Diazyme Laboratories is a Division of General Atomics located in Poway, California. Diazyme uses its proprietary enzyme and immunoassay technologies to develop diagnostic reagents which can be used on most automated chemistry analyzers in user-friendly formats. Diazyme is a cGMP and ISO 13485 certified medical device manufacturer. Diazyme’s products include test kits for diagnosis of cardiovascular disease, liver disease, cancer markers, renal disease, diabetes and electrolytes.

MISSION STATEMENT

Our mission is to improve the quality of healthcare by providing innovative products in clinical diagnostics.
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1. What Is Lithium?

Lithium is a metallic element that was discovered in 1818. Because it was found in a mineral, it was called ‘lithium’, which is derived from the Greek word lithos, stone. Lithium is identified by the symbol Li on the periodic table at the position number 3 with an atomic mass of 6.94. Lithium is used in a range of industries, typically in the form of alloys and compounds, since it is extremely reactive. Well known lithium applications include the lithium-ion battery and lithium carbonate tablet for treatment of bipolar disorder and mood stabilization.

2. Medical Use of Lithium

2.1. What is lithium used for?

Psychiatrists use lithium as a therapeutic agent mainly for treating the following disorders:

1. Bipolar (manic depression) disorder
2. As a mood stabilizing agent
3. Schizophrenia and Alzheimer’s Disease

Lithium is the first modern recognized treatment for bipolar disorder and has served a unique role for this and other conditions for over 40 years. It became U.S. FDA-approved for treating acute manic episodes in 1970, and approved for maintenance therapy for patients of manic symptoms in 1974. All clinical practice guidelines recommend lithium as the choice for acute and prophylactic treatment of manic and mixed states, bipolar depression, and rapid cycling.

2.2. What is bipolar disorder?

Bipolar disorder was previously referred to as manic depressive disorder or manic depression. It’s a serious mental illness, one that can lead to risky behavior, damaged relationships and careers, and even suicidal tendencies if not treated. Bipolar disorder is characterized by extreme changes in mood (poles) - from mania to depression. Between these mood swings, a person with bipolar disorder may experience normal moods.
2.3. What causes bipolar disorder?

While the exact cause of bipolar disorder is not entirely known, genetic, neurochemical and environmental factors probably interact at many levels to play a role in the onset and progression of bipolar disorder. There is a great deal of scientific evidence that indicates bipolar disorder is due to a chemical imbalance in the brain, or a malfunction of the neurotransmitter glutamate in the brain. Excessive amounts of glutamate in the space between neurons causes mania, and too little, depression.

2.4. How many people are affected by bipolar disorder?

World Wide: 222 million, according to AstraZeneca’s bipolar statistics: “Between 3 and 4% of the world’s adult population is affected by bipolar disorder. That is 222 million adults worldwide.”

The United States: 6 million, according to the latest National Institute of Mental Health, “Bipolar disorder affects approximately 5.7 million adult Americans, or about 2.6% of the U.S. population age 18 and older every year.”

China and India: 15 and 12 million respectively, when using 1.2% of the population as the prevalence rate for extrapolation.

Bipolar disorder statistics from the World Health Organization (WHO), indicate that bipolar disorder is the 6th leading cause of disability in the world.

2.5. How does lithium work on bipolar disorder?

Studies indicate that lithium keeps the quantity of the neuro-transmitter glutamate stable and at optimal levels. Dr. Lowell Hokin, a University of Wisconsin professor of pharmacology, theorized that lithium works to control bipolar because of its stabilizing effect on glutamate receptors, exerting a dual effect on receptors for the neurotransmitter glutamate, acting to keep the amount of glutamate active between cells at a stable, healthy level, neither too much nor too little.
2.6. How effective is lithium therapy?

Despite the potential difficulties with lithium treatment, lithium remains the best medication for treating bipolar disorder and for stabilizing mood in most people. Even after 43 years since it was approved by the FDA, lithium is still the gold standard and first choice for treatment of bipolar disorder and mood stabilization.

Lithium is successful in improving both the manic and depressive symptoms in up to as many as 70 to 80% of patients. It is still considered the drug of choice for reduction of suicide risk in bipolar patients. Lithium therapy can lead to fewer, less severe, and shorter manic or hypomanic episodes. Many people find lithium an effective medicine that helps to control their mood disorder and greatly improve their quality of life.

2.7. How often is lithium taken?

Lithium carbonate (Li₂CO₃) is the most commonly used pharmaceutical form of lithium. It is formulated in tablet form and administrated orally.

Lithium tablets are normally taken as a single dose at night as this is more convenient and reduces the problems with some of the side effects. Lithium is usually taken for one to two years to derive full benefit from its use. Many people need to stay on it long-term to prevent the illness from relapsing.

When initiating lithium therapy, dosage must be individualized according to serum levels and clinical responses.

For Acute Mania: Optimal patient response can usually be established and maintained with 1,800 mg per day. Such doses will normally produce the desired serum lithium level ranging between 1.0 and 1.5 mM.

For Long-Term Control: The desirable serum lithium levels are 0.6 to 1.2 mM. Dosage will vary from one individual to another, but usually 900 mg to 1,200 mg per day will maintain this level. Serum lithium levels in uncomplicated cases receiving maintenance therapy during remission should be monitored at least every two months.

2.8. What are the side effects of lithium therapy?

- dry mouth
- a metallic taste
- slight tremor
- a feeling of mild weakness
- loose bowel movements (diarrhea)
These usually settle as the patient’s body adapts to the medication. However, lithium, when existing in excessive amounts in the blood, can be dangerously toxic. Excess lithium can slow or stop breathing, cause seizures, coma and even death. This is because lithium has a very narrow therapeutic window and its effective dose is uncomfortably close to its toxic dose. To avoid lithium toxicity, patients must have their blood levels monitored regularly to assure that they remain within an acceptable therapeutic range. Blood lithium levels need to be monitored more frequently during the early stages of treatment. As the treatment stabilizes, monitoring can occur every two to three months.

2.9. Why and when are lithium blood levels tested?

Lithium has a narrow therapeutic range (0.4-1.4 mM), and too low of a dosage leads to ineffectiveness and too high leads to severe toxicity. Therefore regular monitoring of the patient’s clinical state and serum lithium levels is required to:

1. Identify and/or prevent potential toxicity associated with high levels
2. Assure ongoing efficacy and effectiveness
3. Monitor the patient’s adherence to the prescribed regimen

The lithium test may be ordered frequently (every few days) when a patient first begins taking lithium or if a patient is returning to its use after an absence. This is done to help adjust the dose to the desired blood level. The test may be ordered at regular intervals or as needed to monitor blood concentrations. One or more lithium tests may be ordered if a patient starts taking additional medications (to judge their effect, if any, on lithium levels) and may be ordered if the doctor suspects toxicity.

Once stable blood concentrations in the therapeutic range have been achieved, lithium may then be monitored at regular intervals to ensure that it remains in this range.

The test may also be ordered when a patient’s condition does not appear to be responding to initial lithium dosage levels in order to determine whether concentrations are too low, the medication is ineffective, and/or to determine if the patient is complying with therapy (taking the lithium regularly). It may also be ordered when a patient experiences a troublesome level of side effects and/or exhibits symptoms that the doctor suspects may be due to toxicity.

Patients should talk to their doctor about the timing of the sample collection. Lithium blood levels are generally performed 12-18 hours after the last dose. Since dosage timing varies and some formulations are time released, collection specifics may vary.
Methods used for lithium testing in clinical laboratories are continuously evolving. Before 1987, lithium was measured by flame atomic emission spectrometry (FAES) in about 90% of laboratories and by flame atomic absorption spectrometry (FAAS) in the rest. In 1987, the first generation Ion-Selective Electrode (ISE) technique based lithium analyzer (NOVA Biomedical, Co. Waltham, MA) was introduced, and within 2 years, (by 1989), the ISE lithium test reached approximately 20% of the total clinical lithium testing, owing to its cost advantages and ease of use in comparison to the FAES method. In 2001, a colorimetric assay was developed by Trace American Inc. (now Thermo Fisher) utilizing a reaction between lithium and a porphyrin dye. This dye based lithium assay immediately became popular in clinical laboratories as it can be used in general chemistry analyzers and does not require a specially dedicated instrument, even though it is a relatively expensive test. In 2008, a new colorimetric, liquid stable enzymatic lithium test was introduced by Diazyme Laboratories. The enzymatic lithium test utilizes a recombinant enzyme that is highly sensitive to the inhibitory effect of lithium. This novel lithium test offers several key advantages over older lithium test methods especially in assay accuracy, reagent and calibration curve stability, user friendliness, and cost effectiveness. The enzymatic lithium assay is expected to become the first of choice for clinical laboratories around the world. A brief introduction of lithium test methods is depicted on the next page.
3.1. Flame Atomic Emission Spectrometry (FAES) Method

Flame atomic emission spectrometry (FAES) uses quantitative measurement of the optical emission from excited atoms to determine analyte concentration. Analyte atoms in solution are aspirated into the excitation region where they are desolvated, vaporized, and atomized by a flame, discharge, or plasma as shown in the scheme to the right. This method is not automated, and often requires sample preparations, and is a costly method.

3.2. Ion-Selective Electrode (ISE) Method

Ion-Selective-Electrode (ISE) methods utilize techniques which involve crown ethers having a core which accommodate the Li+ ion. While early ISE techniques were prone to interferences caused by sodium and other ions present in the test sample, more recent ISE analyzers are capable of accurate and precise lithium measurement. Although ISE analyzers are less expensive and easier to operate than flame photometer equipment, the electrode probe maintenance is costly, and requires dedicated instrumentation and trained personnel.
3.3. *Porphyrin Dye Spectrometry Method*

The porphyrin dye based lithium assay employs the dye porphyrin which reacts with Li in an alkaline condition to form a noncovalent binary complex, resulting in a change in absorbance at 510 nm, which is in direct proportion to Li concentration in the sample. This method is fully automated and can be used on most chemistry analyzers. However, there are some limitations for this method.

These include:

- *Highly sensitive to light*
- *Extremely high pH (pH >12) of the reagent*
- *Short on-board reagent stability and calibration curve stability*
- *Requires sample preparation (dilution)*
- *Reagent is corrosive to instruments and hazardous to ship*
- *Absorbs atmospheric carbon dioxide (CO₂), resulting in poor precision.*
- *High cost per test*

3.4. *Liquid Stable Enzymatic Method*

The Diazyme Enzymatic Lithium Assay is based on a lithium sensitive enzyme whose activity is lithium concentration dependent. The enzyme, a phosphatase, converts its substrate adenosine biphosphate (PAP) to hypoxanthine through a coupled enzymatic reaction to generate hydrogen peroxide (H₂O₂), which is quantified by the conventional Trinder reaction. The lithium concentration in the sample is inversely proportional to the enzyme activity or the amount of H₂O₂ produced in the reaction.
The Diazyme Liquid Stable Enzymatic method offers significant advantages over current existing lithium testing methods including flame atomic emission spectrometry (FAES) method, Ion-Selective-Electrode (ISE) method and the porphyrin dye method in the following aspects:

- Highly lithium specific and less interference
- Traceable to NIST standard
- On-board reagent stability is 4 weeks, and calibration curve stability is 2 weeks
- No sample preparation (dilution) required
- Less sensitive to light
- Neutral pH, not corrosive to instruments, and not hazardous to ship
- Not affected by atmospheric CO₂
- More cost effective
- Fully automated for all chemistry analyzers

**Product Features**

Compared to existing methods, the new Diazyme Liquid Stable Enzymatic Lithium Assay provides improved reagent stability and a dramatically reduced cost per test. The assay features excellent accuracy and precision and offers an extended reportable range of 0.19 - 3.0 mmol/L lithium, which will reduce the need for retesting elevated patient samples. The method also demonstrates insignificant bias from endogenous ions and other interfering substances including hemoglobin, bilirubin, triglycerides and ascorbic acid. The assay can be used on most common clinical chemistry analyzers, and application parameters are available from Diazyme.
**Assay Principle**

The Diazyme Liquid Stable Enzymatic Lithium Assay is based on a lithium sensitive enzyme whose activity is lithium concentration dependent. The enzyme, a phosphatase, converts its substrate adenosine biphosphate (PAP) to hypoxanthine through a coupled enzymatic reaction to generate uric acid and hydrogen peroxide ($\text{H}_2\text{O}_2$). The $\text{H}_2\text{O}_2$ generated is then quantified by a Trinder reaction.

**Assay Procedure**

The Diazyme Liquid Stable Enzymatic Lithium Assay consists of two liquid stable reagents, R1, and R2, and the assay is performed in a kinetic mode using 5 µl of serum sample and a three point calibration curve. The reaction is monitored at 550 nm and completed within 10 minutes.

**Performance Data**

Diazyme’s Liquid Stable Enzymatic Lithium Assay precision was evaluated according to NCCLS EP5-A guidelines. In the study, two specimens containing 1.0 mmol/L and 2.5 mmol/L lithium were tested with 2 runs per day with duplicates over 10 working days. The results of the precision study are summarized in the next table.

<table>
<thead>
<tr>
<th>Within Run Precision</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.0 mM Li+ (10 days, n=4)</td>
</tr>
<tr>
<td><strong>Mean</strong></td>
<td>0.97 mM</td>
</tr>
<tr>
<td><strong>CV%</strong></td>
<td>4.3%</td>
</tr>
</tbody>
</table>
Accuracy

Comparison to ISE

To demonstrate accuracy, the Diazyme Liquid Stable Enzymatic Lithium Assay was tested with individual serum samples with comparison to a currently marketed and FDA cleared method. The Diazyme Liquid Stable Enzymatic Lithium Assay and lithium values obtained by ISE were compared. A total of forty seven (47) serum samples and one serum sample spiked with fifteen (15) concentrations of lithium acetate were tested in duplicate. Lithium concentrations obtained with the Diazyme Liquid Stable Enzymatic Lithium Assay are plotted against that obtained with the ISE value.

As shown in the figure to the left, the 62 samples range from 0.1 to 3.1 mM lithium, the slope is 1.0344 and the correlation coefficient between the two methods is 0.9916.

Linearity

Two levels of linearity sets were prepared by diluting a specimen containing 3.1 mmol/L lithium with saline according to Clinical and Laboratory Standards Institute (formerly NCCLS) EP6-A.

The assay has a linear range at least from 0.19 - 3.0 mmol/L lithium.
**Interference**

To determine the level of interference from the substances normally present in the serum, Diazyme’s Liquid Stable Enzymatic Lithium Assay was tested with 1.0 mmol/L and 2.5 mmol/L lithium serum samples spiked with various concentrations of substances following Clinical and Laboratory Standards Institute (formerly NCCLS) EP7-A “Interference Testing in Clinical Chemistry”: Dose-Response Guidelines.

**Result:** The following substances normally present in the serum produced less than 10% deviation when tested at levels equal to the concentrations above.

To determine the level of interference from other cations and substances normally present in the serum, Diazyme’s Liquid Stable Enzymatic Lithium Assay was tested with 1.0 mmol/L and 2.5 mmol/L lithium serum samples spiked with various concentrations of different cations. The following cations and substances normally present in the serum produced less than 10% deviation when tested at levels equal to the concentrations listed on the left.

<table>
<thead>
<tr>
<th>Interference</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascorbic Acid</td>
<td>5 mmol/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>45 mg / dL</td>
</tr>
<tr>
<td>Bilirubin Conjugate</td>
<td>20 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>500 mg / dL</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1000 mg / dL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Interference</th>
<th>Concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH4⁺</td>
<td>1.0 mmol/L</td>
</tr>
<tr>
<td>P_i</td>
<td>3.0 mmol/L</td>
</tr>
<tr>
<td>Ca²⁺</td>
<td>4 mmol/L</td>
</tr>
<tr>
<td>Na⁺</td>
<td>200 mmol/L</td>
</tr>
<tr>
<td>K⁺</td>
<td>20 mmol/L</td>
</tr>
<tr>
<td>Cu²⁺</td>
<td>0.5 mmol/L</td>
</tr>
<tr>
<td>Fe³⁺</td>
<td>0.5 mmol/L</td>
</tr>
<tr>
<td>Zn²⁺</td>
<td>0.5 mmol/L</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>45 mg / dL</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>1000 mg/dL</td>
</tr>
<tr>
<td>Ascorbic Acid</td>
<td>5 mg/dL</td>
</tr>
</tbody>
</table>

*Lab testing for blood lithium using automated chemistry analyzers*
Stability

Stability studies were conducted with more than one lot of reagents and control recovery was evaluated for each study. The acceptance criterion for control value recovery is indicated in each section.

Reagent stability

Reagent On-Board Stability on Hitachi 917

One lot of Diazyme’s Liquid Stable Enzymatic Lithium Assay reagent was tested on a Roche Hitachi 917 for its on-board stability. The reagent was stored in the Roche Hitachi 917 reagent bottle in the reagent chamber. In this study, two levels of controls containing 1.08 mmol/L, and 2.03 mmol/L were tested daily and after each calibration. Based on the test results, the reagent on-board stability on the Hitachi 917 instrument is a minimum of 4 weeks.

Reagent Calibration Frequency

The calibration stability was performed on a Roche Hitachi 917 using the appropriate parameters including reagent and calibrators, and two levels of serum controls containing approximately 1.1 mmol/L, and 2.2 mmol/L lithium. After running the calibration at day 0, two levels of controls and one serum sample were tested on the same day followed by another fourteen (14) days. Controls and sample recovered within 10% deviation from the expected values. Based on the test results, the reagent calibration curve stability on the Roche Hitachi 917 instrument is a minimum of 14 days.
5. Frequently Asked Questions Regarding Lithium Testing

1. Why use enzymatic lithium testing?
   The method is more accurate and more cost effective. It has longer on-board and calibration curve stability, and the reagent is not corrosive to instruments and the environment.

2. What are the advantages of the enzymatic lithium test over the Thermo Trace porphyrin dye based lithium test?
   The advantages include:
   - Highly specific and less interference
   - Longer on-board reagent stability (4 weeks*) and longer calibration curve stability (2 weeks)
   - Results traceable to NIST standard SRM 956c
   - No sample preparation (dilution) needed
   - Less sensitive to light
   - Neutral pH, not corrosive to instrument and environment
   - Not affected by atmospheric CO₂
   - Much more cost effective
   - Fully automated for all chemistry analyzers

3. What is the dynamic range of the enzymatic lithium test?
   The measurable range is 0.19 - 3.0 mmole/L

4. What is the calibration frequency for the enzymatic lithium test?
   Minimum of 2 weeks on Hitachi 917

5. What is the on-board stability of the enzymatic lithium test?
   One month*

6. What is the shelf life of the enzymatic lithium reagent?
   15 months

7. What is the test precision of the enzymatic lithium test?
   Total CV’s = 1.3% for 2.5 mM lithium
   Within-Run CV’s = 4.8% for 1.0 mM

8. Is the enzymatic lithium test traceable to NIST standard?
   Yes, it is traceable to SRM 956c

9. Is the enzymatic lithium reagent light sensitive?
   Not extremely sensitive

* Analyzer Dependent
10. Does the enzymatic lithium reagent absorb atmospheric CO$_2$?
   Not detectable

11. Is the enzymatic lithium reagent harmful to instruments and hazardous to ship?
   No, it is not corrosive, the reagent pH is close to neutral.

12. Does the enzymatic lithium test require sample dilution?
   No

13. Do other ions in the sample interfere with the enzymatic lithium assay?
   No

14. Is the enzymatic lithium test more cost effective?
   Yes

15. What sample types are used for the enzymatic lithium test?
   Human serum only

16. What parameters are available for various chemistry analyzers?
   Lithium application parameters are available for most general chemistry analyzers including but not limited to Roche Hitachi 717, 911, 917, Modular P, Beckman AU400, Beckman Synchron CX4/7, and LX 20.

17. What wavelength is used for the enzymatic lithium test?
   540-560 nm

18. What type of reaction mode is used for the enzymatic lithium test?
   Kinetic

19. How many calibration points are used?
   3 points

20. How should the enzymatic lithium reagent be stored?
   2-8°C

21. Do you have a quick comparison table for the enzymatic method versus porphyrin dye method?
   Yes, see the table on the next page.

22. Who should I contact if there is a technical problem in running the enzymatic lithium test?
   Diazyme Technical Support at 858-455-4768 or (888) DIAZYME
### Lithium Assay

<table>
<thead>
<tr>
<th>Method</th>
<th>Enzymatic - A lithium sensitive phosphatase catalyzes the conversion of adenosine biphosphate (PAP) to hypoxanthine and hydrogen peroxide which is then quantified by a Trinder reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Traceability</td>
<td>Lithium calibrator and control are traceable to NIST standard and an ISE method</td>
</tr>
</tbody>
</table>
| Method Correlation to Predicate | $R^2 = 0.99$ regression  
$y = 1.03x - 0.04$ |
| Precision | The Within-Run CVs  
4.3% at 1.0 mmol/L, 1.2% at 2.5 mmol/L  
The total CVs  
4.8% at 1.0 mmol/L, 1.3% at 2.5 mmol/L |
| On-Board Stability* | 4 weeks |
| Calibration Interval* | 2 weeks |
| Calibrator | Liquid stable calibrator set, no serial dilutions are required |
| Sample Type | Serum |
| Sample Volume | 5 µL |
| Assay Range | 0.19 - 3.0 mmol/L |
| Instrument Specific Packaging | Universal kit packaging  
**Beckman** - *Synchron AU*; **Roche** - *Hitachi* |
| Regulatory Status | 510 (k) Cleared, CE, Health Canada |

* Instrument dependent
6. References


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<thead>
<tr>
<th>Company</th>
<th>Address</th>
<th>Web Address</th>
<th>Contact Information</th>
</tr>
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<tbody>
<tr>
<td>Diazyme Europe GmbH</td>
<td>Zum Windkanal 21, 01109 Dresden, Deutschland</td>
<td><a href="http://www.diazyme.com">www.diazyme.com</a></td>
<td>Tel: +49 (0) 351 886 3300 Fax: +49 (0) 351 886 3366 <a href="mailto:sales@diazyme.com">sales@diazyme.com</a></td>
</tr>
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<td></td>
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<td></td>
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</tr>
<tr>
<td>12889 Gregg Court</td>
<td>12889 Gregg Court, Poway, CA 92064</td>
<td><a href="http://www.diazyme.com">www.diazyme.com</a></td>
<td>Tel: 858-455-4768</td>
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<td></td>
<td></td>
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<td>Fax: 858-455-3701</td>
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<td></td>
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<td><a href="mailto:sales@diazyme.com">sales@diazyme.com</a></td>
</tr>
<tr>
<td>Shanghai Diazyme Co., Ltd.</td>
<td>Room 201, 1011 Halei Road, Zhangjiang Hi-tech Park Shanghai, 201203 People's Republic of China</td>
<td><a href="http://www.lanyuanbio.com">www.lanyuanbio.com</a></td>
<td>Tel: 086-21-51320668 Fax: 086-21-51320663 <a href="mailto:service@lanyuanbio.com">service@lanyuanbio.com</a></td>
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