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The symbols glossary is provided electronically and can be found in the Dialog section at www.diasorin.com using the part and lot numbers associated with the corresponding IVD product.

LIAISON® XL murex HBc IgM ([REF] 318140)

1. INTENDED USE

The LIAISON® XL murex HBc IgM assay is an *in vitro* chemiluminescent immunoassay (CLIA) for the qualitative detection of IgM antibodies to hepatitis B virus core antigen (HBc IgM) in human adult and pediatric (2 to 21 years) serum and plasma (lithium and sodium heparin, sodium citrate and K_2 EDTA), including separator tubes, on the LIAISON® XL Analyzer. Assay results, in conjunction with other hepatitis B virus (HBV) serological markers and clinical information may be used as an aid in the diagnosis of HBV infection in patients with symptoms of hepatitis or who may be at risk for HBV infection. The presence of anti-HBc IgM is indicative of acute or recent HBV infection.

This assay is not approved for use in screening blood, plasma or tissue donors.

Caution: U.S. Federal Law restricts this device to sale by or on the order of a licensed practitioner

2. SUMMARY

Hepatitis B is a liver infection caused by the hepatitis B virus (HBV). HBV is an enveloped deoxyribose nucleic acid (DNA) virus.

The complete hepatitis B virus, also called the Dane particle, is composed of an outer surface or envelope that carries the hepatitis B surface antigen (HBsAg). The envelope surrounds an inner core that contains the hepatitis B core antigen (HBcAg). Inside the core is the HBV deoxyribonucleic acid (DNA) genome. Another antigen, the hepatitis B e antigen (HBeAg), is a viral core protein found in the bloodstream during active replication of HBV. Following an infection with the HBV, this antigen can be recognized by the infected person's immune system, which will produce antibodies targeting this antigen. The detection of these antibodies against these antigens, form the basis of some serological tests used for diagnosis.

HBV is spread when an uninfected person comes into contact with infected blood or body fluids. Most infections occur via contact with infected blood, but semen, saliva and cervical secretions can also be infectious and Mother-to-Child Transmission (MTCT) of HBV remains an important source of incident cases of HBV. The virus can live on surfaces for at least seven days which means it can also be transmitted via objects that have been contaminated with infected body fluids (e.g. used needles) (1).

HBV is a non-cytopathic virus that causes liver damage through immunopathogenesis (2). Common symptoms of HBV infection include malaise, fever, gastroenteritis and jaundice. However, some patients may have chronic HBV infection and be asymptomatic. Most infected adults (>90%) will completely recover from an HBV infection, only experiencing a mild, asymptomatic acute illness. In contrast, ~90% of infants and young children will develop a more severe chronic infection (2; 3). Chronic HBV infection is characterized by the persistence of HBsAg (Hepatitis B surface Antigen) for at least six months and can lead to serious complications such as cirrhosis, hepatocellular carcinoma and liver related mortality. HBV is endemic throughout the world, despite the availability of an efficient vaccine (4, 5, 6).

Diagnosis of HBV infection is achieved through blood or serum detection of viral nucleic acid or serological markers (i.e. proteins produced by the virus or antibodies produced by the host that target viral proteins). Serological tests are commonly used to detect HBV infection status and are the first testing strategy to screen for HBV exposure. Common HBV serological markers include HBsAg, antibody to HBsAg (anti-HBs), total antibody to HBcAg (total anti-HBc), immunoglobulin M (IgM) antibody to HBcAg (IgM anti-HBc), HBeAg and antibody to HBeAg (anti-HBe). The detection of these serological markers allows identification of past or ongoing HBV infection, assessment of the clinical phases of the disease, monitoring of antiviral therapy and determination of the immune status of the patient (7-11).

IgM isotype antibodies directed to HBcAg typically develop during an acute HBV infection and may decline to undetectable levels within 6 months. In contrast, the IgG isotype of anti-HBc typically persists indefinitely and may be the only detectable serological marker following acute HBV infection (12). However, the IgM isotype can be detected by very sensitive assays during chronic HBV infection (13). In patients who develop chronic hepatitis B, IgM anti-HBc can persist at low levels during viral replication and can result in positive tests for IgM anti-HBc (14).This assay can be used as an aid in the diagnosis of acute HBV infection in patients with symptoms of hepatitis or who may be at risk for HBV infection, and is particularly useful if the infected individual has an undetectable anti-HBs response (an antibody response directed against the virus surface antigen, HBsAg) as an IgM HBc response may be the only detectable response.

3. PRINCIPLE OF THE PROCEDURE

The method for qualitative determination of IgM antibodies to HBV core antigen is an antibody capture chemiluminescence immunoassay (CLIA). IgG to human IgM (mouse monoclonal) is used for coating magnetic particles (solid phase) and recombinant HBcAg is linked to an isoluminol derivative (isoluminol-HBcAg conjugate). During the first incubation, IgM antibodies present in calibrators, samples or controls bind to the solid phase. During the second incubation, the HBcAg conjugate reacts with IgM anti-HBc already bound to the solid phase. After each incubation, the unbound material is

removed with a wash cycle. Subsequently, the starter reagents are added and a flash chemiluminescence reaction is thus induced. The light signal, and hence the amount of isoluminol-HBcAg conjugate, is measured by a photomultiplier as relative light units (RLU) and is indicative of IgM anti-HBc concentration present in calibrators, samples or controls.

4. MATERIALS PROVIDED

Reagent integral

Magnetic particles (1.3 mL)	**[SORB]**	Magnetic particles coated with IgG to human IgM (mouse monoclonal), BSA, phosphate buffer, < 0.1% sodium azide.
Calibrator 1 (3.6 mL)	**[CAL|1]**	Low levels of chimeric IgM anti-HBc antibodies (human and mouse monoclonal), animal proteins, buffer, 0.2% ProClin® 300, preservatives, an inert red dye.
Calibrator 2 (3.6 mL)	**[CAL|2]**	High levels of chimeric IgM anti-HBc antibodies (human and mouse monoclonal), animal proteins, buffer, 0.2% ProClin® 300, preservatives, an inert blue dye.
Conjugate (1.3 mL)	**[CONJ]**	HBcAg (obtained in *E.coli* by the recombinant DNA technology) conjugated to an isoluminol derivative, BSA, phosphate buffer, 0.2% ProClin® 300, preservatives.
Specimen diluent (15.5 mL)	**[DIL|SPE]**	Non-specific human IgG (polyclonal), BSA, phosphate buffer, EDTA, 0.2% ProClin® 300, preservatives, an inert blue dye.
Buffer E (12 mL)	**[BUF|E]**	Human serum, BSA, phosphate buffer, 0.2% ProClin® 300, preservatives.
Number of tests		50

ProClin® is a trademark of the Dow Chemical Company (Dow) or an affiliated company of Dow.

All reagents are supplied ready to use. The order of reagents reflects the layout of containers in the reagent integral.

Materials required but not provided

LIAISON® XL Analyzer
LIAISON® XL Cuvettes ([REF] X0016).
LIAISON® XL Disposable Tips ([REF] X0015).
LIAISON® XL Starter Kit ([REF] 319200).
LIAISON® Wash/System Liquid ([REF] 319100).
LIAISON® XL Waste Bags ([REF] X0025).

Additionally required materials

LIAISON® XL MUREX Control HBc IgM ([REF] 318141).

5. WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use only.
- For Prescription Use Only.
- In the clinical study, the LIAISON XL MUREX HBc IgM assay yielded a higher rate of positive results, relative to the reference assay, among patients with chronic hepatitis. Therefore, a positive result should be interpreted with caution when other laboratory results and clinical information indicate chronic HBV infection. Refer to the Summary of Clinical Performance section for additional information.
- The human blood source material used to produce the components provided in this kit derives from donations found to be non-reactive for HBsAg, antibodies to HCV, HIV-1 and HIV-2 when tested by an FDA-approved method and found to be non-reactive for syphilis when tested by a serological test. Because no test method can offer complete assurance that laboratory specimens are pathogen-free, specimens should be handled at Biosafety Level 2, as recommended for any potentially infectious human serum or blood specimen in the CDCNIH manual, Biosafety in Microbiological and Biomedical Laboratories, 5th Edition, Feb. 2007, and CLSI Approved Guideline M29-A3, Protection of Laboratory Workers from Occupationally Acquired Infections.
- Observe the normal precautions required for handling all laboratory reagents.
- Disposal of all waste material should be in accordance with local guidelines.
- Do not eat, drink, smoke or apply cosmetics in the assay laboratory.
- Do not pipette by mouth.
- Strict adherence to the instructions are necessary to obtain reliable results.
- Avoid direct contact with potentially infected material by wearing laboratory coats, protective goggles, and disposable gloves.
- Wash hands thoroughly at the end of each assay.
- Avoid splashing or forming an aerosol. All drops of biological reagent must be removed with a 10% sodium

- Hypochlorite solution (containing 0.5% active chlorine), and the means used must be treated as infected waste.
- All samples, biological reagents and disposable materials used in the assay must be considered as potentially able to transmit infectious agents. They should therefore be disposed of in accordance with the prevailing regulations and guidelines of the agencies holding jurisdiction over the laboratory and the regulations of each Country.
- Liquid waste must be decontaminated with sodium hypochlorite at a final concentration of 10% for at least half an hour.
- Any materials to be reused must be appropriately sterilized in compliance with the local laws and guidelines. A minimum of one hour at 121°C is usually considered adequate, though the users must check the effectiveness of their decontamination cycle by initially validating it and routinely using biological indicators.
- The LIAISON® Analyzer family should be cleaned and decontaminated on a routine basis. See the relevant Operator's Manual for the procedures.
- Do not use kits or components beyond the expiration date given on the label.
- Do not mix reagents from different reagents packs (even for the same reagent).
- Previously frozen samples should be thoroughly mixed after thawing and prior to testing.

Chemical Hazard and Safety Information

- Reagents in this kit are classified in accordance with the US OSHA Hazard Communication Standard; individual US State Right-to-Know laws; Canadian Centre for Occupational Health and Safety Controlled Products Regulations; and European Union EC Regulation 1272/2008 (CLP) (for additional information see Safety Data Sheet available on www.diasorin.com).
- Hazardous reagents are classified and labelled as follows:

Hazardous reagents are classified and labelled as follow:**REAGENTS:**	[CAL|1], [CAL|2], [CONJ], [BUF|E]	[DIL|SPE]
CLASSIFICATION:	Skin sens. 1 H317	Skin sens. 1 H317
SIGNAL WORD:	Warning	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H317 May cause an allergic skin reaction.	H317 May cause an allergic skin reaction.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P363 Wash contaminated clothing before reuse.	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P363 Wash contaminated clothing before reuse.
CONTAINS: (only substances prescribed pursuant to Article 18 of EC Regulation 1272/2008).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1) (ProClin® 300).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1) (ProClin® 300); Neomycin sulfate.

Reagents containing sodium azide

Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. On disposal, flush with a large volume of water to prevent azide build-up. For further information, refer to “Decontamination of Laboratory Sink Drains to Remove Azide Salts” in the Manual Guide-Safety Management No. CDC-22 issued by the Centers for Disease Control and Preventions, Atlanta, GA, 1976.

Pursuant to EC Regulation 1272/2008 (CLP), [SORB] is labeled as EUH210, safety data sheets available on request.

For additional information, see Safety Data Sheets available on www.diasorin.com.

6. PREPARATION OF REAGENT INTEGRAL

Please note the following important reagent handling precautions:

Resuspension of magnetic particles

Magnetic particles must be completely resuspended before the integral is placed on the instrument. Follow the steps below to ensure complete suspension:

- Before the seal is removed, rotate the small wheel at the magnetic particle compartment until the colour of the suspension has changed to brown.

- Gentle and careful side-to-side mixing may assist in the suspension of the magnetic particles (avoid foam formation).
- Visually check the bottom of the magnetic particle vial to confirm that all settled magnetic particles have been resuspended.
- Carefully wipe the surface of each septum to remove residual liquid.
- Repeat as necessary until the magnetic particles are completely resuspended.

Foaming of reagents

In order to ensure optimal performance of the integral, foaming of reagents should be avoided. Adhere to the recommendation below to prevent this occurrence:

- Visually inspect the reagents, calibrators in particular (position two and three following the magnetic particle vial), to ensure there is no foaming present before using the integral. If foam is present after resuspension of the magnetic particles, place the integral on the instrument and allow the foam to dissipate. The integral is ready to use once the foam has dissipated and the integral has remained onboard and mixing.

Loading of integral into the reagent area

– LIAISON® XL Analyzer is equipped with a built-in solid-state magnetic device which aids in the dispersal of microparticles prior to placement of a reagent integral into the reagent area of the analyzer. Refer to the analyzer operator's manual for details.
  a. Insert the reagent integral into the dedicated slot.
  b. Allow the reagent integral to remain in the solid-state magnetic device for at least 30 seconds (up to several minutes). Repeat as necessary.
– Place the integral into the reagent area of the analyzer with the label facing left and let it stand for 15 minutes before using. The analyzer automatically stirs and completely resuspends the magnetic particles.
– Follow the analyzer operator's manual to load the specimens and start the run.

7. STORAGE AND STABILITY OF REAGENT INTEGRAL

Upon receipt, the Reagent Integral must be stored in an upright position to facilitate resuspension of magnetic particles. See the Preparation of Reagent Integral section for resuspension instructions. When the Reagent Integral is stored sealed and kept upright, the reagents are stable at 2-8°C up to the expiration date. Do not freeze. The Reagent Integral should not be used past the expiration date indicated on the kit and Reagent Integral labels. After removing the seals, the Reagent Integral is stable for twelve (12) weeks when stored at 2-8°C in a refrigerator or on board the analyzer.

8. SPECIMEN COLLECTION AND PREPARATION

Either human serum, serum in serum-separating-tube (SST) or plasma may be used. The results obtained on the serum-plasma paired samples indicated that there is equivalence among serum (with and without gel SST), Lithium Heparin, Sodium Heparin, Sodium Citrate and K_2 EDTA.

Blood should be collected aseptically by venipuncture, allowed to clot (if applicable), and the serum or plasma separated from the red cells as soon as possible. Samples having particulate matter, turbidity, lipemia, or erythrocyte debris may require clarification by filtration or centrifugation before testing. Grossly hemolyzed or lipemic samples as well as samples containing particulate matter or exhibiting obvious microbial contamination should not be tested.

Check for and remove air bubbles and foam before assaying. A limited time of room temperature storage (between 18 and 30°C) for four days (4) does not influence the assay performance. If the assay is performed within seven (7) days of sample collection, the samples may be kept at 2-8°C; otherwise they should be aliquoted and stored deep-frozen (-20°C or below). If samples are stored frozen, mix thawed samples well before testing. Samples are stable through six (6) freeze/thaw cycles. Self-defrosting freezers are not recommended for sample storage.

It is responsibility of the individual laboratory to use all available references and/or its own studies to determinate specific stability criteria for its laboratory.

The minimum specimen volume required for a single determination is 170 µL (20 µL specimen + 150 µL dead volume). Dead volume is the volume left at the bottom of the aliquot tube, which the instrument cannot aspirate.

For shipping, use sterile containers and pack specimens in compliance with government regulations covering the transportation of etiologic agents. Ensure that specimens reach their destination within the following specifications:

- Plasma and Serum separated from the clot can be maintained at 2-8°C during transit. Do not exceed the maximum 2-8°C stability of seven (7) days.
- Plasma and Serum separated from the clot can be stored at -20°C or below and shipped with dry ice. Temperature level during entire shipment should be no greater (warmer) than -20°C.

9. ASSAY PROCEDURE

Strict adherence to the analyzer operator’s manual ensures proper assay performance.

Each test parameter is identified via information encoded in the reagent integral Radio Frequency Identification transponder (RFID Tag). In the event that the RFID Tag cannot be read by the analyzer, the integral cannot be used. Do not discard the reagent integral; contact your local DiaSorin technical support for instruction.

The analyzer operations are as follows:

1. Dispense calibrators, controls or specimens into the reaction cuvette.
2. Dispense specimen diluent into the reaction module (except for calibrators).
3. Dispense coated magnetic particles into the reaction cuvette
4. Incubate.
5. Wash with Wash/System liquid.
6. Dispense conjugate into the reaction cuvette
7. Dispense Buffer E into the reaction cuvette.

8. Incubate.
9. Wash with Wash/System liquid.
10. Add the Starter Kit and measure the light emitted

10. CALIBRATION

Test of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the assigned master curve. Each calibration solution allows four (4) calibrations to be performed.

Recalibration in triplicate is mandatory whenever at least one of the following conditions occurs:

– A new lot of reagent integral or of Starter Kit is used.
– The previous calibration was performed more than eight (8) weeks before.
– The analyzer has been serviced.
– Control values lie outside the expected ranges.

Calibrator values are stored in the Radio Frequency Identification transponder (RFID Tag).

11. QUALITY CONTROL

Quality control must be performed once per day of use or in accordance with local, state, and/or federal regulations or accreditation requirements and your laboratory's quality control procedures. It is recommended that the user refer to CLSI document, C24-A3, and 42 CFR 493.1256(c) for guidance on appropriate quality control practices. LIAISON® controls should be run in singlicate to monitor the assay performance. If control values lie within the expected ranges provided on the control vial labels, the test is valid. If control values lie outside the expected ranges, the test is invalid and patient results cannot be reported. Assay calibration should be performed if a control failure is observed and controls and patient specimens must be retested.

12. LIMITATIONS OF THE PROCEDURE

A skillful technique and strict adherence to the instructions are necessary to obtain reliable results.

Bacterial contamination or heat inactivation of the specimens may affect the test results.

Do not heat-inactivate sera.

This assay is not designed to test body fluids other than human serum or plasma.

Test results are reported qualitatively as Reactive or Non-reactive for the presence of IgM antibodies to HBV core antigen. However, diagnosis of Hepatitis B should not be established on the basis of a single test result, but should be determined in conjunction with clinical findings and other diagnostic procedures as well as in association with medical judgement.

13. INTERPRETATION OF RESULTS

The analyzer automatically calculates HBc IgM levels expressed as index value and grades the results.

For details, refer to the analyzer operator's manual.

The interpretation of results for the LIAISON® XL MUREX HBc IgM is as follows:

- Cut-off of a 0.800 index value determines whether a sample has detectable levels of HBc IgM.
- **Reactive:** Samples with HBc IgM levels equal to or above an index value of 0.900 are considered Reactive and presumed positive for HBc IgM.
- **Non-Reactive:** Samples with HBc IgM levels below an index value of 0.700 are considered Non-reactive and presumed negative for HBc IgM.
- Samples with HBc IgM levels ranging between an index value of 0.700 and 0.900 are considered initially equivocal. Initially equivocal samples must be retested in duplicate. Samples that are repeatedly equal to or above 0.800 (i.e. at least 2 out of 3 results) are considered Reactive and presumed positive for HBc IgM. Samples that are repeatedly below 0.800 (i.e. at least 2 out of 3 results) are considered Non-reactive and presumed negative for HBc IgM.

The result should be used in conjunction with the patient's medical history, clinical examination and other hepatitis B serological markers to determine disease state.

14. SPECIFIC PERFORMANCE CHARACTERISTICS

14.1 Summary of clinical performance

The LIAISON® XL MUREX HBc IgM clinical study population consisted of a total of 3082 specimens of whom 2826 were collected prospectively from individuals at increased risk of HBV infection due to lifestyle, behavior, occupation, disease state or known exposure event, or from individuals with signs and symptoms of a hepatitis infection (asymptomatic and symptomatic). A demographic summary of the overall risk specimen population by gender and race is provided in the following tables:

Demographics of Clinical Study Samples by Gender

	Adult				Pediatric (2-21)				Unknown Age			
	Prospective		Retrospective		Prospective		Retrospective		Prospective		Retrospective	
Gender	**n**	**%**	**N**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	1643	61.7%	54	26.2%	98	60.9%	2	6.5%	1	50.0%	0	0.0%
Male	1017	38.2%	151	73.3%	61	37.9%	29	93.5%	1	50.0%	0	0.0%
Unknown	3	0.1%	1	0.5%	2	1.2%	0	0.0%	0	0.0%	21	100.0%
Total	**2663**	**100.0%**	**206**	**100.0%**	**161**	**100.0%**	**31**	**100.0%**	**2**	**100.0%**	**21**	**100.0%**

Demographics of Clinical Study Samples by Race

	Adult				Pediatric (2-21)				Unknown Age			
	Prospective		Retrospective		Prospective		Retrospective		Prospective		Retrospective	
Race	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
American Indian/ Alaskan Native	2	0.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Asian	21	0.8%	4	1.9%	3	1.9%	0	0.0%	0	0.0%	0	0.0%
Black/African American	832	31.2%	57	27.7%	64	39.8%	4	13.8%	0	0.0%	0	0.0%
Native Hawaiian or Other Pacific Islander	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
White	1664	62.5%	141	68.4%	89	55.3%	27	87.1%	2	100.0%	21	100.0%
Unknown	6	0.2%	1	0.5%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Other	138	5.2%	3	1.5%	5	3.1%	0	0.0%	0	0.0%	0	0.0%
Total	**2663**	**100.0%**	**206**	**100.0%**	**161**	**100.0%**	**31**	**100.0%**	**2**	**100.0%**	**21**	**100.0%**

HBV serological classification for prospective and retrospective specimens is presented in next table. Classification was based on test results of the FDA approved hepatitis-B assays to determine the disease state for serological characterization. The following HBV markers were evaluated: HBsAg (and HBsAg Confirmatory test), Anti-HBs, Anti-HBc IgM, Anti-HBc, Anti-HBe and HBeAg.

Serological Classification by FDA-Approved HBV Panel

HBV Classification	HBsAg	HBeAg	Anti-HBc	Anti-HBc IgM	Anti-HBe	Anti-HBs	Prospective (n)	Retrospective (n)
Acute	R	NR	NR	NR	NR	NR	12	97
Acute	R	R	NR	NR	NR	NR		
Acute	R	R	R	R	NR	NR		
Acute	R	R	R	R	R	NR		
Acute	R	R	R	R	EQV	NR		
Acute	R	NR	R	EQV	R	NR		
Acute	R	NR	R	R	EQV	NR		
Acute	R	EQV	R	R	R	NR		
Acute	R	NR	R	R	NR	NR		
Acute	R	R	R	EQV	NR	NR		
Acute	R	R	R	R	NR	R		
Acute	R	R	R	R	EQV	R		
Acute	R	R	R	R	R	EQV		
Late Acute	R	NR	R	R	R	NR	2	32
Late Acute	R	NR	R	R	R	R		
Chronic	R	NR	NR	NR	R	NR	76	68
Chronic	R	NR	R	NR	NR	R		
Chronic	R	R	R	NR	NR	R		
Chronic	R	R	R	NR	NR	NR		
Chronic	R	EQV	R	NR	NR	NR		
Chronic	R	NR	R	NR	R	NR		
Chronic	R	NR	R	NR	NR	NR		
Chronic	R	NR	R	NR	R	R		
Chronic	R	EQV	R	NR	NR	NR		
Early Recovery	NR	NR	R	R	R	NR	48	9
Early Recovery	NR	NR	R	EQV	R	R		
Early Recovery	NR	NR	R	R	NR	NR		
Early Recovery	NR	NR	R	NR	R	NR		
Early Recovery	NR	NR	R	NR	NR	NR		
Early Recovery	NR	NR	R	R	NR	R		
Early Recovery	NR	NR	R	R	R	R		

HBV Classification	HBsAg	HBeAg	Anti-HBc	Anti-HBc IgM	Anti-HBe	Anti-HBs	Prospective (n)	Retrospective (n)
Recovery	NR	NR	R	NR	R	R	131	36
Recovery	NR	NR	NR	NR	R	R		
Recovery	NR	NR	R	NR	EQV	R		
Immune Due to Natural Infection	NR	NR	R	NR	NR	R	104	3
Immune Due to Natural Infection	NR	NR	R	NR	NR	EQV		
HBV Vaccine Response	NR	NR	NR	NR	NR	R	1144	8
HBV Vaccine Response	NR	NR	NR	NR	NR	EQV		
Not Previously Infected	NR	NR	NR	NR	NR	NR	1302	1
Not Interpretable	NR	NR	NR	NR	R	NR	7	2
Not Interpretable	NR	NR	NR	R	NR	NR		
Not Interpretable	NR	R	NR	NR	NR	NR		
Not Interpretable	NR	R	NR	NR	NR	R		
Not Interpretable	NR	R	R	R	NR	EQV		
Not Interpretable	NR	R	R	R	NR	R		
Not Interpretable	R	NR	NR	NR	NR	R		
Total							2826	256

Based on the HBV classifications, the LIAISON® XL MUREX HBC IgM results for the 2826 prospective and 256 retrospective specimens were compared to a reference HBc IgM assay. The following tables show this comparison and percent agreement with 95% exact confidence intervals with the reference HBc IgM assay results.

Cumulative Clinical Agreement Adult and Pediatric (Combined Prospective & Retrospective)
LIAISON® XL MUREX HBc IgM vs Reference Assay by Characterization

LIAISON® XL MUREX HBc IgM vs Reference Assay by HBV Classification	Reference HBc IgM assay						Total
	Reactive		Eqv		Non-reactive		
	LIAISON® XL MUREX HBc IgM		LIAISON® XL MUREX HBc IgM		LIAISON® XL MUREX HBc IgM		
	Reactive	Non-reactive	Reactive	Non-reactive	Reactive	Non-reactive	
Acute	97	1	2	0	0	9	109
Late Acute	32	2	0	0	0	0	34
Chronic	0	0	0	0	21	123	144
Early Recovery	10	0	0	1	1	45	57
Recovery	0	0	0	0	7	160	167
Immune Due to Natural Infection	0	0	0	0	0	107	107
HBV Vaccine Response	0	0	0	0	2	1150	1152
Not Previously Infected	0	0	0	0	1	1302	1303
Not Interpretable	2	1	0	0	0	6	9
Total	**141**	**4**	**2**	**1**	**32**	**2902**	**3082**

Cumulative Clinical Agreement Adult and Pediatric (Combined Prospective & Retrospective)
LIAISON® XL MUREX HBc IgM vs Reference Assay by Characterization

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	97/98 (99.0%) 95% CI: 94.4% to 100.0%	9/11 (81.8%) 95% CI: 52.3% to 94.9%
Late Acute	32/34 (94.1%) 95% CI: 80.9% to 98.4%	N/A
Chronic	N/A	123/144 (85.4%) 95% CI: 78.7% to 90.3%
Early Recovery	10/11 (90.9%)	45/46 (97.8%)

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
	95% CI: 62.3% to 98.4%	95% CI: 88.7% to 99.6%
Recovery	N/A	160/167 (95.8%) 95% CI: 91.6% to 98.0%
Immune Due to Natural Infection	N/A	107/107 (100.0%) 95% CI: 96.5% to 100.0%
HBV Vaccine Response	N/A	1150/1152 (99.8%) 95% CI: 99.4% to 100.0%
Not Previously Infected	N/A	1302/1303 (99.9%) 95% CI: 99.6% to 100.0%
Not Interpretable	2/3 (66.7%) 95% CI: 20.8% to 93.9%	6/6 (100.0%) 95% CI: 61% to 100.0%
Total	**141/146 (96.6%) 95% CI: 92.2% to 98.5%**	**2902/2936 (98.8%) 95% CI: 98.4% to 99.2%**

Cumulative Pediatric Clinical Agreement (Combined Prospective & Retrospective)
LIAISON® XL MUREX HBc IgM vs Reference Assay by Characterization

HBV Classification	Positive Percent Agreement (PPA)	Negative Percent Agreement (NPA)
Acute	20/20 (100%) 95% CI: 83.9% to 100.0%	N/A
Late Acute	7/7 (100%) 95% CI: 64.6% to 100.0%	N/A
Chronic	N/A	6/7 (85.7%) 95% CI: 48.7% to 97.4%
Early Recovery	1/1 (100%) 95% CI: 20.7% to 100.0%	N/A
Recovery	N/A	5/5 (100%) 95% CI: 56.6% to 100.0%
Immune Due to Natural Infection	N/A	3/3 (100%) 95% CI: 43.9% to 100.0%
HBV Vaccine Response	N/A	63/63 (100%) 95% CI: 94.3% to 100.0%
Not Previously Infected	N/A	84/84 (100%) 95% CI: 95.6% to 100.0%
Not Interpretable	0/1 (0.0%) 95% CI: 0.0% to 79.4%	1/1 (100%) 95% CI: 20.7% to 100.0%
Total	28/29 (96.6%) 95% CI: 82.8% to 99.4%	162/163 (99.4%) 95% CI: 96.6% to 99.9%

14.2 Pediatric samples

Pediatric samples were tested to determine if these types of samples provide equivalent results to adult human serum.

A total of thirty (30) negative pediatric patient samples were used for this study. The pediatric samples encompassed the age range of two (2) months to twenty-one (21) years. Ten (10) negative pediatric samples were spiked with HBc IgM high positive sample to obtain high negative samples. Ten (10) pediatric samples were spiked with HBc IgM high positive sample to obtain low positive samples. Ten (10) pediatric samples were spiked with HBc IgM high positive sample to obtain moderate positive samples. Adult negative pool samples were used as controls, by spiking with HBc IgM high positive sample to achieve the same three (3) levels of samples: high negative, low positive and moderate positive samples. Averaged results for each pediatric sample were compared to results obtained on adult samples. The results of the study suggest that pediatric samples react in the same manner as adult samples.

14.3. Precision with LIAISON® XL Analyzer

A twenty (20) day reproducibility/precision study was performed by using a coded panel that was prepared by either spiking or diluting samples as necessary to obtain negative, low positive and mid positive samples. Kit Control sets were also included in the 20-day study. The panel samples and kit controls were tested on three (3) LIAISON® XL MUREX HBc IgM kit lots in two (replicates) per run, two (2) runs per day for twenty (20) operating days on one (1) LIAISON® XL Analyzer. The CLSI document EP5-A3 was consulted in the preparation of the testing protocol.

	LIAISON® XL MUREX HBcIgM Assay All 3 Lots Combined											
Sample ID	N	Mean	Repeatability		Between-Run		Between-Day		Between-Lot		Within Laboratory	
		Index/RLU	SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Neg #RS-707	240	*570.03	24.42	4.3%	17.56	3.1%	15.70	2.8%	29.19	5.1%	44.76	7.9%
Ctrl Neg #RS-708	240	*571.97	22.28	3.9%	16.43	2.9%	17.51	3.1%	29.22	5.1%	43.89	7.7%
Ctrl Neg #RS-709	240	*572.29	24.09	4.2%	18.34	3.2%	15.99	2.8%	28.94	5.1%	44.83	7.8%
Ctrl Pos #RS-710	240	2.27	0.037	1.6%	0.038	1.7%	0.068	3.0%	0.085	3.8%	0.121	5.3%
Ctrl Pos #RS-711	240	2.95	0.052	1.8%	0.083	2.8%	0.077	2.6%	0.092	3.1%	0.155	5.2%
Ctrl Pos #RS-712	240	2.6	0.045	1.7%	0.067	2.6%	0.060	2.3%	0.090	3.5%	0.134	5.2%
HBCM-1-U1	240	0.43	0.008	1.8%	0.009	2.0%	0.016	3.7%	0.032	7.5%	0.038	8.8%
HBCM-1-U2	240	0.60	0.011	1.8%	0.010	1.7%	0.025	4.1%	0.032	5.3%	0.043	7.2%
HBCM-1-U3	240	0.63	0.011	1.7%	0.013	2.0%	0.023	3.7%	0.036	5.7%	0.046	7.3%
HBCM-1-U4	240	0.63	0.011	1.7%	0.011	1.7%	0.026	4.1%	0.017	2.7%	0.034	5.5%
HBCM-2-U5	240	3.76	0.048	1.3%	0.078	2.1%	0.107	2.9%	0.083	2.2%	0.164	4.4%
HBCM-2-U6	240	1.75	0.022	1.2%	0.023	1.3%	0.038	2.2%	0.056	3.2%	0.075	4.3%
HBCM-2-U7	240	4.43	0.062	1.4%	0.083	1.9%	0.126	2.8%	0.080	1.8%	0.181	4.1%
HBCM-2-U8	240	1.74	0.018	1.0%	0.026	1.5%	0.050	2.9%	0.086	5.0%	0.105	6.0%
HBCM-1-U9	240	2.00	0.027	1.3%	0.030	1.5%	0.052	2.6%	0.057	2.8%	0.087	4.3%
HBCM-1-U10	240	3.22	0.045	1.4%	0.058	1.8%	0.090	2.8%	0.089	2.7%	0.146	4.5%

* Samples below the reading range of the assay, precision calculations are based on signal (RLU)

A 5-day reproducibility/precision study was conducted at three (3) external laboratories. Each site used a different lot of LIAISON® XL MUREX HBc IgM assay. The coded panel used in the 5-day study was the same panel used in the 20-day study. The coded panel was tested at all three (3) sites, using six (6) replicates per run in one (1) run per day for five (5) operating days. The CLSI document EP15-A3 was consulted in the preparation of the testing protocol. The mean, standard deviation, and coefficient of variation (%CV) of the results were computed for each of the tested specimens across sites.

Sample ID	N	Mean	Repeatability		Between-Day/Run		Within Laboratory Precision		Between-Site/Lots		Total Reproducibility	
			SD	%CV	SD	%CV	SD	%CV	SD	%CV	SD	%CV
Ctrl Neg (all 3 lots)	90	*482.28	19.71	4.1%	15.44	3.2%	25.04	5.2%	24.33	5.0%	34.03	7.1%
Ctrl Pos (all 3 lots)	90	2.386	0.046	1.9%	0.118	5.0%	0.127	5.3%	0.492	20.6%	0.505	21.2%
HBCM-1-U1	90	0.469	0.011	2.4%	0.028	5.9%	0.030	6.3%	0.052	11.1%	0.059	12.5%
HBCM-1-U2	90	0.662	0.015	2.3%	0.033	4.9%	0.036	5.4%	0.093	14.0%	0.098	14.9%
HBCM-1-U3	90	0.679	0.015	2.2%	0.031	4.6%	0.035	5.1%	0.100	14.8%	0.105	15.5%
HBCM-1-U4	90	0.682	0.015	2.1%	0.028	4.1%	0.032	4.6%	0.082	12.1%	0.087	12.8%
HBCM-2-U5	90	3.845	0.075	1.9%	0.167	4.3%	0.183	4.7%	0.281	7.3%	0.326	8.5%
HBCM-2-U6	90	1.779	0.024	1.4%	0.078	4.4%	0.082	4.6%	0.106	6.0%	0.129	7.3%
HBCM-2-U7	90	4.482	0.078	1.7%	0.182	4.1%	0.198	4.4%	0.241	5.4%	0.301	6.7%
HBCM-2-U8	90	1.795	0.027	1.5%	0.058	3.2%	0.063	3.5%	0.175	9.7%	0.184	10.3%
HBCM-1-U9	90	2.056	0.032	1.6%	0.089	4.3%	0.095	4.6%	0.120	5.8%	0.147	7.2%
HBCM-1-U10	90	3.297	0.057	1.7%	0.138	4.2%	0.149	4.5%	0.203	6.2%	0.244	7.4%

*Precision calculations are based on signal (RLU) for the negative control.

14.4. Analytical Sensitivity as Seroconversion Panel Performance

Eight (8) commercially available HBV seroconversion panels were tested using LIAISON® XL MUREX HBc IgM and a commercially available FDA-approved comparator assay to determine the sensitivity of the assay. The results are summarized in the following table:

		LIAISON XL MUREX HBc IgM Assay		Comparator assay		Difference In number of days	Difference in number of blood draws
Panel ID	Number of samples	Last Bleed (Day) with Non-Reactive Result	First Bleed (Day) with Reactive Result	Last Bleed (Day) with Non-Reactive Result	First Bleed (Day) with Reactive Result		
HBV-001	20	31	36	36	43	-7	-1
HBV-004	30	65	71	71	76	-5	-1
HBV-002	20	25	57	57	60	-3	-1
9092	37	78	85	85	92	-7	-1
6278	10	33	41	33	41	0	0
6281	12	36	41	41	43	-2	-1
9099	20	61	74	74	78	-4	-1
9093	31	42	49	42	49	0	0

The sensitivity of the LIAISON® XL MUREX HBc IgM was comparable to the comparator assay in the eight (8) seroconversion panels tested.

14.5. Matrix Comparison

Twenty-five (25) paired sets of matched serum (with and without gel SST) and plasma (lithium and sodium heparin, sodium citrate and K_2 EDTA) were tested to determine if these sample types provide equivalent results on the LIAISON® XL MUREX HBc IgM assay. Each sample was divided into three aliquots. Two sets of aliquots were spiked with a HBc IgM high positive sample to achieve two (2) levels of samples: high negative and low positive samples. The third set of aliquots was un-spiked to serve as control samples. Where possible, native samples identified as high negative and low positive during the initial screening, were used instead of spiking these samples. The results of the negative and low positive samples did not change the classification of the expected result. The results obtained on the serum-plasma paired samples indicated that there is equivalence among serum (with and without gel SST), K_2 EDTA, Lithium Heparin, Sodium Heparin and Sodium Citrate plasma.

14.6. Potential interfering substances

Controlled studies of potentially interfering substances at two (2) HBc IgM levels showed no interference at the concentration for each substance listed below in the LIAISON® XL MUREX HBc IgM assay. The testing was based on CLSI-EP07.

Substances	Tested concentrations
Triglycerides	3000 mg/dL
Hemoglobin	1000 mg/dL
Unconjugated bilirubin	20 mg/dL
Conjugated bilirubin	20 mg/dL
Albumin	6000 mg/dL
Cholesterol	350 mg/dL

14.7. Cross-reactivity

The cross-reactivity study for the LIAISON® XL MUREX HBc IgM assay was designed to evaluate potential interference from other viruses that may cause symptoms similar to HBV infection (EBV, CMV,HAV, HCV), other organisms that may cause infectious disease (HIV) and from other conditions that may result from atypical immune system activity (i.e. rheumatoid factor, anti-nuclear antibodies, HAMA). None of the tested cross reactant pathologies returned consistent with a conclusion of Cross reactivity. There is no evidence of cross reactivity with the tested pathologies.

Organism / Condition	N	Comparator HBc IgM assay	LIAISON® XL MUREX HBc IgM	
			Non reactive	Reactive
Anti-nuclear antibodies (ANA)	10	Negative	10	0
Auto-immune hepatitis	10	Negative	10	0
C. trachomatis	11	Negative	11	0
CMV (IgG / IgM)	11	Negative	11	0
EBV (IgM)	11	Negative	11	0
Fatty liver disease	11	Negative	11	0
HAMA	11	Negative	11	0
Hemodialysis patient	11	Negative	11	0
Hepatitis A Virus (anti-HAV IgM)	11	Negative	11	0
Hepatitis C Virus (anti-HCV)	11	Negative	11	0
Hepatocellular carcinoma	11	Negative	11	0
HIV-1 (anti-HIV-1)	11	Negative	11	0
HIV-2 (anti-HIV-2)	11	Negative	11	0
HSV (IgG / IgM)	11	Negative	11	0
HTLV-1/2 (anti-HTLV)	11	Negative	11	0
IgG monoclonal gammopathy	11	Negative	11	0
IgM monoclonal gammopathy	10	Negative	10	0
Influenza vaccine recipients	11	Negative	11	0
Multiparous pregnancies	11	Negative	11	0
Multiple myeloma	11	Negative	11	0
Multiple transfusion recipients	11	Negative	11	0
N. gonorrhoeae	11	Negative	11	0
Pregnancy 1st trimester	11	Negative	11	0
Pregnancy 2nd trimester	11	Negative	11	0
Pregnancy 3rd trimester	11	Negative	11	0
Rheumatoid Factor	11	Negative	11	0
T. pallidum	11	Negative	11	0
T.cruzi (anti-T. cruzi)	11	Negative	11	0

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The symbols glossary is provided electronically and can be found in the Dialog section at www.diasorin.com using the part and lot numbers associated with the corresponding IVD product.

LIAISON® XL murex Control HBc IgM ([REF] 318141)

1. INTENDED USE

The LIAISON® XL MUREX Control HBc IgM (negative and positive) is intended for use as assayed quality control samples to monitor the performance of the LIAISON® XL MUREX HBc IgM assay. The performance characteristics of LIAISON® XL MUREX Control HBc IgM have not been established for any other assays or instrument platforms.

Caution: **U.S. Federal Law restricts this device to sale by or on the order of a licensed practitioner**.

2. MATERIALS PROVIDED

Negative control (2 x 0.9 mL)	**[CONTROL|-]**	Human serum without IgM anti-HBc antibodies, with BSA, phosphate buffer, 0.2% ProClin® 300 and preservatives.
Positive control (2 x 0.9 mL)	**[CONTROL|+]**	Chimeric IgM anti-HBc antibodies (human and mouse monoclonal), human serum IgM free, animal proteins, buffer, 0.2% ProClin® 300, preservatives and an inert yellow dye.

ProClin® is a trademark of the Dow Chemical Company (Dow) or an affiliated company of Dow.

All reagents are supplied ready to use. The range of concentrations of each control is reported on the certificate of analysis and indicates the limits established by DiaSorin for control values that can be obtained in reliable assay runs. Each laboratory is responsible for adopting different limits to meet individual requirements.

The certificate of analysis bar codes give specific information on the lot of controls and should be read by the hand-held bar code scanner of the LIAISON® XL Analyzer prior to loading the control vials on board. For details, refer to the analyzer operator's manual.

3. WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use.
- Controls are not kit lot specific and may be safely interchanged even with different reagent integral lots.
- All materials used to produce the components provided in this kit have been tested for the presence of HBsAg, anti-HCV, anti-HIV-1, anti-HIV-2 and found to be non-reactive. As, however, no test method can offer absolute assurance that pathogens are absent, all specimens of human origin should be considered potentially infectious and handled with care.
- Observe the normal precautions required for handling all laboratory reagents.
- Disposal of all waste material should be in accordance with local guidelines.
- Do not eat, drink, smoke or apply cosmetics in the assay laboratory.
- Do not pipette by mouth.
- Avoid direct contact with potentially infected material by wearing laboratory clothing, protective goggles, and disposable gloves. Wash hands thoroughly at the end of each assay.
- Avoid splashing or forming an aerosol. All drops of biological reagent must be removed with a sodium hypochlorite solution with 0.5% active chlorine, and the means used must be treated as infected waste.
- All samples and reagents containing biological materials used for the assay must be considered as potentially able to transmit infectious agents. The waste must be handled with care and disposed of in compliance with the laboratory guidelines and the statutory provisions in force in each Country.
- Any materials for reuse must be appropriately sterilized in compliance with the local laws and guidelines. Check the effectiveness of the sterilization/decontamination cycle.
- Do not use kits or components beyond the expiration date given on the label.

Chemical Hazard and Safety Information

Reagents in this kit are classified in accordance with the US OSHA Hazard Communication Standard; individual US State Right-to-Know laws; Canadian Centre for Occupational Health and Safety Controlled Products Regulations; and European Union EC Regulation 1272/2008 (CLP) (for additional information see Safety Data Sheet available on www.diasorin.com).

Hazardous reagents are classified and labelled as follows:

REAGENTS:	[CONTROL|-], [CONTROL|+]
CLASSIFICATION:	Skin sens. 1 H317
SIGNAL WORD:	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H317 May cause an allergic skin reaction.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P363 Wash contaminated clothing before reuse.
CONTAINS: (only substances prescribed pursuant to Article 18 of EC Regulation 1272/2008).	reaction mass of: 5-chloro-2-methyl-4-isothiazolin-3-one [EC no. 247-500-7] and 2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1). (ProClin® 300).

For additional information, see Safety Data Sheets available on www.diasorin.com.

4. STORAGE AND STABILITY

Upon receipt, the controls must be stored at 2-8°C in an upright position to prevent adherence of the solution to the vial cap. Do not freeze. When controls are stored sealed and kept upright, they are stable at 2-8°C up to the expiry date. Once opened controls are stable for twelve weeks (12) when properly stored at 2-8°C between multiple uses. Avoid bacterial contamination of controls. The controls should not be used past the expiry date indicated on the vial labels.

5. PREPARATION OF REAGENTS

- Place the control vials in type C racks on the analyzer. Each control solution allows at least 20 tests to be performed.
- The minimum volume required is 420 µL (20 µL control + 400 µL dead volume).
- At the time of use, equilibrate controls to room temperature (20-25°C) before opening the vials and keep them on board the instrument only for the amount of time required for quality control testing.
- After use, stopper the vials promptly and store them at 2-8°C in an upright position.
- During handling, use appropriate precautions to avoid bacterial contamination of controls.

6. TARGET VALUES

The range of concentration of each control is reported on the certificate of analysis and indicates the limits established by DiaSorin for control values that can be obtained in reliable assay runs. If control values obtained after successful calibration lie repeatedly outside the expected ranges, the test should be repeated using an unopened control vial.

7. QUALITY CONTROL

Quality control should be performed once per day of use, or according to guidelines or requirements of local regulations or accredited organizations. It is recommended that the user refer to CLSI document, C24-A3, and 42 CFR 493.1256(c) for guidance on appropriate quality control practices.

LIAISON® XL controls are intended to monitor for reagent failure. Whenever LIAISON® XL controls lie outside the expected ranges provided on the certificate of analysis, calibration should be repeated and controls and samples retested. Do not report patient results until control results are within expected ranges.

Strict adherence to the instructions of the LIAISON® XL MUREX HBc IgM kit are necessary to obtain reliable results.

8. LIMITATIONS

Control values for assays other than the LIAISON® XL MUREX Control HBc IgM assay have not been established.

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