12 months	50 mg*	50 mg*		
1–3 years	15 mg	15 mg		
4–8 years	25 mg	25 mg		
9–13 years	45 mg	45 mg		
14–18 years	75 mg	65 mg	80 mg	115 mg
19+ years	90 mg	75 mg	85 mg	120 mg

*Adequate intake

Table 14 : The maximum average bias from the reference and baseline at each ingestion of ascorbic acid on FreeStyle Libre 2

Dosing Period	Bias from Reference, mg/dL	Bias from Baseline, mg/dL
Pre-dose (baseline)	-2.4	0
Post 1st dose	6.9	9.3
Post 2nd dose	15.9	18.4
Post 3rd dose	17.3	19.7

[10]Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2020; Diabetes Care 2020;43(Suppl. 1):S48–S65 | https://doi.org/10.2337/dc20-S005

[11]Pharmacokinetics of Vitamin C: insights into the oral and intravenous administration of ascorbate, Duconge, et al., PRHSJ Vol. 27 No. 1 (2008) 7-19

[12]Vitamin C pharmacokinetics in healthy volunteers: Evidence for a recommended dietary allowance, Levine, et al, Proc. Natl. Acad. Sci. USA, Vol. 93, pp. 3704-370

A maximum average sensor bias of 9.3 mg/dL was observed around 3 hours after the 1000 mg ascorbic acid dose. After the second dose of ascorbic acid the maximum average sensor bias increased, with minimal change in sensor bias after the third dose, suggesting that saturation had occurred by the second 1000 mg dose of ascorbic acid. The maximum average sensor bias after the three 1000 mg doses of ascorbic acid was less than 20 mg/dL.[2] It should be noted that this level of interference is independent of the glucose level. This magnitude of interference will have minimal impact on insulin dosing. However, the biases are large enough for the sensors to potentially miss hypoglycemic conditions, specifically severe hypoglycemia.

The interference from ascorbic acid is proportional to its concentration in the ISF. Therefore, the maximum interference from 500mg supplement of ascorbic acid is expected to be approximately 5 mg/dL, supporting the limitations stated in the instructions for use.

INTERFERENCE PROFILE OF THE DEXCOM G6 SYSTEM

With repeated doses of Tylenol, the Dexcom G6 system may give elevated sensor results causing the sensor to potentially miss severe hypoglycemic events. Dexcom G6 system is also affected by hydroxyurea and uric acid.

Except for acetaminophen, interference from other common endogenous or exogenous compounds on Dexcom G6 has not been published. Abbott had previously demonstrated under in-vitro conditions Dexcom G4® and G5® sensors had significant interference from acetaminophen.[13] In Dexcom G6, a permselective membrane has been incorporated to block the diffusion of acetaminophen to the electrode surface and hence minimize the effect of acetaminophen. Dexcom has recently updated their label to include hydroxyurea as an interfering agent. Under in-vitro conditions, Abbott has observed that the Dexcom G6 system is also affected by other common endogenous compounds and drugs such as uric acid.[14] The magnitude of the observed interference in the presence of these compounds at 90mg/dL glucose concentration are provided in Table 15.

The Dexcom G6 instructions for use provide the following information to the user. "In previous generations of Dexcom CGM systems (G4/G5), acetaminophen could affect your sensor readings, making them look higher than they really were. However, with the G6, you can take a standard or maximum acetaminophen dose of 1 gram (1,000 mg) every 6 hours and still use the G6 readings to make treatment decisions. Taking higher than the maximum dose of acetaminophen (e.g. > 1 gram every 6 hours in adults) may affect the G6 readings and make them look higher than they really are."

The ability of the permselective membrane to reduce the interference was demonstrated by Dexcom in a head-to-head clinical study where the interference from 1-gram dose of acetaminophen was determined.[3] 65 adult subjects wore both a Dexcom G6 and a Dexcom G4 PLATINUM with SW505 CGM system. The G4/G5 sensor was used as a comparator for establishing the time to reach a peak acetaminophen concentration (~1 hour), in the interstitial fluid from the time the acetaminophen was administered. The observed peak plasma acetaminophen concentration ranged from 0.2 to 2.6 mg/dL. To assess whether this peak acetaminophen concentration had an interference effect on the G6 readings, the readings were compared to reference plasma glucose measurements with YSI. Venous blood was sampled every 10-15 minutes from 1 hour before and up to 6 hours after the acetaminophen was administered. The observed mean maximum bias of the Dexcom G6 readings to the reference YSI measurements at the time of peak acetaminophen concentration across all subjects was +5.2 mg/dL, significantly lower than the performance goal of <10 mg/dL (one-sided upper 95% CI of 6.4 mg/dL, $p < 0.001$).

Table 15: In-vitro interference profile of Dexcom G6

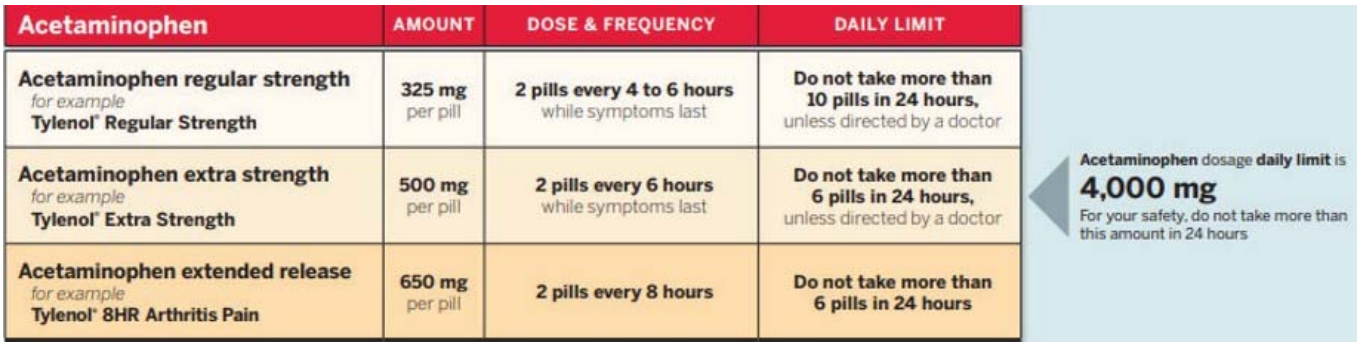
Compound	Highest concentrations under therapeutic treatment/endogenous reference interval mg/dL	EP37[15] Recommended test level, mg/dL	Test Concentration, mg/dL	Magnitude of interference, mg/dL
Acetaminophen	5.2	15.1	2.0	19.3
Uric Acid	7.2	23.5	7.2	16.7

[13] https://doi.org/10.1177/1932296kjk818761742

[14] Data on file at Abbott Diabetes Care

[15] Supplemental tables for interference testing in clinical chemistry, CLSI, 1st edition. 2018

In this clinical study, the study subjects were not allowed to take any acetaminophen for at least 5 days prior to the testing (stopped taking acetaminophen 24 hours prior to sensor insertion).[16] However, acetaminophen dosage chart (Figure 6) for 12 years and older suggests repeated doses in a given day, with a maximum daily limit of 4000 mg per day.



Acetaminophen	AMOUNT	DOSE & FREQUENCY	DAILY LIMIT
Acetaminophen regular strength *for example* **Tylenol® Regular Strength**	325 mg per pill	2 pills every 4 to 6 hours while symptoms last	Do not take more than 10 pills in 24 hours, unless directed by a doctor
Acetaminophen extra strength *for example* **Tylenol® Extra Strength**	500 mg per pill	2 pills every 6 hours while symptoms last	Do not take more than 6 pills in 24 hours, unless directed by a doctor
Acetaminophen extended release *for example* **Tylenol® 8HR Arthritis Pain**	650 mg per pill	2 pills every 8 hours	Do not take more than 6 pills in 24 hours

Figure 6: Acetaminophen (Tylenol) dose chart for patients 12 years or older.

Since the interference from acetaminophen in the Dexcom G6 system is reduced by using a permselective membrane, the ability of the membrane to prevent the diffusion of acetaminophen was not demonstrated by challenging the membrane with repeated dosing of acetaminophen. Abbott performed a clinical study to evaluate the eff of repeated dose of acetaminophen on Dexcom G6 system.[17] Data from 14 adult subjects with diabetes were collected over a 13-hour period. Each subject had a one-hour baseline phase where venous blood was collected every 10 minutes. After this first hour, a dose of 1000 mg acetaminophen was given with a meal and venous samples were collected every 20 minutes for the next four hours. Subjects then received a second dose of 1000 mg acetaminophen with a meal and the same process was continued for another 4 hours. A third dose of 1000 mg acetaminophen was then given, and study subjects were followed for 4 more hours. The maximum average bias from the reference and baseline at each administration of acetaminophen are presented in Table 16.

A maximum average sensor bias of 7.2 mg/dL was observed around 4 hours after the 1000 mg acetaminophen dose (the magnitude of the interference is consistent with the +5.2mg/dL reported by Dexcom in the Instructions for Use).

Table 16: The maximum average bias from the reference and baseline at each ingestion of acetaminophen on Dexcom G6

Dosing Period	Bias from Reference, mg/dL	Bias from Baseline, mg/dL
Pre-dose (baseline)	15.1	0
Post 1st dose	22.3	7.2
Post 2nd dose	23.7	8.6
Post 3rd dose	29.1	14.0

After the second dose, the maximum average sensor bias was 8.6 mg/dL, which increased to 14.0 mg/dL after the third dose, suggesting that the membrane has a limited capacity to block acetaminophen and repeated dose of the drug will result in increase in the sensor signal.[18] This study did not follow the subjects over multiple days and therefore, the effect of continued use of the acetaminophen over multiple days on the sensor performance is not known.

[16]Resistance to Acetaminophen Interference in a Novel Continuous Glucose Monitoring System, Peter Calhoun, Terri Kang Johnson, Jonathan Hughes, David Price, and Andrew K. Balo, Journal of Diabetes Science and Technology 2018, Vol. 12(2) 393–396
[17]Data on file at Abbott Diabetes Care
[18]https://simul-europe.com/2018/attd/Files/(shridhara.alva@abbott.com)ATTD8-0410.pdf

Repeated dosing of 1 gram of acetaminophen every 4-hours results in approximately 14 mg/dL maximum bias on first day. Impact of repeated use of acetaminophen on multiple days is not known. As with the interference of ascorbic acid on FreeStyle Libre 2, the magnitude of interference from acetaminophen on G6 will have minimal impact on insulin dosing. However, the biases are large enough for the sensors to potentially miss hypoglycemic conditions, specifically severe hypoglycemia.

As shown in Table 15 there are other drugs or endogenous compounds that also could affect the performance of Dexcom G6. If all these compounds coexist, for example a patient with elevated uric acid and taking maximum strength acetaminophen over multiple days to manage pain and fever, these interferences will add up and could affect the insulin dosing as well. The acetaminophen interference studies by either Dexcom or Abbott did not evaluate these situations.

It is also of interest to note that two separate studies performed against YSI (Table 16 and Figure 2) suggest that the Dexcom G6 sensors tend to have large positive bias compared to FreeStyle Libre 2 ((Table 14 and Figure 2) further increasing the impact of interference from compounds namely, acetaminophen, hydroxyurea and uric acid.

RESTARTING THE SENSOR

The user cannot extend the use life of the FreeStyle Libre 2 sensor. The Dexcom G6 sensor use life can be extended and in the extended period the product will no longer meet the iCGM requirements.

Previous generations of Dexcom systems were approved for 7 days. However, one could easily extend the use life of the sensor by restarting it. Though the previous generations of Dexcom systems require calibration to maintain accuracy, the system does not require the user to continue calibrating the sensor after the initial calibration. The impact of not calibrating or extending the sensor use beyond its indicated use life on the sensor accuracy is not communicated to the user. An Abbott sponsored clinical study was performed to demonstrate the impact of Dexcom G5 system (G4 system with 505 software) when these type of real-life use scenarios exist.[19] The study evaluated the performance of the sensor when the product was used as indicated but extended the use life as well as providing only the initial calibration and extending the use life. Table 17 summarizes the impact on accuracy under these use scenarios.

Table 17: Performance of the G5 system with extended use life and with and without providing required calibrations

Calibration	Sensor Wear Days	Mean Bias (%)	MARD (%)	% Within 20mg/dL /20%, %	N
Per label	1-7	-1.8	11.0	88.1	2169
	8-14	-6.8	13.2	81.2	2192
At start-up only	1-7	12.4	18.9	67.6	2082
	8-14	-14.8	20.2	57.0	2121

One of the iCGM requirements (requirement 5)[1] is to ensure that the device must include appropriate measures to ensure that disposable sensors cannot be used beyond its claimed sensor wear period. However, there are numerous reports that Dexcom G6 can be used beyond its approved use life of 10 days. The system allows the user to easily restart the sensors and continue to use the system, including the latest version of the transmitter.[20] Dexcom has not provided any data to support the accuracy of the system when the sensor is used beyond its approved use life. In the previous generations of the sensor, even with the required calibrations, the sensor performance was compromised once restarted.[21] With factory calibration, the user has no way of knowing if the sensor is working as intended and if the iCGM performance is still maintained.

An Abbott sponsored clinical study was performed to evaluate the performance of the sensor after restart.[21] The study enrolled 27 subjects who wore the Dexcom G6 device on the abdomen. The sensor was restarted after about 10 days of wear and allowed to go for up to 10 additional days. Sensor performance was compared to the YSI plasma reference. YSI reference measurements were performed over four time periods: days 1-3 and 6-9 for the first wear period and days 14-16 and 16-19 to cover the period after restart. Sensors used as factory calibrated for both wear periods. System performance during the normal wear period and the restarted wear period are presented in Table 18.

As can be seen from the data, the performance deteriorated after the restart of the sensor and suggests that the product will not meet iCGM requirements after the restart and therefore, fail to meet the indications for use. When used for making manual or automated insulin dosing decisions, this should be considered.

[19] https://www.reddit.com/r/dexcom/comments/e7tw4l/dexcom_g6_restart_on_new_firefly_transmitter/
[20] https://simul-europe.com/2018/attd/Files/(shridhara.alva@abbott.com)ATTD8-0410.pdf
[21] Data on file at Abbott Diabetes Care

Table 18: Summary of performance of the Dexcom G6 system before and after restarting the sensor use

Wear Period	Mean % Bias	MARD (%)	Within 20/ mg/dL or 20%, %	Within 40/ mg/dL or 40%, %
Normal	-3.4	10.2	90.5	97.3
Restarted	-6.7	12.5	84.3	98.6

FreeStyle Libre 2 sensors are designed to restrict the ability of a user to extend beyond the sensor's use life to ensure patient safety. The FreeStyle Libre 2 is a 14-day product and the performance of the system has been demonstrated to be appropriate to make insulin dosing decisions. Unlike with Dexcom G6, there is no concern that the user could intentionally extend the sensor use by restarting the sensor, which could create a potentially unsafe situation.

SUMMARY

Both FreeStyle Libre 2 and Dexcom G6 systems are cleared as continuous glucose monitoring devices indicated for the management of diabetes under the iCGM performance standards. However, there are distinct differences between the two systems as discussed in the previous sections. The FreeStyle Libre 2 system has significantly better performance in the first 12 hours compared to the Dexcom G6 system. Ingestion of high doses of ascorbic acid (vitamin C) supplements (not food) could cause one to potentially miss a severe low glucose event while using the FreeStyle Libre 2 system. Repeated doses of extra strength Tylenol could cause one to potentially miss severe low glucose event while using the Dexcom G6 system. The Dexcom G6 system may also be affected by other compounds, such as, hydroxyurea and elevated uric acid levels. This information could be of importance when end users and their health care providers are deciding on which system to use for managing diabetes.

FREESTYLE LIBRE 2 INDICATIONS AND IMPORTANT SAFETY INFORMATION

The FreeStyle Libre 2 Flash Glucose Monitoring System is a continuous glucose monitoring (CGM) device with real time alarms capability indicated for the management of diabetes in persons age 4 and older.
It is intended to replace blood glucose testing for diabetes treatment decisions, unless otherwise indicated.

The System also detects trends and tracks patterns and aids in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments. Interpretation of the System readings should be based on the glucose trends and several sequential readings over time.

The System is also intended to autonomously communicate with digitally connected devices. The System can be used alone or in conjunction with these digitally connected devices where the user manually controls actions for therapy decisions.

Contraindications:
The System must not be used with automated insulin dosing (AID) systems, including closed loop and insulin suspend systems. Remove the sensor before MRI, CT scan, X-ray, or diathermy treatment.

Warnings/Limitations:
Do not take high doses of vitamin C (more than 500 mg per day), as this may falsely raise your Sensor readings. Failure to use the System according to the instructions for use may result in missing a severe low blood glucose or high blood glucose event and/or making a treatment decision that may result in injury. If glucose alarms and readings from the System do not match symptoms or expectations, use a fingerstick blood glucose value to make diabetes treatment decisions. Seek medical attention when appropriate and contact Abbott Toll Free (855-632-8658) or visit www.freestylelibre.us for detailed indications for use and safety information.

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Any questions related to the content of this document can be sent to ADC.Scientific.Affairs.com.