

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device generic name:	Continuous Glucose Monitoring System
Device trade name:	Paradigm REAL-Time System and Guardian REAL-Time System (Pediatric Versions)
Applicant's name and address:	Medtronic MiniMed 18000 Devonshire Street Northridge, California 91325
PMA number:	P980022/S015
Date of Panel recommendation:	None
Date of notice of approval to the applicant:	March 8, 2007

The original Guardian REAL-Time system and the continuous glucose monitoring features of the Paradigm REAL-Time system were approved for adults only, age 18 and older, on June 14, 2006 and April 7, 2006 respectively. This supplement is for pediatric versions of Paradigm REAL-Time system and the Guardian REAL-Time system intended for use by children and adolescents, age 7 -17.

II. INDICATIONS FOR USE

- Paradigm REAL-Time System (Pediatric Version)

The Paradigm REAL-Time system (pediatric version) consists of the Paradigm MMT-522k or MMT-722k insulin infusion pumps, the MMT-7002 or MMT-7003 glucose sensor and the MMT-7701 transmitter. The Paradigm MMT-522k and MMT-722k insulin infusion pumps are indicated for the continuous delivery of insulin, at set and variable rates, for the management of diabetes mellitus in persons requiring insulin. Use of the MMT-522k and MMT-722k insulin pumps with the optional sensor and transmitter components is indicated for continuous or periodic monitoring of glucose levels in the fluid under the skin, and possible low and high blood glucose episodes in children and adolescents (ages 7 through 17). The system provides an alert if glucose levels fall below or rise above preset values. Glucose values provided by the system are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a fingerstick may be required. All therapy adjustments should be based on measurements obtained using a home glucose monitor and not on the sensor glucose readings provided by the Paradigm REAL-Time system.

- Guardian REAL-Time System (Pediatric Version)

The Guardian REAL-Time system (pediatric version) consists of the model CSS7100k monitor, the MMT-7002 or MMT-7003 glucose sensor and the MMT-7701 transmitter. This system is

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

indicated for continuous or periodic monitoring of glucose levels in the fluid under the skin, in children and adolescents (ages 7 through 17) with diabetes mellitus, for the purpose of improving diabetes management. The monitor provides an alert if a glucose level falls below, or rises above, preset values. Values are not intended to be used directly for making therapy adjustments, but rather to provide an indication of when a meter blood glucose measurement may be required. All therapy adjustments should be based on measurements obtained using a home glucose meter and not on Guardian REAL-Time system values. The Guardian REAL-Time system provides real-time glucose values that allow users to track patterns in glucose concentrations and to possibly identify episodes of low and high blood glucose. It also stores the data so that it can be analyzed to track patterns. Glucose data can be further downloaded to PC software for analysis of historical glucose values.

III. CONTRAINDICATIONS

Use of the MMT-522k and MMT-722k insulin infusion pumps and the CSS7100k monitor is not recommended for patients whose impaired vision or hearing does not allow full recognition of the devices' display information and alarms or alerts.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the MMT-522k and MMT-722k insulin infusion pump and CSS7100k monitor labeling.

V. DEVICE DESCRIPTION

- Paradigm REAL-Time Insulin Infusion Pumps (MMT-522k and MMT-722k)

The Paradigm MMT-522k and MMT-722k insulin infusion pumps are identical to the previously approved model MMT-522 and MMT-722 insulin infusion pumps (P980022/S013) with the exception of the programmable values available for the pumps' low glucose alarm. The minimum value that may be selected for the low glucose alarm for the MMT-522 and MMT-722 pumps is 40 mg/dL whereas the software used in the MMT-522k and MMT-722k pumps has been modified to limit the minimum programmable value for the low glucose alarm to 90 mg/dL.

- Guardian REAL-Time Monitor (CSS7100k)

The Guardian REAL-Time Monitor (CSS7100k) is identical to the previously approved CSS7100 monitor (P980022/S017) with the exception of the programmable values available for the monitor's low glucose alarm. The minimum value that may be selected for the low glucose alarm for the CSS7100 monitor is 40 mg/dL whereas the software used in the CS7100k monitor has been modified to limit the minimum programmable value for the low glucose alarm to 90 mg/dL.

V. ALTERNATIVE PRACTICES AND PROCEDURES

Periodic glucose self-monitoring using home blood glucose meters will provide information regarding variations in glucose levels. Additionally, adult (18 and older) patients may use the previously approved MMT-522 and MMT-722 insulin infusion pumps or CSS7100 monitor to display and record interstitial glucose concentrations and to provide high and low glucose alerts.

VI. MARKETING HISTORY

As of December 2006, the MMT-522k and MMT-722k insulin pumps and the CSS7100k monitor have not been marketed in the United States or any foreign country.

VII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Inaccurate glucose values or inappropriate alarms provided by the MMT-522k and MMT-722k insulin pumps and the CSS7100k monitor could result in inappropriate administration of insulin or ingestion of carbohydrates. Such inappropriate treatment decisions could cause or exacerbate hypoglycemic or hyperglycemic episodes.

VIII. SUMMARY OF PRE-CLINICAL STUDIES

Since, except for the application software used, the MMT-522k and MMT-722k insulin pumps and the CSS7100k glucose monitor are identical to previously qualified and approved devices, pre-clinical studies for these devices were limited to validation activities for the minor software modifications required to limit the minimum programmable value for the low glucose alert to 90 mg/dL. This validation testing confirmed that programmable values were correctly limited and that the software change did not adversely impact any other aspects of device operation.

IX. SUMMARY OF CLINICAL STUDIES

A clinical trial was conducted to evaluate the accuracy of the Guardian® RT System when used by individuals ages 7 through 17. The primary accuracy assessment was based on the overall percent of Guardian® RT values being within 20% (or within +/- 20 mg/dl for reference values from 40-80 mg/dl) of the One-Touch® Ultra® Meter reference value.

The results of this study are directly applicable to the Guardian REAL-Time System (CSS7100k monitor) and the continuous glucose monitoring functions of the Paradigm REAL-Time System (MMT-522k and MMT-722k insulin pumps) since these systems all use the same glucose sensor and algorithms for conversion of sensor information into glucose concentration and therefore will all provide the same glucose reading for a given sensor signal.

Study Design

The subjects in this study were pediatric males and females, aged 7 through 17, with a previous diagnosis of Type 1 Diabetes Mellitus. Subjects must also have been using an intensive therapy regimen (CSII or MDI) to treat their diabetes for a minimum of three months prior to study enrollment. The protocol called for a maximum of sixty (60) subjects, containing equal numbers of subjects from each of the four following groups:

- Females ages 7 through 12 years
- Females ages 13 through 17 years
- Males ages 7 through 12 years
- Males ages 13 through 17 years

All subjects in this study were assigned to use Guardian® RT System for a period of approximately six (6) days. A minimum of two (2) consecutive sensors were worn for up to 74 hours each. However, subjects wore sensors continuously for a minimum of 6 days, not to exceed 7 days, regardless of sensor life. In the event that a sensor did not last the full 74 hours,

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

was accidentally removed, or was dislodged due to tape issues, it was to be replaced as soon as possible. Subjects were instructed to test their capillary blood glucose level a minimum of seven (7) times per day (pre-prandial, 1 hour post-prandial and before bed) using a One-Touch® Ultra® blood glucose meter.

Subjects Enrolled

Of 61 subjects who enrolled in the study, 57 completed the entire study. A total of 60 subjects contributed meter and sensor data. Additional information regarding subject participation and details regarding the four subjects who did not complete the study are provided in the following table.

Disposition of subjects and reasons for discontinuations

		Boys	Girls	Boys	Girls
	Total	7-12 Years	7-12 Years	13-17 Years	13-17 Years
All Subjects, n(%)	61 (100.0%)	15 (100.0%)	15 (100.0%)	15 (100.0%)	16 (100.0%)
Completed Study, n(%)	57 (93.4%)	13 (86.7%)	14 (93.3%)	14 (93.3%)	16 (100.0%)
Discontinued Early, n(%)	4 (6.6%)	2 (13.3%) ^{1,2}	1 (6.7%) ³	1 (6.7%) ⁴	0 (0.0%)

¹ Subject Refused To Allow Reinsertion Of Sensor By Parent

² Subject Requested to Drop Study And Parent Agreed

³ Subject Said She Did Not Want To Be In Study Anymore

⁴ Subject Refused To Continue In Study - Turned Monitor Off At School

Results

A total of 2599 paired Guardian RT sensor and one OneTouch Ultra fingerstick glucose values were collected during the study and analyzed. The Guardian RT sensor measurement was within 20% (or 20 mg/dL for OneTouch Ultra values of 80 mg/dL or below) of the reference value for 1776 (68.3%) of the 2599 paired measurements. The 95% confident interval for the percent of sensor values with 20% (or 20mg/dL) of the reference meter value is 66.6% to 70.1%. This compares favorably with the result of a previous study of adult subjects where 58.3% (95% confidence interval of 54.7% to 61.8%) of the sensor readings were within 20% (or 20 mg/dL for meter readings of 80 mg/dL or below) of the reference fingerstick glucose measurement.

The number and percent of sensor readings within ± 20% (or 20 mg/dL for meter readings of 80 mg/dL or below) of the reference meter readings, stratified by meter glucose range (mg/dL) and subject age group and gender is summarized in the table that follows.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Range of Comparative Glucose Readings (mg/dL)	n in agreement/ n in range (%)	Boys	Girls	Boys	Girls
		7-12 Years	7-12 Years	13-17 Years	13-17 Years
		n=15	n=14	n=15	n=16
40-80	184/360 (51.1%)	41/92 (44.6%)	53/113 (46.9%)	51/80 (63.8%)	39/75 (52.0%)
81-120	287/482 (59.5%)	72/119 (60.5%)	74/138 (53.6%)	78/116 (67.2%)	63/109 (57.8%)
121-240	782/1055 (74.1%)	218/288 (75.7%)	183/266 (68.8%)	178/234 (76.1%)	203/267 (76.0%)
240-400	523/702 (74.5%)	176/226 (77.9%)	142/195 (72.8%)	96/125 (76.8%)	109/156 (69.9%)
Overall	1776/2599 (68.3%)	507/725 (69.9%)	452/712 (63.5%)	403/555 (72.6%)	414/607 (68.2%)

¹ For comparative glucose readings ≤ 80 mg/dL, agreement is within ± 20 mg/dL

Overall, the median sensor glucose value measured by the sensor was 160.8 mg/dL and for the meter it was 164.0 mg/dL. The median absolute relative error (ARE) between the sensor and the reference meter was 13.6% and the median Bias was -1.3 mg/dL. The following table provides additional details regarding the numerical agreement between the sensor and reference value by age and gender groupings.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

	Total	Boys 7-12 Years n=15	Girls 7-12 Years n=14	Boys 13-17 Years n=15	Girls 13-17 Years n=16
SENSOR GLUCOSE					
n	2599	725	712	555	607
Mean (SD)	173.2 (76.21)	183.3 (79.05)	170.9 (77.61)	163.9 (73.85)	172.3 (71.92)
Median	160.8	168.5	157.2	148.6	165.7
Min,Max	40.0, 400.0	48.7, 400.0	40.0, 400.0	40.0, 400.0	47.7, 400.0
METER GLUCOSE					
n	2599	725	712	555	607
Mean (SD)	179.2 (88.49)	189.0 (93.34)	176.5 (89.70)	167.1 (82.52)	181.8 (85.05)
Median	164.0	176.0	158.5	151.0	176.0
Min,Max	40.0, 400.0	43.0, 399.0	40.0, 400.0	40.0, 399.0	40.0, 399.0
ABSOLUTE RELATIVE ERROR					
n	2599	725	712	555	607
Mean (SD)	19.0 (19.73)	18.2 (18.50)	20.9 (20.22)	18.3 (22.99)	18.6 (17.07)
Median	13.6	13.1	15.5	12.3	13.9
Min,Max	0.0, 237.8	0.0, 200.3	0.0, 181.6	0.0, 237.8	0.0, 116.3
BIAS					
n	2599	725	712	555	607
Mean (SD)	-6.0 (39.68)	-5.7 (38.30)	-5.6 (41.73)	-3.1 (37.51)	-9.5 (40.60)
Median	-1.3	0.0	-0.6	-1.0	-3.6
Min,Max	-219, 206.9	-182, 188.3	-219, 147.3	-172, 206.9	-201, 98.1

The best agreement between the sensor and reference meter was observed in the normal and high glucose ranges with less agreement at glucose levels of 80 mg/dL or below. As indicated in the table that follows, the sensor tended to read higher than the reference meter for reference values below 80 mg/dL with the difference increasing at very low glucose levels. Therefore the minimum programmable values for the low glucose alert has been limited to 90 mg/dL in the MMT-522k and MMT-722k insulin infusion pumps and the CSS7100k glucose monitor to increase the probability that the device will alarm in the event of hypoglycemia when these devices are used by children and adolescents.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Meter glucose (mg/dl)	n/Total (%)	Difference (Meter-Sensor)	Difference (Meter-Sensor)
		Mean ± SD	Median (Min, Max)
40-50	11/44 (25.0)	-30.0 ± 16.55	-25.4 (-89.0, -2.1)
50-60	37/81 (45.7)	-24.4 ± 19.03	-21.4 (-92.9, 16.0)
60-70	62/119 (52.1)	-21.5 ± 20.26	-18.9 (-117.7, 20.8)
70-80	74/116 (63.8)	-13.3 ± 21.41	-11.6 (-121.0, 25.7)

Clarke Error Grid Analysis

The Clarke Error Grid analysis performed on the paired sensor/meter values showed that 1733 sensor values (66.7%) fell in zone A, 665 (25.6%) in zone B, 7 (0.3%) in zone C, 193 (7.4%) in zone D and one (0.0%) in zone E. The following table provides more detailed information regarding the Clarke Error Grid distribution of sensor values by reference meter range.

Range of Comparative Glucose Readings (mg/dL)	Total count	Clarke Error Grid Zones					
		A + B	A	B	C	D	E
40-80	360 (13.9%)	201 (55.8%)	141 (39.2%)	60 (16.7%)	1 (0.3%)	157 (43.6%)	1 (0.3%)
81-120	482 (18.5%)	478 (99.2%)	287 (59.5%)	191 (39.6%)	4 (0.8%)	0 (0%)	0 (0%)
121-240	1055 (40.6%)	1053 (99.8%)	782 (74.1%)	271 (25.7%)	2 (0.2%)	0 (0%)	0 (0%)
240-400	702 (27.0%)	666 (94.9%)	523 (74.5%)	143 (20.4%)	0 (0%)	36 (5.1%)	0 (0%)
Overall	2599 (100.0%)	2398 (92.3%)	1733 (66.7%)	665 (25.6%)	7 (0.3%)	193 (7.4%)	1 (0.0%)

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Low and High Glucose Alerts

An analysis of the predicted performance of the available low and high low glucose alerts was performed using paired sensor and reference meter readings where the sensor or reference value met the defined alert threshold. It should be noted that the analysis performed is conservative since it does not account for the continuous nature of the sensor information.

Low Glucose Alert Performance

Out of 244 paired points with meter readings below 70 mg/dL, 59 were detected by the Guardian® RT System (sensitivity, 24.2%). Out of 2355 paired points with meter readings above 70 mg/dL, 2301 were detected by the sensor (specificity, 97.7%). Out of 113 paired points with sensor readings below 70 mg/dL, 54 (47.8%) were proved to be false alerts by meter readings.

There were 185 meter readings less than or equal to 70 mg/dL which were not detected by the sensor, and the median (min, max) sensor glucose value of those readings was 85.3 mg/dL (70.6, 180.7). Of the 54 sensor readings less than or equal to 70 mg/dL which were proved false by meter readings, the median (min, max) meter glucose value was 88.0 mg/dL (71.0, 157.0). The table that follows provides additional details, including information regarding sensitivity, specificity and false alerts for threshold settings above the reference meter reading (70 mg/dL or below) that would be classified as a true low glucose event.

Low Alert Threshold, mg/dL	Sensitivity	Specificity	False Alerts
70	24.2	97.7	47.8
75	41.0	96.6	44.1
80	51.6	95.5	45.7
85	61.1	93.8	49.3
90	69.7	92.2	52.0
95	77.9	90.3	54.6
100	85.3	88.2	57.3

High Glucose Alert Performance

Out of 632 paired points with meter readings above 250 mg/dL, 404 were detected by the Guardian® RT System (sensitivity, 63.9%). Out of 1967 paired points with meter readings below 250 mg/dL, 1906 were detected by the sensor (specificity, 96.9%). Out of 465 paired points with sensor readings above 250 mg/dL, 61 (13.1%) were proved to be false alerts by meter readings.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

There were 228 meter readings greater than or equal to 250 mg/dL which were not detected by the sensor, and the median (min, max) sensor glucose value of those readings was 223.7 mg/dL (97.7, 249.5). Of the 61 sensor readings greater than or equal to 250 mg/dL which were proved false by meter readings, the median (min, max) meter glucose value was 229.0 mg/dL (87.0, 249.0). The table that follows provides additional details, including information regarding sensitivity, specificity and false alerts for threshold settings below the reference meter reading (250 mg/dL or above) that would be classified as a true low glucose event.

High Alert Threshold, mg/dL	Sensitivity	Specificity	False Alerts
180	95.4	76.1	43.8
185	94.8	78.1	41.8
190	93.7	80.0	39.9
195	92.7	81.8	37.9
200	90.8	83.9	35.5
205	89.9	86.0	32.7
210	87.8	88.0	29.7
215	86.1	90.0	26.6
225	81.3	92.9	21.4
250	63.9	96.9	13.1

Device Related Adverse Events

There were a total of five device related adverse events reported during the course of this study. None of these events were severe in nature and all were anticipated potential adverse effects associated with the use of a continuous glucose monitoring system. The table that follows provides additional details regarding these five events.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

Event	Start Date	Stop Date	Device Causality	Intensity	Action Taken	Outcome
Rash	12/12/05	On going	Probable	Moderate	None	Ongoing and Improving
Bleeding	12/22/05	12/22/05	Probable	Mild	Device Use Discontinued ¹	Recovered Completely
Pain	12/26/05	On going	Probable	Mild	None	Ongoing and Improving
Skin Irritation	01/09/06	On going	Probable	Mild	None	Ongoing and Improving
Skin Irritation	12/06/05	On going	Probable	Mild	Concomitant Medication	Ongoing and Improving

¹ Although the action taken for this event was recorded as "Device Use Discontinued", in reality, only use of the sensor was discontinued. The subject experienced bleeding upon insertion of the sensor. The sensor was removed and a new one was inserted with no complications.

X. CONCLUSIONS DRAWN FROM STUDIES

A. Safety Conclusions

No serious adverse health consequences were observed in the clinical study. All reported adverse events were related to sensor insertion and were similar to results observed in earlier studies in adults (refer to the SSED for the approved PMA (P980022) for additional details).

B. Effectiveness Conclusions from the Preclinical Laboratory Studies

The software validation/verification testing performed confirmed that the minor software modifications to the application software used in devices previously approved by FDA correctly limited the minimum programmable value for the low glucose alert to 90 mg/dL. This testing also confirmed that these modifications did not adversely impact any other aspect of device function.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

C. Effectiveness Conclusions from the Clinical Study

Clinical data collected shows device performance in children and adolescents similar to that observed in adults (see SSED for PMA P980022). Analysis of the data from the pediatric study conducted in support of this submission showed that 68.3% of sensor values were within 20% of the reference meter values and 81.8% were within 30% of the reference values. In a previous adult study, 62% and 79% of sensor values were within 20% and 30% of the reference meter values, respectively.

The agreement (percent of readings within 20% or 20 mg/dL) between meter and sensor values varied between 51.1% in the 40-80 mg/dL reference range to 74.5% in the 240-400 mg/dL reference range. While agreement was not as good in the lower blood glucose ranges, particularly in the 40-80 mg/dL range, further examination of the data reveals that accuracy increased substantially as the comparative glucose values increase toward the upper limit of this range (80 mg/dL).

The predicted sensitivity and specificity for the low alerts (sensor set at 70 mg/dL) in this study were 24 % and 98%. For the alerts set at 250 mg/dL, the sensitivity and specificity for the high glucose alert were 63.9% and 96.9%. It should be noted that based on the strict definition of agreement used during analysis, cases with almost perfect agreement between the sensor and reference meter could be classified as false positives or false negatives. For example, if the sensor reading was 69 mg/dL and the reference meter read 71 mg/dL, this would be classified as a false alarm (if the hypoglycemic alert was set to 70 mg/dL). Under normal conditions of use, this situation would not be perceived as a false positive. Therefore these sensitivity and specificity statistics provide a conservative estimate of device performance.

Alerts set for higher blood glucose levels had better detection of hypoglycemic episodes than those set in the low glucose range. Further analysis of the data showed that as the low alert threshold was increased, the sensitivity increased with only minor decreases in specificity. When the threshold was set to 90 mg/dL, the sensitivity to detect reference values of 70 mg/dL or below increased to 70% with only a 5% loss of specificity (92.2%).

Overall, the clinical data demonstrated acceptable sensor accuracy when the device was used by pediatric subjects. In light of the tendency of the sensor to read higher than the reference meter in the low glucose range, the minimum programmable value for the low glucose alert for the pediatric devices discussed in this supplement is 90 mg/dL to increase the probability of detection of hypoglycemia in children and adolescents. This is consistent with American Diabetes Association recommendations for higher target glucose ranges (relative to adult target ranges) for children and adolescents with diabetes.

XI. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA supplement was not referred to the Chemistry and Toxicology Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the supplement substantially duplicates information previously reviewed by this panel.

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

XII. CDRH DECISION

FDA issued an approval order on March 8, 2007.

XIII. APPROVAL SPECIFICATION

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

Postapproval Requirements and Restrictions: See approval order.