# Clinical Evaluation of a Faster, Smaller Sample Volume Blood ß-Ketone Test Strip


## Executive Summary

### Objective:

To evaluate the clinical performance of a new (1.5 µL, 10-second) blood ß-Ketone test strip, for use with certain Precision and Optium brand meters for fingertip testing with fresh capillary whole blood or venous whole blood samples (healthcare professional). The blood ß-Ketone test strip measures ß-hydroxybutyrate, the predominant and most important of the three ketone bodies circulating in the bloodstream.

### Method:

The accuracy evaluation was conducted at four hospitals. Capillary blood from fingersticks and venous blood were tested on three lots of the new ß-Ketone test strip followed by reference testing of ß-hydroxybutyrate on a laboratory analyzer. To evaluate lay user performance, three lots of the new ß-Ketone test strip were tested with capillary blood from the fingertip by lay users and trained operators at two diabetes clinics. Lay user results were compared to trained operator results on the new test strip. Subjects participating in the user performance evaluation were also asked to assess ease of use. Laboratory studies were performed at Abbott Diabetes Care Inc. to validate performance under various testing conditions.

### Results:

Accuracy of the new test strip was demonstrated with capillary and venous whole blood by comparing results of duplicate tests from 48 subjects on three lots of ß-Ketone test strips with the reference method ($r=0.98$, slope = 1.06, intercept = 0.07 mmol/L, $n=288$). In the user performance evaluation conducted at 2 diabetes clinics, lay user results were comparable to trained operator results on the new test strips. One hundred twenty subjects were surveyed on the ease of use with the new ß-Ketone test strip. Using a rating scale of 1 to 6 (6 reflecting the greatest ease), the overall mean rating was 5.5, indicating that these first-time users found the new test strip easy to use.

In the laboratory studies, precision of the new ß-Ketone test strip, determined as coefficients of variation (CV), ranged from 3.1% to 3.8%. The new test strip produced accurate results at high altitude (10,000 feet or 3,048 meters above sea level), across a hematocrit range of 30-60% and a ketone measurement range of 0.0-8.0 mmol/L and with a minimum sample volume of 1.5 µL. Additional studies showed that the following produced no clinically significant effect on the accuracy of the new ß-Ketone test strip: meter movement, second blood drop application within 30 seconds, various sample application techniques, and numerous drugs and endogenous substances at elevated concentrations.

### Conclusions:

In the clinical studies, accuracy and ease of use of the new (1.5 µL, 10-second) ß-Ketone test strip were verified with capillary and venous whole blood samples. Additional studies demonstrated that the new test strip maintained accuracy in various challenging conditions that may be encountered in everyday home testing, and the test strip received a high ease-of-use rating by first-time users.


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### Overview

In diabetes, there is either insufficient or ineffective insulin action. Insulin helps glucose cross the cellular membrane and enter the cell. When insufficient insulin is available to use glucose effectively, the body will begin to break down fat for energy. The byproducts of the breakdown of fat are called ketones.

The accumulation of ketones in the blood is called ketosis and may lead to diabetic ketoacidosis (DKA). If left untreated, DKA can lead to coma and death. ß-hydroxybutyrate (ß-OHB) and acetoacetate are the two main ketone bodies. Acetone, the third ketone body, is present in a much lower concentration. The ratio of ß-OHB to acetoacetate is about 1:1 after a meal, but can rise to 10:1 in DKA[1]. Various studies have shown that blood ß-OHB is more effective than urine ketones for detecting ketosis and tracking the resolution of DKA.[2]

In the American Diabetes Association (ADA) position statement, it is recommended that people with type 1 diabetes test for ketones during acute illness or stress, during pregnancy, when blood glucose levels are consistently elevated (> 300 mg/dL or 16.7 mmol/L) or when symptoms of ketoacidosis are present[3]. Ketones can be measured in both urine and blood, but testing in urine has some distinct disadvantages:[1-3]

- Urine ketone methods that employ nitroprusside-containing reagents are prone to interference from sulfhydryl medications, including the antihypertensive agent, captopril[1].
- False positive readings have been reported when test strips are exposed to air for an extended period of time or when highly acidic urine is used for testing.
- Urine ketone testing is qualitative and relies on the ability of the user to differentiate color to obtain a result.
- Detection of ketone bodies in urine depends on the ability to pass urine and levels often lag 2 to 4 hours behind the levels in blood.

The ADA also warns, “Heathcare professionals should be aware, however, that currently available urine ketone tests are not reliable for diagnosing or monitoring treatment of ketoacidosis. Blood ketone testing methods that quantify ß-hydroxybutyric acid, the predominant ketone body, are available and are preferred over urine testing for diagnosing and monitoring ketoacidosis.”[3]

### Introduction

For monitoring blood ketone, a new biosensor test strip that measures ß-hydroxybutyrate has been developed for use with Precision and Optium brand meters that allow for ketone testing. This ß-Ketone test strip allows the user to apply blood to either the top or the end of the strip. The blood is automatically drawn into the reaction area. The sample volume requirement is 1.5 µL and test time is 10 seconds. Multi-center studies were conducted to evaluate accuracy, user performance and ease of use. Additional studies were performed to validate performance claims under various testing conditions.

## Materials and Methods

### Test Method

ß-hydroxbutyrate in the blood specimen reacts with a NAD (nicotinamide adenine dinulceotide) co-enzyme in the presence of the enzyme ß-hydroxybutyrate dehydrogenase (HBDH). This chemical reaction releases electrons, which are transferred from the reduced co-enzyme (NAD) to the electrode by a mediator. These electrons generate a small current, which is proportional to the concentration of ß-OHB in the specimen and measured by the meter. The analysis time is 10 seconds.

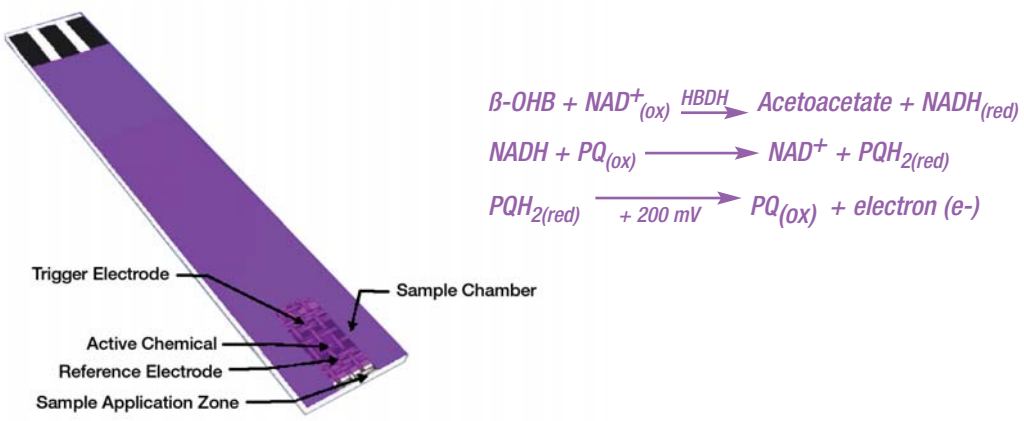
The new ß-Ketone test strip (Figure 1) contains three electrodes (working, reference, and fill trigger electrodes). The circuit between the fill trigger and reference electrodes must be detected by the meter before the test will start. This can occur only when the applied sample flows beyond the reference and working electrodes to contact the fill trigger electrode. The fill trigger electrode is designed to minimize the potential for errors that may occur when not enough blood is applied to the test strip and to reduce wasting of test strips.

Upon application of sufficient blood sample, the test is automatically initiated. HBDH enzyme, NAD co-enzyme and an electron mediator (PQ) are present on the working electrode of the test strip. The HBDH catalyzes the oxidation of ß-OHB by NAD to acetoacetate by accepting an electron from the ß-OHB molecule, and the co-enzyme NAD is reduced to NADH. The oxidized form of the electron mediator reacts with the reduced co-enzyme (NADH) and accepts the electron, thus the mediator is reduced and the co-enzyme returns to its oxidized state (NAD). The reduced mediator is oxidized at the working electrode, which produces a small electric current proportional to the concentration of ß-OHB in the sample. In this electrochemical reaction, a low applied potential is used to minimize interference by reducing substances such as vitamin C, uric acid and acetaminophen.

The combination of the fill-trigger and the HBDH-NAD based chemistry with a low applied electric potential is the basis of the chemistry of the new ketone test strip, designed to minimize errors from insufficient blood samples and interfering substances.

1. Laffel L. Sick-day management in type 1 diabetes. Endo Metab Clin N Amer 2000; 29:707-723.
2. Guerci B, Tubiana-Rufi N, Bauduceau B. Advantages to using capillary blood ß-hydroxybutyrate determination for the detection and treatment of diabetic ketosis. Diab Metab 2005; 401-40.
3. ADA Position Statement: Tests of Glycemia in Diabetes, Diabetes Care, 2004; 27 (Supplement 1):91.

*Figure 1. The new ketone test strip*




## Comparative Methods

The comparative method in the accuracy and laboratory studies was the Randox Ranbut assay kit (RB1007) used on the RX Daytona™ clinical chemistry analyzer (Randox Laboratories Ltd.). The ß-Ketone test strip is calibrated to reflect plasma equivalent ß-OHB values.

## Accuracy Studies

The accuracy of the new ß-Ketone test strip was evaluated by comparing results from (1) capillary whole blood samples obtained from fingerstick tests and (2) from venous whole blood samples obtained by venipuncture to the reference method. Four hospitals in the United Kingdom participated in the study, and a total of 48 samples were collected from 16 subjects.

Each sample was analyzed in duplicate with three lots of ß-Ketone test strips so that six measurements were obtained for each sample. The samples were then centrifuged and the remaining plasma was returned to Abbott Diabetes Care, for testing on the RX Daytona reference system using the Randox Ranbut assay.

## User Performance Evaluation

User performance of the new ß-Ketone test strip was evaluated at two diabetes clinics using three lots of the new test strip. Two lots of test strips were used at each clinic and by each subject. One hundred twenty-one subjects enrolled in the study. Two subjects were excluded due to protocol deviations and 1 subject withdrew yielding 118 subjects. Ketone results obtained with the new test strip by lay users were compared to results obtained by trained operators.

## Ease-of-use Surveys

In the user performance evaluation, a total of 120 patients at two diabetes clinics evaluated the new ß-Ketone test strip. These lay users performed the tests on their own after reading the instructions for use. They were also asked to perform a urine ketone test following the blood ketone tests. After testing, the lay users completed a questionnaire rating various ease-of-use topics including handling of the test strips and application of blood specimens. A scale of 1 to 6 was used, with a rating of 6 reflecting the greatest ease. An overall ease of use rating was obtained by averaging all responses for each statement.

## Laboratory Studies

The following studies were performed at Abbott Diabetes Care Inc.

### *Precision*

Precision of the new ß-Ketone test strip was assessed at five ß-OHB levels by analyzing heparinized venous blood in 20 successive replicates. Three lots of test strips were used. For the lowest ß-OHB levels (less than 1.5 mmol/L), the standard deviation values were averaged across the three lots. For the other three ß-OHB levels, the coefficient of variation (CV) values of the three lots were averaged.

### *Sample Volume Requirements*

The effect of sample volume on the performance of the new ß-Ketone test strip was evaluated by applying 1.2, 1.5 and 2.5 µL of venous blood to the test strips. Three concentrations of ß-OHB (approximately 0.5, 2.5 and 5.0 mmol/L) were tested on three different days with three lots of test strips. Twenty-four replicates of testing were performed each day for each sample volume and ß-OHB level. For each sample volume, ß-OHB level and test strip lot, the difference in mean bias or mean percent bias between each volume and the control volume (5 µL) was calculated.

### *Effect of Meter Movement*

The effect of performing testing while holding the meter was evaluated with three lots of the new ß-Ketone test strip using capillary blood samples. On each of two days, twenty subjects tested their own fingertip blood specimens in duplicate with all three lots of test strips using an equal number of meters which were hand-held and meters that remained stationary on a flat surface (control condition) throughout the experiment. The difference in bias between the test condition and the control condition was calculated for each sample across the test strip lots and examined for clinical significance.

### *Effect of Hematocrit*

Three lots of the new ß-Ketone test strip were tested with venous blood adjusted to three ß-OHB concentrations (approximately 0.5, 2.5 and 5.0 mmol/L) and six hematocrit levels (30, 35, 40, 45, 55 and 60%). Twelve consecutive tests were performed at each level of ß-OHB and hematocrit on each test strip lot. The difference in mean bias (for ketone <1.5 mmol/L) or mean percent bias [for ketone ≥ 1.5 mmol/L) between the test conditions and the control condition (45% hematocrit) was calculated for each ß-OHB level, hematocrit, and test strip lot number.

### *Interference Studies*

Over 50 substances at concentrations higher than normal or therapeutic levels, along with 5 anticoagulants and pH were tested for interference on the previous version of the ketone test strip. No interfering substances were identified.

Differences in the designs between the new ß-Ketone test strip and the previous version could potentially influence the resistance to interference from some of the previously tested substances, based on their biochemical and electrochemical properties. Thus, twenty-four of the previously tested substances along with 2 additional sugars were tested on the new test strip. Three of the anticoagulants and pH were also retested. Venous blood samples adjusted to a ß-OHB concentration of 1.0 mmol/L were divided into two portions: a test sample and a control sample. A concentrated solution of the substance was added to the test sample and an equal volume of the solvent that was used to dissolve the substance was added to the control sample. Paired-difference testing was conducted with twenty-four assays per sample. An interfering substance is defined as one that produces a bias greater than 0.3 mmol/L from the control sample in the paired-difference testing and is confirmable by dose-response testing at varying concentrations of the interfering substance.

### *Effect of Sample Re-application*

Three lots of the new ß-Ketone test strip were tested over three days at three ß-OHB concentrations (approximately 0.5, 2.5 and 5.0 mmol/L). An initial sample volume of 0.5 µL followed by a second sample of 5.0 µL was applied at five different time delays (1, 5, 10, 20 and 30 seconds). Twelve consecutive tests were conducted on each day for each test strip lot number, time delay, and ß-OHB level. The difference in mean bias [for ketone < 1.5 mmol/L] or mean percent bias [for ketone ≥ 1.5 mmol/L] was calculated for each test strip lot between each test condition and the control condition (a single 5 µL drop).

### *Effect of Sample Application Technique*

Three lots of the new ß-Ketone test strip were evaluated with 20 donors over two days using four different blood application methods: (1) hanging drop (control method), (2) touching the finger to the test strips during application (3) smearing the finger lightly over the target area of the test strip during application and (4) end fill or applying the blood at the end of the test strip. Duplicate results were obtained for each day, blood sample, lot of test strips and blood application method. The mean bias between the different application methods and the control condition was calculated and averaged over the three batches.

### *Linearity*

Testing was conducted over two days; for each day capillary whole blood samples were collected from twenty donors. The capillary samples were spiked to varying ß-OHB concentrations, distributed throughout the blood ketone testing range. Three lots of the new ß-Ketone test strip were tested with duplicate measurements performed for each lot of test strips, day and blood sample.

### *Altitude Testing*

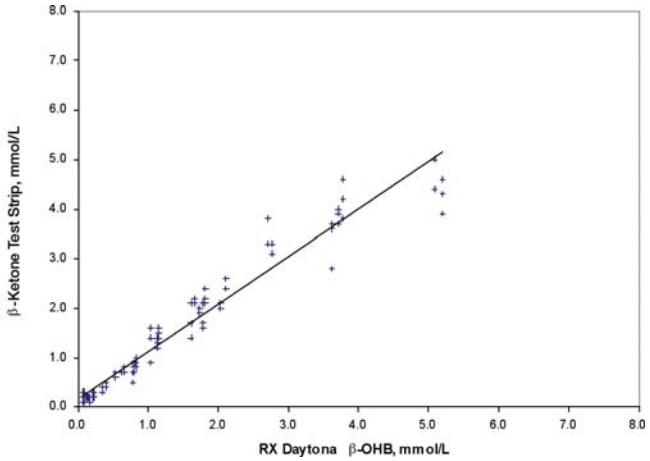
Testing with three levels of control solution was conducted using three lots of the new ß-Ketone test strip. Testing was performed at sea level and at 10,000 feet. At both altitudes and for each lot number, twelve replicate measurements were performed for each level of control solution.

## Results

### Accuracy Studies

The new ß-Ketone test strip provided accurate results in fingertip and venous testing (Figure 2). Good correlation was found between test strip results and comparative method results ($r = 0.98$; slope = 1.06 and intercept = 0.07 mmol/L, $n = 288$) by regression analysis. The mean bias was 0.1 mmol/L for samples under 1.5 mmol/L and 10% for samples 1.5 mmol/L and above. The hematocrit range of the capillary blood specimens in this study was 34-54%.

*Figure 2. Accuracy Testing*




## User Performance Evaluation

For each subject, one ketone test was performed on each of two lots by the lay user and by the trained operator. Three lots of the new ß-Ketone test strip were included in the evaluation. The lay user results were comparable to the trained operator results (Table 1). In addition, the lay users were asked to perform a urine ketone test in the study. After testing, 88% of the lay users concluded that they prefer to test blood rather than urine for ketone testing.

*Table 1. User Performance Data*

| Testing Performed by | Mean ß-OHB Result (mmol/L) | Median Result (mmol/L) | Range of Results (mmol/L) | n |
|---|---|---|---|---|
| Trained Operator | 0.18 | 0.2 | 0.1-1.8 | 235 |
| Lay User | 0.18 | 0.2 | 0.1-1.7 | 236 |

## Ease-of-use Surveys

One hundred twenty lay users at two study centers completed a questionnaire rating the new ß-Ketone test strip for ease of use in fingertip testing. A scale of 1 to 6 was used, with 6 reflecting the greatest ease. An overall ease-of-use rating of 5.5 was obtained when all responses were averaged, indicating that the lay users found the new test strip easy to use (Table 2).

The ages of the lay users ranged from 9 to 70 years old. Thirty-nine percent of the subjects were male and 61% were female. Their education levels spanned from grade school to post graduate. All had type 1 diabetes.

*Table 2. Ease of use rating of the new ß-Ketone test strip by 120 lay users*

| Statement | Mean Rating<br>The rating scale is 1 to 6 for each statement; (6 reflecting greatest ease). |
|---|---|
| The test strip is easy to handle | 5.4 |
| It is easy to insert the test strip into the meter | 5.8 |
| It is easy to see where to apply the blood | 5.5 |
| It's easy to see the test strip filling with blood | 5.5 |
| It is easy to apply blood to the test strip | 5.4 |
| It's easy to see that the test has started | 5.6 |
| The test strip uses a small amount of blood | 4.5 |
| I had enough time to apply blood to the test strip | 5.6 |
| The test is quick | 5.6 |
| The test instructions were easy to follow | 5.7 |
| The test strip is easy to use | 5.7 |
| I prefer to test blood rather than urine for ketone testing | 5.3 |
| **Overall Mean** | **5.5** |

## Laboratory Testing

### *Precision*

In the precision study using three lots the new ß-Ketone test strip and fresh venous blood samples, the standard deviation (SD) was ≤ 0.04 mmol/L for ß-OHB < 1.5 mmol/L and the coefficient of variation (CV) ranged from 3.1 to 3.8% for ß-OHB ≥1.5 mmol/L (Table 3).

*Table 3. Precision*

| | | | | | |
|---|---|---|---|---|---|
| Mean ß-OHB (mmol/L) | 0.34 | 1.13 | 2.36 | 4.09 | 6.32 |
| SD | 0.03 | 0.04 | | | |
| CV, % | | | 3.8% | 3.4% | 3.1% |

### *Sample Volume Requirements*

In this study, the various sample volumes tested gave clinically acceptable results on the three lots of new ß-Ketone test strips. None of the tests started at 1.2 µL. Compared to the control volume (5.0 µL), all mean biases at 1.5 and 2.5 µL were less than or equal to 0.02 mmol/L or 1.8% (Table 4).

*Table 4. Effect of Sample Volume*

| ß-OHB*,mmol/L | Mean Bias (mmol/L or %) vs. the Control Volume (5.0 µL) | | |
|---|---|---|---|
| | **1.2 µL** | **1.5 µL** | **2.5 µL** |
| 0.5 | Did not start | 0.01 mmol/L | 0.02 mmol/L |
| 2.5 | Did not start | 1.8% | 1.4% |
| 5.0 | Did not start | 0.4% | 0.4% |

*Approximate concentrations.

### *Effect of Meter Movement*

The effect of performing the testing while holding the meter in the hand was evaluated with three lots of the new ß-Ketone test strips. On each of two days, twenty capillary samples were tested using equal numbers of meters which were (1) hand held and (2) remained stationary throughout the experiment. The difference in mean percent bias between the stationary and hand held results was 0.01 mmol/L, thus there was no clinically significant difference between the two testing conditions.

### *Effect of Hematocrit*

Three lots of the new ß-Ketone test strips were tested at three ß-OHB concentrations (approximately 0.5, 2.5 and 5.0 mmol/L) and six hematocrit levels (30, 35, 40, 45, 55 and 60%). For each lot at each level of ketone and hematocrit, the mean bias/mean % was within 0.06 mmol/L or 24% of the control condition (45% hematocrit), indicating clinically acceptable performance across a hematocrit range of 30-60%.

### *Interference Studies*

Of the twenty-six substances, three anticoagulants and pH tested in this study, none interfered with the new ß-Ketone test strip. This finding is consistent with those on the previous version of the test strip. Table 5 lists all substances tested to date.

*Table 5. Substances tested for interference with ß-Ketone test strips**

| Substance | Upper Limit of Therapeutic or Normal Concentration | | Concentration Tested | |
|---|---|---|---|---|
| **Exogenous** | | | | |
| Acarbose (Glucobay) | - | - | 120 mg/dL | 1859 µmol/L |
| *Acetaminophen (Tylenol)* | 3 mg/dL | 199 µmol/L | 25 mg/dL | 1655 µmol/L |
| Amoxicillin-(Augmentin) | - | - | 200 mg/dL | 5473 µmol/L |
| Ampicillin | 0.5 mg/dL | 14 µmol/L | 5 mg/dL | 143 µmol/L |
| *Ascorbic Acid (Vitamin C)* | 1.5 mg/dL | 85 µmol/L | 4 mg/dL | 227 µmol/L |
| *Captopril (Lopirin)* | - | - | 0.5 mg/dL | 23 µmol/L |
| Cefaclor (Ceclor) | 0.7-2.3 mg/dL | - | 23 mg/dL | 596 µmol/L |
| Chlorpropamide (Diabinese) | 14 mg/dL | 506 µmol/L | 75 mg/dL | 2710 µmol/L |
| Diltiazem (Cardizem) | 0.02 mg/dL | 0.44 µmol/L | 75 mg/dL | 1663 µmol/L |
| *Dopamine* | 0.03 mg/dL | 1.96 µmol/L | 0.09 mg/dL | 5.88 µmol/L |

*Substances in *italic* were tested with the new ß-Ketone test strip; other substances were tested with previous versions of the test strip.

*Table 5.* *Substances Tested for Interference with ß-Ketone Technology Test Strips* (continued)*

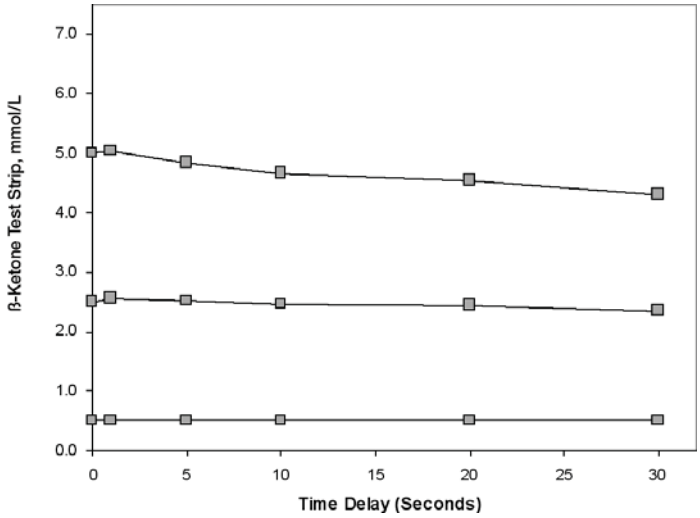
| Substance | Upper Limit of Therapeutic or Normal Concentration | | Concentration Tested | |
|---|---|---|---|---|
| *Ephedrine* | 1.8 mg/dL | 89 µmol/L | 5.4 mg/dL | 267 µmol/L |
| *Ethanol* | 100 mg/dL | 22 mmol/L | 400 mg/dL | 86.8 mmol/L |
| Fluoxetine (Prozac) | - | - | 0.3 mg/dL | 9 µmol/L |
| *Gentisic Acid* | 0.6 mg/dL | 39 µmol/L | 1.8 mg/dL | 117 µmol/L |
| Glibenclamide/Glyburide | - | - | 0.25 mg/dL | 5 µmol/L |
| Glipizide (Glucotrol) | - | - | 8 mg/dL | 180 µmol/L |
| Ibuprofen (Motrin, Advil) | 7 mg/dL | 340 µmol/L | 40 mg/dL | 1940 µmol/L |
| *Icodextrin* | - | - | 460 mg/dL | 4600 mg/L |
| *Levadopa* | 10 mg/dL | 508 µmol/L | 0.6 mg/dL | 30 µmol/L |
| Metformin (Glucophage) Diabex) | - | - | 50 mg/dL | 3019 µmol/L |
| *Methyldopa (Aldomet)* | 0.75 mg/dL | 35.54 µmol/L | 1.5 mg/dL | 71 µmol/L |
| Omeprazole (Prilosec) | - | - | 8 mg/dL | 232 µmol/L |
| Ranitidine (Zantac) | 2 mg/dL | 57 µmol/L | 20 mg/dL | 570 µmol/L |
| *Salicylic Acid (Aspirin)* | 30 mg/dL | 2170 µmol/L | 60 mg/dL | 4340 µmol/L |
| Simvastatin (Zocor) | - | - | 8 mg/dL | 191 µmol/L |
| *Tetracycline* | 0.5 mg/dL | 11.26 µmol/L | 1.5 mg/dL | 33.8 µmol/L |
| *Tolazamide (Tolinase)* | 5 mg/dL | 160.8 µmol/L | 15 mg/dL | 482 µmol/L |
| *Tolbutamide (Orinase)* | 24.03 mg/dL | 890 µmol/L | 64 mg/dL | 2370 µmol/L |
| Warfarin (Coumadin) | 1 mg/dL | 32 µmol/L | 10 mg/dL | 324 µmol/L |
| **Endogenous** | | | | |
| *Acetoacetate* | 1 mg/dL | 0.1 mmol/L | 6 mg/dL | 0.6 mmol/L |
| Acetone | 2.0 mg/dL | 0.3 mmol/L | 60 mg/dL | 10.3 mmol/L |
| Bicarbonate | 29 mmol/L | 29 mmol/L | 40 mmol/L | 40 mmol/L |
| *Bilirubin, unconjugated* | 1.2 mg/dL | 21 µmol/L | 20 mg/dL | 342 µmol/L |
| *Cholesterol* | 300 mg/dL | 7.77 mmol/L | 500 mg/dL | 12.92 mmol/L |
| Cholic Acid | 1.5 µmol/L | 1.5 µmol/L | 6.0 µmol/L | 6.0 µmol/L |
| *Creatinine* | 1.5 mg/dL | 133 µmol/L | 4.5 mg/dL | 397.8 µmol/L |
| Gamma Globulin | 1.2 g/dL | 12 g/L | 6 g/dL | 60 g/L |
| Glutathione | - | - | 1.0 mg/dL | 33 µmol/L |
| *Hemoglobin (plasma concentrate)* | 4 mg/dL | 0.62 µmol/L | 9 mg/dL | 1.41 µmol/L |
| Lactic Acid | 20 mg/dL | 2.2 mmol/L | 100 mg/dL | 11.1 mmol/L |
| Pyruvic Acid | 0.9 mg/dL | 103 µmol/L | 2.0 mg/dL | 228 µmol/L |
| *Triglycerides* | 190 mg/dL | 2.15 mmol/L | 1,875 mg/dL | 21.2 mmol/L |
| Urea | 38 mg/dL | 13.6 mmol/L | 500 mg/dL | 178.5 mmol/L |
| *Uric Acid* | 7 mg/dL | 0.41 mmol/L | 24 mg/dL | 1.42 mmol/L |
| **pH** | 7.35-7.45 | 7.35-7.45 | 6.80-7.76 | 6.80-7.76 |
| **Sugars** | | | | |
| Fructose | 7.5 mg/dL | 0.42 mmol/L | 30 mg/dL | 1.66 mmol/L |
| Galactose | 20 mg/dL | 1.11 mmol/L | 60 mg/dL | 3.33 mmol/L |
| *Glucose* | - | - | 360 mg/dL | 20.0 mmol/L |
| *Maltose* | - | - | 110 mg/dL | 3.05 mmol/L |
| *Maltotetraose* | - | - | 60 mg/dL | 0.9 mmol/L |
| *Maltotriose* | - | - | 120 mg/dL | 2.38 mmol/L |
| *Xylose* | - | - | 100 mg/dL | 6.66 mmol/L |
| **Anticoagulants** | | | | |
| *Potassium EDTA* | - | - | 720 mg/dL | 24.8 mmol/L |
| *Lithium Heparin* | - | - | 5,600 U/dL | 56,000 U/L |
| *Sodium Citrate* | - | - | 0.042M | 0.042M |
| Sodium Fluoride | - | - | 1000 mg/dL | 238 mmol/L |
| Potassium Oxalate | - | - | 800 mg/dL | 43.4 mmol/L |

*Substances in *italic* were tested with the new ß-Ketone test strip; other substances were tested with previous versions of the test strip.

### *Effect of Sample Re-Application*

In this study, an initial sample volume of 0.5 µL was followed by a second sample of 5.0 µL applied at five different time delays (1, 5, 10, 20 and 30 seconds) at three different ß-OHB concentrations (approximately 0.5, 2.5 and 5.0 mmol/L). The initial sample of 0.5 µL was insufficient to start the test. Comparable results were obtained from sample re-application compared to the control condition (a single 5.0 µL drop). Representative data are shown in Figure 3. The data indicates that if a test fails to start due to insufficient blood, a second drop of blood may be applied to the same ß-Ketone test strip within 30 seconds of the first blood drop.

*Figure 3. Effect of Sample Re-application*




### *Effect of Sample Application Technique*

Four different sample application methods were evaluated: hanging drop (control method), touching (lightly touching the finger to the test strip during blood application), smearing (smearing the finger lightly over the target area of the test strip during blood application) and end fill (applying the blood at the end of the test strip with the donor's finger palm up). There were no clinically significant differences between the three application methods and the control method. Representative data on the mean differences between methods are shown in Table 6.

*Table 6. Effect of Sample Application Techniques*

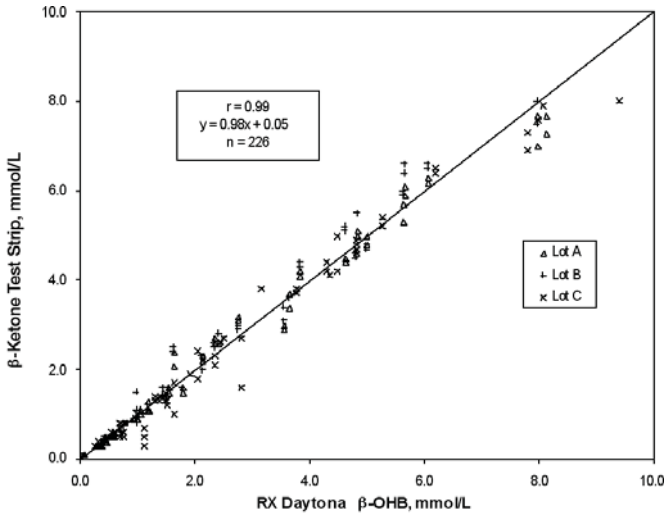
| Comparison | Mean Bias, mmol/L |
|---|---|
| Hanging Drop* vs. Touching | -0.008 |
| Hanging Drop* vs. Smearing | 0.014 |
| Hanging Drop* vs. End Fill | 0.005 |

* Control method

### *Linearity*

Capillary samples were spiked to varying ß-OHB concentrations, distributed throughout the measurement range. Three lots of new ß-Ketone test strip were tested with duplicate measurements performed for each lot of test strips, day and blood sample. Clinically accurate results were obtained across the dynamic range of the blood ß-Ketone test strips with spiked capillary whole blood. The regression analysis demonstrates good correlation and linearity when compared to the reference (Figure 4).

*Figure 4. Linearity*




### *Altitude Testing*

The difference in response between the test condition (10,000 ft) and the control condition (sea level) was averaged over 3 lots of ß-Ketone test strips. The average difference was less than 4.5% across all test strip lots and control solution levels.

## Discussion

The new ß-Ketone test strip showed excellent performance in the multi-center studies:

### Convenience and Ease-of-Use

The ß-Ketone test strip is designed to be easy and convenient for monitoring of blood ketone:

- **Speed:** It takes only 10 seconds per test. This feature was highly rated (5.6 out of a possible 6.0) on the ease of use questionnaire by first time users.
- **Easier application of blood:** The user has multiple options and techniques available to apply blood. The user can apply blood to the top or the end of the ß-Ketone test strip and the blood is automatically drawn into the reaction area. The see-through target area provides visual confirmation of sample application. Blood application features scored well (rating: 5.4-5.5) among first time users. The design provides equal convenience to left-handed and right-handed users. These features also make testing easier for caregivers or users with limited dexterity.
- **Convenience:** The same meter can be used for both ketone and glucose testing. Eighty-eight percent of the first time users expressed a preference for testing blood ketone over urine ketone.
- **Auto-calibration:** Simply insert calibrator into strip port. It reprograms the meter for upgrade to the new strip technology. Users get the latest technology without switching meters—no need to retrain. The technology is used to transfer strip lot-specific calibration information to the meter and is also designed to prevent use of expired test strips.
- **Easy-to-use:** The lay users in the user studies rated the new ß-Ketone test strip very easy-to-use (rating: 5.7).
- **Requires less blood:** The new ß-Ketone test strip requires 70% less blood than the previous ketone test strip.
- **Quantitative results:** The blood ketone tests give a numerical result, which may be easier to interpret than comparing a color to a chart.
- **Allows re-application of sample:** If there is insufficient blood on the test strip to start a test, the user may add a second blood drop to the same test strip within 30 seconds of the first blood drop. It is not necessary to repeat the test with a new test strip if the blood is re-applied during this 30 second window. This may reduce the need to perform another finger-stick.
- **Autostarts** when sample is detected.

## Reliable and Accurate Results for Home Monitoring

The new ß-Ketone test strip uses innovative technology, designed to maximize clinical accuracy in everyday testing.

### *Reduced Analytical Error*

The ß-Ketone test strip is based on a unique chemistry to increase performance. Accuracy was verified for capillary and venous blood, across a hematocrit range of 30-60%, a linearity range of 0.0-8.0 mmol/L, and at high altitude (10,000 feet; 3,048 meters).

### *Reduced Use Error*

The new ß-Ketone test strip is designed to reduce errors in everyday testing conditions:

- Unlike urine ketone strips, there is no color to interpret.
- The fill trigger electrode of the new test strip minimizes error from insufficient sample.
- Maintains accuracy when double-dosing (re-application with a second drop of blood)
- Maintains accuracy if the target area of the test strip is touched or the blood is smeared during sample application (reaction area is under a protective cover and adjacent to the sample application area).
- No timing error to worry about
- Biosensor technology is not affected by the ambient lighting conditions, and there are no optical components to clean.
- The ß-Ketone test strip design minimizes interference from medications and endogenous substances. By using a lower applied potential in the electrochemical reaction, the test strip is not affected by high levels of reducing substances such as acetaminophen (paracetamol), uric acid or gentisic acid.
- Each ß-Ketone test strip is individually foil wrapped to protect it against moisture, which can deteriorate unfoiled ketone test strips.

## Cost Savings

The new ß-Ketone test strip is designed with many strip-saving features:

- Double-dosing (applying a second drop of blood when the first drop is inadequate) minimizes the need to complete a test with another test strip.
- No meter optics means no wasted strips from invalid results due to bright light conditions or dirty optics.
- Individually foil wrapped test strips eliminate waste due to deterioration of test strips in vials.

In summary, the new ß-Ketone test strip is uniquely designed to assure accuracy, reliability, ease of use, and cost savings for self-monitoring of blood ketone. Some of the key benefits provided by this new test strip are summarized in Table 7. Favorable responses from the lay users in this study confirm the advantages of the new test strip.

*Table 7. Comparing performance of blood ketone testing vs. urine ketone testing*

| | Abbott ß-Ketone Test Strip | Urine Ketone Test Strip |
|---|---|---|
| **Easy to use**—can test using existing blood glucose meter | **Yes** | No |
| **Convenience** (speed)—fast test time of 10 seconds or less | **Yes** | No |
| **Reduces Use Error**—no user timing or visual interpretation of colors | **Yes** | No |
| **Reduces cost** (strip waste)—foil wrapped strips maintain integrity | **Yes** | Some* |
| **Reduces medical errors**—results not affected by high levels of common medications or endogenous substances | **Yes** | No** |
| **More accurate clinical information**—early, real-time indicator of ketosis | **Yes** | No |

*Only foiled urine ketone strips have this benefit

**Affected by high levels of ascorbic acid (Vitamin C), captopril, etc.

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