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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® Biotrin Parvovirus B19 IgG Plus ([REF] 311550)

1. INTENDED USE

The LIAISON® Biotrin Parvovirus B19 IgG Plus, a chemiluminescent immunoassay (CLIA), is intended for the qualitative detection of IgG antibodies to B19 virus (B19V, previously known as human parvovirus B19) in human serum, lithium heparin, dipotassium EDTA (K_2-EDTA), and sodium citrated plasma. The test may be used for testing women of childbearing age where there is a suspicion of exposure to human B19V. The test may also be used for all patients as an aid in the diagnosis of fifth disease (erythema infectiosum). The test must be performed on the LIAISON® XL Analyzer.

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

2. BACKGROUND ON THE PARVOVIRUS B19 (B19)

Parvovirus B19 (B19) is a small, non-enveloped ssDNA erythrovirus of 20-25 nm in diameter with a 5.6 kb genome and a single promoter. Given the absence of a lipid envelope and its limited DNA content, B19 is very resistant to the routine treatment of blood products. The discovery of variants of parvovirus B19 led to a subdivision that includes now genotypes 2 and 3, strains A6/K71 and V9, respectively, in addition to genotype 1 (B19). [1-11]

Most commonly, transmission of B19 happens by personal contact, via aerosol or respiratory secretions. The virus can also be transmitted transplacentally from an infected mother to her fetus, and iatrogenically by contaminated blood products. Viral entry into target cells is mediated by cellular receptors. After initial replication, which likely occurs in the respiratory tract, the virus enters bone marrow reticulocytes and replicates there, inhibiting normal erythropoiesis. B19 is cytotoxic to erythroid progenitor cells, inducing apoptosis-like events and expression of the interleukin 6. The resulting erythropoietic stress can cause complications, especially to immunocompromised individuals and subjects with underlying hemolytic diseases. [1–11]

B19 viremia occurs one week after exposure and usually lasts about 5 days. In general, IgM antibodies to B19 appear 7-10 days after infection, and persist for approximately 3 months. Anti-B19 IgG antibodies become detectable about 15 days post-infection and increase exponentially in the subsequent days, to remain high for the rest of the individual's life, providing long-term protection. [1–11]

Infections with parvovirus B19 are very common during childhood, and it is estimated that 40-60% of adults have evidence of a history of infection, a percentage that reaches 90% in the elderly population. Despite such high prevalence, viremia is actually rare, most likely as a consequence of virus neutralization by immunoglobulins in healthy subjects. B19 causes erythema infectiosum (EI), a common mild childhood illness characterized by erythematous rashes affecting face, trunk and limbs. EI is also known as fifth disease, as it is the fifth most-common rash-causing illness during childhood. [2,5,6,8,12]

Infections in pregnant women are at risk of possible transplacental viral transmission to the fetus. Although not common, this may be the cause of serious complications such as fetal anemia, neurological anomalies, hydrops fetalis, and fetal death in about 5% of transmissions.[1,2,5,8,9] It is estimated that the percentage of pregnant women susceptible to B19 infection is high (30-50%), but only a minor fraction of them will actually be infected. The prevalence of seroconversion among pregnant women is 1.5-3% in normal endemic times, and can rise to 10-14% during epidemics. [3,4,6,7,11]

Clinical diagnosis of B19 infections can be made based on EI, when present. When laboratory confirmation is required, or in those cases where the typical rashes of EI are not present, serologic detection of anti-B19-specific IgM and IgG antibodies is the diagnostic method of choice to diagnose parvovirus infections in immunocompetent individuals.[2-10,12]. Considering the time of onset of immunoglobulins and their above described development, serology can also provide information on the infection phase. Pregnant women showing an IgM+/IgG- profile should repeat serology in 3-4 weeks or be referred for ultrasound and standard workup against fetal complications. Detection of both IgM and IgG diagnoses a recent infection, whereas the absence of anti-B19 IgM and IgG antibodies indicates that the subject has no active infection ongoing; however, in the latter case, another serologic assessment after 2 weeks and/or PCR assessment of viral load is recommended, especially in pregnant women. A positive anti-B19 IgG result with a negative IgM result indicates immunity. Such an outcome is particularly important to reassure recently exposed pregnant women or pregnant women with symptoms that they are immune. Nevertheless, in rare cases, the presence of IgG antibodies without IgM may be due to premature clearance of IgM immunoglobulin and needs attention, again especially in pregnant women. [2-4,6,9,12]

3. PRINCIPLE OF THE PROCEDURE

The method for qualitative detection of specific IgG to parvovirus B19 is an indirect sandwich chemiluminescence immunoassay (CLIA). Recombinant parvovirus B19 VP2 antigen is used for coating magnetic particles (solid phase) and mouse monoclonal antibody directed against human IgG is linked to an isoluminol derivative (isoluminol-antibody conjugate). During the first incubation, parvovirus B19 antibodies, if present in calibrators, patient samples or controls, bind to the solid phase. During the second incubation, the antibody conjugate reacts with any human anti-parvovirus B19 IgG 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-antibody conjugate, is measured by a photomultiplier as relative light units (RLU) and indicates the presence or absence of IgG to parvovirus B19 in calibrators, samples or controls. Test calibrators allow the relative light unit (RLU) values to be converted into the AU output. Results are reported as Negative or Positive.

4. MATERIALS PROVIDED

Reagent integral

Magnetic particles (2.45 mL)	**[SORB]**	Magnetic particles coated with recombinant parvovirus B19 VP2 antigen (obtained in baculovirus), BSA, phosphate buffer, < 0.1% sodium azide.
Calibrator 1 (2.0 mL)	**[CAL|1]**	Human serum/plasma containing low parvovirus B19 IgG levels, BSA, phosphate buffer, detergents, ProClin™ 300, an inert yellow dye.
Calibrator 2 (2.0 mL)	**[CAL|2]**	Human serum/plasma containing high parvovirus B19 IgG levels, BSA, phosphate buffer, detergents, ProClin™ 300, an inert blue dye.
Specimen diluent (2 x 28 mL)	**[DIL|SPE]**	Casein, BSA, phosphate buffer, detergents, ProClin™ 300, an inert blue dye.
Conjugate (28 mL)	**[CONJ]**	Mouse monoclonal IgG antibodies to human IgG conjugated to an isoluminol derivative, BSA, phosphate buffer, ProClin™ 300, preservatives.
Number of tests		100

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 (system related)

LIAISON® XL Analyzer
LIAISON® XL Cuvettes ([REF] X0016).
LIAISON® XL Disposable Tips ([REF] X0015) or
LIAISON® Disposable Tips ([REF] X0055).
LIAISON® XL Starter Kit ([REF] 319200) or
LIAISON® EASY Starter Kit ([REF] 319300).
LIAISON® Wash/System Liquid ([REF] 319100).
LIAISON® XL Waste Bags ([REF] X0025).

Additional required materials

LIAISON® Biotrin Control Parvovirus B19 IgG Plus ([REF] 311551).

5. WARNINGS AND PRECAUTIONS

- For *in vitro* diagnostic use.
- For Prescription Use Only. **U.S. Federal Law restricts this device to sale by or on the order of a licensed practitioner.**
- The human blood source material used to produce the components provided in this kit are **potentially biohazard materials**. Source materials derive 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.
- Observe the normal precautions required for handling all laboratory reagents.
- Disposal of all waste material should be in accordance with local guidance.
- 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 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, 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.
- The LIAISON® XL analyzers 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 reagent packs (even for the same reagents).
- Visually inspect the integral vials for leakage at the membrane seals or elsewhere. If the vials are found to be leaking, the local customer service should be notified immediately.
- Previously frozen samples should be thoroughly mixed after thawing and prior to testing.

Reagents Containing Human Source Material:

Warning - Treat as potentially infectious. Each serum/plasma donor unit used in the preparation of this product has been tested by an U.S. FDA approved method and found non-reactive for the presence of the antibody to Human Immunodeficiency Virus 1 and 2 (HIV 1/2), the Hepatitis B surface antigen (HBsAg), and the antibody to Hepatitis C (HCV). While these methods are highly accurate, they do not guarantee that all infected units will be detected. This product may also contain other human source diseases for which there is no approved test. Because no known test method can offer complete assurance that HIV, Hepatitis B Virus (HBV) and HCV or other infectious agents are absent, all products containing human source material should be handled following universal precautions; and as applicable in accordance with good laboratory practices as described in the Centers for Disease Control and the National Institutes of Health current manual, Biosafety in Microbiological and Biomedical Laboratories (BMBL); or the World Health Organization current edition, Laboratory Biosafety Manual.

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 labeled as follows:

REAGENTS:	[CAL|1], [CAL|2], [DIL|SPE], [CONJ]
CLASSIFICATION:	Skin sens. 1A H317 Aquatic chronic 3 H412
SIGNAL WORD:	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H317 May cause an allergic skin reaction. H412 Harmful to aquatic life with long lasting effects.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P273 Avoid release to the environment. P362 Take off contaminated clothing and wash 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] and2-methyl-2H -isothiazol-3-one [EC no. 220-239-6] (3:1) (ProClin™ 300).

Reagent containing sodium azide (Magnetic Particles [SORB])

Sodium azide may react with lead or copper plumbing to form highly explosive metal azides. Immediately after 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 THE 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.
Incomplete magnetic particle resuspension may cause variable and inaccurate results. 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 resuspended.
- Repeat as necessary until the magnetic particles are completely resuspended.
- After removal of the seal carefully wipe the surface of each septum to remove residual liquid if necessary.

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 (located in position two and three following 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 THE REAGENT INTEGRAL

Upon receipt, the Reagent Integral must be stored in an upright position to facilitate resuspension of the Magnetic Particles.

Refer to Reagent Integral Preparation (Section 6) for resuspension instructions.

– **When the Reagent Integral is stored sealed and kept upright, the reagents** are stable at 2-8°C until the expiry date.After removing the seals, the Reagent Integral is stable up to eleven (11) weeks when stored at 2-8°C in a refrigerator or on board the analyzer.
– Use the storage rack provided with the LIAISON® XL Analyzer for upright storage of the reagent integral.
– Do not freeze.
– Keep upright for storage to facilitate later proper resuspension of magnetic particles
– Keep away from direct light.

8. SPECIMEN COLLECTION AND PREPARATION

The correct specimen type must be used in the assay. The following matrices have been tested and may be used:

– Serum;
– Sodium citrate plasma;
– Lithium heparin plasma;
– K_2-EDTA plasma.

Blood should be collected aseptically by venipuncture and the serum or plasma separated from clot, red cells, or gel separator after centrifugation, carefully following the tube manufacturers' instructions and according to good laboratory practices.

Centrifugation conditions of collection tubes may vary depending on the manufacturer. A minimum of 1,000 g for 10 minutes is reported. Use of centrifugation conditions should be evaluated and validated by the laboratory.

Package and label specimens in compliance with applicable state, federal, and international regulations covering the transportation of clinical specimens and infectious substances.

Specimens may be shipped on dry ice (frozen), on wet ice (for 2°-8°C), following the sample storage limitations described below.

Uncontrolled transport conditions (in terms of temperature and time) may cause inaccurate analytical results. During validation studies, specimen collection tubes commercially available at the time of testing were used. Therefore, not all collection tubes from all manufacturers have been evaluated. Blood collection devices from various manufacturers may contain substances which could affect the test results in some cases (Bowen et al., Clinical Biochemistry, 43, 4-25, 2010).

A dedicated study on storage limitations was performed on serum or plasma specimens removed from clot, red cells, or gel separator. The following storage conditions showed no significant differences:

– 15°-30°C for one (1) day;
– 2°-8°C for three (3) days, otherwise they should be aliquoted and stored deep-frozen (–20°C or below);
– Up to three (3) freeze-thaw cycles, more freeze-thaw cycles should be avoided;
– Up to six (6) months at -20°C or below.

If samples are stored frozen, mix thawed samples well before testing.

Further centrifugation of specimens removed from red cells, clot, or gel separator (preferably between 3,000 and 10,000 g for 10 minutes) is recommended to guarantee the consistency of results whenever one of the following conditions is identified:

– Samples previously centrifuged and stored at 2-8°C;
– Samples with particulate matter, fibrin, turbidity, lipaemia or erythrocyte debris;
– Samples frozen and thawed;
– Samples requiring repeat testing.

Specimens with a lipid layer on the top should be transferred into a secondary tube, by transfering only the clarified material.

Grossly haemolyzed or lipaemic samples as well as samples containing particulate matter or exhibiting obvious microbial contamination should not be tested. Heat inactivation of the specimens may affect the test results. Check for and remove air bubbles before assaying.

The minimum specimen volume required for a single determination is 170 µL (20 µL reaction sample volume + 150 µL sample dead volume).

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 instructions.

The analyzer operations are as follows:

1. Dispense specimen (calibrator or control), coated magnetic particles, specimen diluent into the reaction cuvettes
2. Incubate and wash
3. Dispense the Conjugate into the reaction cuvettes
4. Incubate and wash
5. Add the Starter Reagents and measure the light emitted.

10. CALIBRATION

Testing of assay specific calibrators allows the detected relative light unit (RLU) values to adjust the assigned master curve.

Each calibration solution allows five (5) 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.
– Control values lie outside the expected ranges.
– The analyzer has been serviced.

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

11. QUALITY CONTROL

The LIAISON® Biotrin Control Parvovirus B19 IgG Plus ([REF] 311551) is recommended for the determination of quality control requirements for this assay and should be run in singlicate to monitor the assay performance.

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 the user refer to CLSI document C24-A3 and 42 CFR 493.1256 (c) for guidance on appropriate quality control practices.

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 should be obtained in reliable assay runs.

Control values must lie within the expected ranges: whenever one or both controls lie outside the expected ranges, calibration should be repeated, and controls retested. If control values obtained after successful calibration lie repeatedly outside the predefined ranges, the test should be repeated using an unopened control vial. If control values lie outside the expected ranges, the run is considered invalid, patient results must not be reported, and samples should be retested. Only results from valid runs should be reported.

12. LIMITATIONS OF THE PROCEDURE

Assay performance characteristics have not been established when the LIAISON® Biotrin Parvovirus B19 IgG Plus test is used in conjunction with other manufacturers' assays for the detection of specific parvovirus B19 serological markers. Under these conditions, users are responsible for establishing their own performance characteristics.

- The performance characteristics of these assays have not been established for other B19V associated diseases or testing neonates.
- The reagent should be used only on the LIAISON® XL platform
- The test should be performed on human serum, lithium heparin, K_2-EDTA, and sodium citrated plasma only. The use of whole blood or other plasma specimens has not been evaluated.
- Single components of the reagent integral should not be removed from the integral.
- This kit must not be used after the expiry date printed on the package label.
- The use of icteric or lipemic sera, or sera exhibiting hemolysis or microbial growth should be avoided.
- Bacterial contamination or heat inactivation of the specimens may affect the test results.
- A skillful technique and strict adherence to the instructions are necessary to obtain reliable results.
- Performance has not been established for the use of bodily fluids other than human.
- A single result may not be sufficient for diagnosis but should be determined in conjunction with clinical findings, patient history and always in association with medical judgment.
- Results obtained with LIAISON® Biotrin Parvovirus B19 IgG Plus assay may not be used interchangeably with values obtained with different manufacturers' assay methods.
- Specimens from patients receiving preparations of mouse monoclonal antibodies for therapy or diagnosis may contain human anti-mouse antibodies (HAMA). Such specimens may interfere in a monoclonal antibody-based immunoassay and their results should be evaluated with care.

13. INTERPRETATION OF RESULTS

The analyzer automatically calculates the LIAISON® Biotrin Parvovirus B19 IgG Plus AU test output and grades the results as indicated in the table below. For details, refer to the analyzer operator's manual.

Sample results should be interpreted as follows:

LIAISON® Biotrin Parvovirus B19 IgG Plus		
AU	**Results**	**Interpretation**
< 1.00	Negative	A result below 1.00 AU may indicate the absence, or a level of IgG antibodies to parvovirus B19 below the assay threshold.
≥ 1.00	Positive	A result above or equal to 1.00 AU indicates detection of IgG antibodies to parvovirus B19.

A negative result for IgG antibodies to parvovirus B19 generally indicates that the patient has not been infected, but does not exclude the possibility of acute parvovirus B19 infection, because the infection may be in its very early stage and the patient may be still unable to synthesize parvovirus B19 specific antibodies, or the antibodies may be present in undetectable levels. It should be underlined that the test scores negative during the first weeks after infection. If clinical exposure to parvovirus B19 is suspected despite a negative result, a second sample should be collected and tested for IgM and IgG during the course of infection.

A positive result for IgG antibodies to parvovirus B19 generally indicates a previous infection thereby inferring immunity. A single specimen, however, can only help estimate the serological status of the individual. Interpretation of the serological results must be made in the context of the clinical presentation of each patient.

14. SPECIFIC PERFORMANCE CHARACTERISTICS

14.1. Analytical specificity

Analytical specificity may be defined as the ability of the assay to accurately detect specific analyte in the presence of potentially interfering factors in the sample matrix (e.g., anticoagulants, haemolysis, exogenous substances, effects of sample treatment), or potential cross-reactive antibodies.

Potential Interference.

The LIAISON® Biotrin Parvovirus B19 IgG Plus assay was evaluated for potential interference caused by endogenous and exogenous substances using 3 samples in claimed matrices containing IgG Parvovirus antibodies (high negative, around cut-off, low positive). Controlled studies of potentially interfering substances showed no interference at the concentration for each substance listed below when using the LIAISON® Biotrin Parvovirus B19 IgG Plus assay. The testing was based on CLSI-EP07.

Substance	Tested Concentrations
Endogenous Substances	
Unconjugated bilirubin	40 mg/dL
Conjugated bilirubin	40 mg/dL
Hemoglobin	1000 mg/dL
Triglycerides	1500 mg/dL
Total protein (high)	≥ 120 g/L
Total protein (low)	≤ 60 g/L
Cholesterol	400 mg/dL
Human Albumin	6000 mg/dL
Total IgG	2000 mg/dL
Total IgM	400 mg/dL
Human anti-mouse antibody (HAMA)	753 ng/mL
Rheumatoid Factor (RF)	2000 IU/mL
Exogenous Substances	
Biotin	3500 ng/mL
Vitamin A	800 µg/dL
Vitamin B12	2850 pg/mL
Vitamin C	20 mg/dL
Vitamin D	450 ng/mL
Vitamin E	120 mg/L
Folic Acid	160 ng/mL
Acetaminophen	15.6 mg/dL
Ibuprofen	21.9 mg/dL
Naproxen	36.0 mg/dL
Penicillin	110 mg/dL
Streptomycin (sulphate)	25.8 mg/dL
Erythromycin	13.8 mg/dL

Potential Cross-reactivity.

The cross-reactivity of the LIAISON® Biotrin Parvovirus B19 IgG Plus assay was evaluated by testing 220 samples (serum, lithium heparin, K_2-EDTA and sodium citrated plasma) containing antibodies to other microorganisms that may cause infectious diseases, as well as from other conditions. Samples for these studies were pre-screened with another commercially available parvovirus B19 IgG assay. If found negative for parvovirus B19 IgG antibodies, those specimens were used to study potential cross-reactivity. The presence of potential cross-reactants in the samples was confirmed using US-marked assays prior to performing the potential cross-reactivity testing on LIAISON® Biotrin Parvovirus B19 IgG Plus assay. Only one false positive result was observed out of the 14 samples containing parainfluenza antibodies, among a total of 220 samples that were evaluated. The potential cross-reactant and number of samples evaluated are listed in the table below.

ID	Potential Cross reactants	Number of tested samples
1	CMV (anti-CMV positive)	10
2	Epstein-Bar Virus (anti-EBV positive)	10

3	Herpes Simplex Virus (anti-HSV1/2 positive)	11
4	Rubella (anti-Rubella positive)	10
5	Hepatitis C Virus (anti-HCV positive)	8
6	Human Immunodeficiency Virus (anti-HIV antibodies)	7
7	Hepatitis A Virus (anti-HAV positive)	11
8	*Borrelia burgdorferi* (anti-*B. burgorferi* antibodies)	10
9	*Toxoplasma. gondii* (anti-*T. gondii* antibodies)	7
10	Varicella Zoster Virus (anti-VZV positive)	14
11	Measles virus (anti-Measles antibodies)	12
12	Mumps virus (anti-Mumps antibodies)	10
13	Adenovirus (anti-Adenovirus antibodies)	10
14	Anti-Influenza A antibodies	8
15	Anti-Influenza B antibodies	7
16	*Mycoplasma pneumonia* (anti-*M. pneumonia* antibodies)	13
17	Respiratory syncytial virus (RSV) antibodies	8
18	*Treponema Pallidum* (anti-*T. pallidum* antibodies)	9
19	Rheumatoid Factor (anti-Fc Immunoglobulin)	7
20	Human anti-mouse antibodies (HAMA)	8
21	Anti-nuclear antibodies (ANA)	16
22	Parainfluenza antibodies	**14***
	TOTAL	**220**

*A false positive result was observed in one out of fourteen (14) parainfluenza antibodies samples

14.2. Precision

Within Laboratory Precision: A twelve-day (12) precision study was performed using a coded panel of six (6) samples prepared by either spiking or diluting human serum samples as necessary to obtain negative, low positive and positive parvovirus B19 IgG antibodies samples. Kit Controls set was also included in the study. The panel samples and kit controls were tested with the LIAISON® Biotrin Parvovirus B19 IgG Plus assay in two (2) replicates per run, two (2) runs per day for twelve (12) operating days on one (1) LIAISON® XL Analyzer, on three (3) assay lots. CLSI document EP05-A3 was consulted in the preparation of the testing protocol. A summary of the study results is illustrated in the following table:

Sample ID	N	Mean (AU)	Within Run		Between Run		Between Day		Between-Lot		Total	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Negative Control A	144	499 (*)	55.5	11.1%	50.7	10.2%	49.3	9.9%	52.0	10.4%	103.8	20.8%
Negative Control B	144	661 (*)	41.1	6.2%	19.4	2.9%	54.1	8.2%	38.9	5.9%	80.6	12.2%
Positive Control A	144	4.36	0.112	2.6%	0.215	4.9%	0.239	5.5%	0.101	2.3%	0.355	8.1%
Positive Control B	144	5.38	0.137	2.5%	0.274	5.1%	0.340	6.3%	0.000	0.0%	0.458	8.5%
Positive Control C	144	5.16	0.111	2.2%	0.244	4.7%	0.462	9.0%	0.000	0.0%	0.534	10.4%
Sample 1	144	0.605	0.023	3.9%	0.025	4.1%	0.030	5.0%	0.059	9.7%	0.074	12.3%
Sample 2	144	0.595	0.024	4.0%	0.028	4.8%	0.026	4.4%	0.048	8.1%	0.066	11.1%
Sample 3	144	1.72	0.048	2.8%	0.026	1.5%	0.058	3.4%	0.077	4.4%	0.111	6.4%
Sample 4	144	2.57	0.048	1.9%	0.055	2.1%	0.101	3.9%	0.171	6.7%	0.212	8.2%
Sample 5	144	7.03	0.184	2.6%	0.196	2.8%	0.290	4.1%	0.069	1.0%	0.401	5.7%
Sample 6	144	8.10	0.146	1.8%	0.127	1.6%	0.432	5.3%	0.120	1.5%	0.488	6.0%

* Precision calculations based on signal (RLU).

Reproducibility: A five-day (5) reproducibility study was performed. The coded samples panel used in the 5-day reproducibility study was the same panel used in the 12-day within-laboratory precision study. The same samples panel was tested at all three (3) sites, using three (3) replicates per run in two (2) runs per day for five (5) operating days. Each site used a different lot of LIAISON® Biotrin Parvovirus B19 IgG Plus assay. The CLSI Document EP-05A3 was consulted in the preparation of the testing protocol. The means, standard deviation, and coefficient of variation (%CV) of the results were computed for each of the tested specimens across sites.

Sample ID	N	Mean (AU)	Repeatability		Between Run		Between Day		Between Site		Reproducibility	
			SD	CV%	SD	CV%	SD	CV%	SD	CV%	SD	CV%
Negative Control	90	565*	38.8	6.9%	26.7	4.7%	35.6	6.3%	67.1	11.9%	89.4	15.8%
Positive Control	90	4.35	0.151	3.5%	0.174	4.0%	0.329	7.6%	0.201	4.6%	0.449	10.3%
Sample 1	90	0.666	0.035	5.2%	0.032	4.9%	0.046	6.9%	0.048	7.1%	0.081	12.2%
Sample 2	90	0.811	0.030	3.7%	0.018	2.2%	0.028	3.4%	0.097	11.9%	0.106	13.1%
Sample 3	90	1.83	0.054	3.0%	0.037	2.0%	0.057	3.1%	0.113	6.2%	0.143	7.8%
Sample 4	90	2.76	0.078	2.8%	0.059	2.2%	0.115	4.2%	0.230	8.3%	0.275	10.0%
Sample 5	90	6.83	0.251	3.7%	0.211	3.1%	0.395	5.8%	0.646	9.5%	0.825	12.1%
Sample 6	90	8.28	0.191	2.3%	0.190	2.3%	0.508	6.1%	0.811	9.8%	0.994	12.0%

* Based on RLU value .

14.3. High-dose saturation effect

Whenever samples containing extremely high antibody concentrations are tested, the saturation effect can potentially affect the performance of an assay showing lower numerical output values than expected, increasing the risk of false negative results.

High dose hook effect was evaluated by diluting three samples containing high-levels of parvovirus IgG antibodies. No false negative results were observed reflecting no sample misclassification and no high-dose saturation effect.

14.4. Analytical sensitivity at the cutoff

The analytical sensitivity at the cutoff of LIAISON® Biotrin Parvovirus B19 IgG Plus assay was determined using serial dilutions of the WHO 2nd International Standard for Anti-Parvovirus 19, NIBSC Code 01/602 in human negative serum tested using 3 lots of the LIAISON® Biotrin Parvovirus B19 IgG Plus assay. The analytical sensitivity of LIAISON® Biotrin Parvovirus B19 IgG Plus assay at cutoff is the highest concentration of the reference standard detected among the 3 lots that corresponds to the cut-off value of 1.00 AU is 1.00 IU/mL

14.5. Clinical Performance Evaluation

A multi-site clinical agreement study was conducted to determine the clinical performance of the LIAISON® Biotrin Parvovirus B19 IgG Plus assay on samples collected from patients that would be routinely tested for parvovirus IgG antibodies.

The LIAISON® Biotrin Parvovirus B19 IgG Plus clinical study population consisted of a total of 750 specimens collected prospectively . This population included 250 pregnant women (n=83 first trimester, n=84 second trimester and n=83 third trimester) and 500 specimens collected from subjects that were suspected of having parvovirus from three geographic regions (California, North Carolina, and Texas) sent to the laboratory for routine parvovirus testing. Samples were tested with the LIAISON® Biotrin Parvovirus B19 IgG Plus assay and a commercially available FDA-approved comparator assay following their respective package inserts, and results were compared.

The majority of the prospectively collected specimens were from women (n=661 out of 750; 88.1%). Of the 750 prospective specimens, 631 were collected from adult subjects ranging in ages from 22 to 87 years and 119 pediatric subjects ranging in ages from 0 to 21 years.

Demographics of Collected Clinical Study Specimens by Age and Gender

Gender	Adult Prospective	Pediatric (0-21) Prospective
Female	572 (90.6%)	89 (74.8%)
Male	59 (9.4%)	29 (24.4%)
Unknown	0	1 (0.8%)
Total	631	119

Specimens in the tables below which were repeatedly equivocal by the comparator **Parvovirus B19** IgG test were further tested for resolution following the comparator package insert. Specimens that could not be resolved and were repeatedly equivocal with the comparator test were counted against the performance of the LIAISON® Biotrin Parvovirus B19 IgG Plus assay. Comparative data is summarized below.

LIAISON® Biotrin Parvovirus B19 IgG Plus Agreement for Pregnant Cohort

LIAISON Biotrin Parvovirus B19 IgG Plus	Comparator			Total
	Positive	Equivocal	Negative	
Positive	154	0	3	157
Negative	13	0	80[a]	93
Total	167	0	83	250

Positive Percent Agreement (PPA)	154/167	92.22%	95% CI = 87.14% - 95.40%
Negative Percent Agreement (NPA)	80/83	96.39%	95% CI = 89.90% - 98.76%

[a]One (1) specimen repeatedly equivocal by the comparator test was further tested following the comparator package insert and resulted negative

LIAISON® Biotrin Parvovirus B19 IgG Plus Agreement for Routine Laboratory Specimens

LIAISON Biotrin Parvovirus B19 IgG Plus	Comparator			Total
	Positive	Equivocal	Negative	
Positive	328[c]	0	6	334
Negative	20	1[b]	145[a]	166
Total	348	1	151	500
Positive Percent Agreement (PPA)	328/349	93.98%	95% CI = 90.98% - 96.03%	
Negative Percent Agreement (NPA)	145/151	96.03%	95% CI = 91.60% - 98.17%	

[a]One (1) specimen repeatedly equivocal by the comparator was further tested following the comparator package insert and resulted negative
[b]One (1) specimen repeatedly equivocal by the comparator was further tested following the comparator package insert and remained equivocal
[c]Four (4) specimens repeatedly equivocal by the comparator were further tested following the comparator package insert and resulted positive

14.6. Matrix Comparison

Fifty-five (55) paired sets of matched serum and plasma (lithium heparin, K_2-EDTA, and sodium citrated plasma), native and contrived, spanning the assay range, were tested to determine if these sample types provide equivalent results on the LIAISON® Biotrin Parvovirus B19 IgG Plus assay. The results obtained on the serum-plasma paired samples indicated that there is equivalence among serum, lithium heparin, K_2-EDTA, and sodium citrated plasma.

14.7. Analytical Sensitivity with Parvovirus B19 Seroconversion Panels

Eight (8) commercially available seroconversion panels were tested using the LIAISON® Biotrin Parvovirus B19 IgG Plus assay and a commercially available FDA-approved comparator assay to determine the analytical sensitivity with seroconversion panels. Each panel contained different number of serial bleeds drawn from individual patients. Each blood drawn was tested and the results are summarized in the following table:

Panel ID*	Number of Specimens (Bleeds)	LIAISON® Biotrin Parvovirus B19 IgG Plus		Comparator Test		Difference in Number of Days	Difference in number of Blood Draws
		Last Bleed Day (Draw) with Negative Results	First Bleed Day (Draw) with Positive Results	Last Bleed Day (Draw) with Negative Results	Last First Day (Draw) with Positive Results		
SCP46 Donor 0	4	4	8	8	11	-3	-1
SCP46 Donor 1	3	5	14	5	14	0	0
SCP46 Donor 3	3	0	9	0	9	0	0
SCP46 Donor 4	2	0	4	0	4	0	0
SCP46 Donor 5	3	5	7	5	7	0	0
SCP46 Donor 6	3	4	12	4	12	0	0
Access Biologicals B19V001SCP	6	7	11	7	11	0	0

* Out of the 8 panels tested, Panel SCP46 Donor 2 was excluded from the summary table since all bleeds were positive for Parvovirus B19 IgG, so seroconversion was not detected.

The sensitivity of the LIAISON® Biotrin Parvovirus B19 IgG Plus assay was comparable to the comparator assay in the seven (7) seroconversion panels tested.

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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® Biotrin Control Parvovirus B19 IgG Plus ([REF] 311551)

1. INTENDED USE

The LIAISON® Biotrin Control Parvovirus B19 IgG Plus (negative and positive) is intended for use as assayed quality control samples to monitor the performance and reliability of LIAISON® Biotrin Parvovirus B19 IgG Plus assay. The performance characteristics of LIAISON® Biotrin Control Parvovirus B19 IgG Plus have not been established for any other assays or instrument platforms different from the automated LIAISON® XL Analyzer.

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 0.7 mL)	[CONTROL|-]	Human serum non-reactive for parvovirus B19 IgG antibodies, ProClin™ 300 and preservatives.
Positive control (2 x 0.7 mL)	[CONTROL|+]	Human serum / plasma reactive for parvovirus B19 IgG antibodies, ProClin™ 300 and preservatives.

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 code gives, in the relevant area, 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.
- For Prescription Use only. **U.S. Federal Law restricts this device to sale by or on the order of licensed practitioner**.
- Controls are not kit lot specific and may be safely interchanged with different LIAISON® Biotrin Parvovirus B19 IgG Plus 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.
- The LIAISON® XL analyzers 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.
- Visually inspect the vials for leakage. If the vials are found to be leaking, the local customer service should be notified immediately.

Reagents Containing Human Source Material:

Warning - Treat as potentially infectious. Each serum/plasma donor unit used in the preparation of this product has been tested by an U.S. FDA approved method and found non-reactive for the presence of the antibody to Human Immunodeficiency Virus 1 and 2 (HIV 1/2), the Hepatitis B surface antigen (HBsAg), and the antibody to Hepatitis C (HCV). While these methods are highly accurate, they do not guarantee that all infected units will be detected. This product may also contain other human source diseases for which there is no approved test. Because no known test method can offer complete assurance that HIV, Hepatitis B Virus (HBV) and HCV or other infectious agents are absent, all products containing human source material should be handled following universal precautions; and as applicable in accordance with good laboratory practices as described in the Centers for Disease Control and the National Institutes of Health current manual, Biosafety in Microbiological and Biomedical Laboratories (BMBL); or the World Health Organization current edition, Laboratory Biosafety Manual.

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 labeled as follows:

REAGENTS:	[CONTROL|-], [CONTROL|+]
CLASSIFICATION:	Skin sens. 1A H317 Aquatic chronic 3 H412
SIGNAL WORD:	Warning
SYMBOLS / PICTOGRAMS:	 GHS07 Exclamation mark
HAZARD STATEMENTS:	H317 May cause an allergic skin reaction. H412 Harmful to aquatic life with long lasting effects.
PRECAUTIONARY STATEMENTS:	P261 Avoid breathing dust/fume/gas/mist/vapours/spray. P280 Wear protective gloves/protective clothing/eye protection/face protection. P273 Avoid release to the environment. P362 Take off contaminated clothing and wash 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 the 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 (12) weeks when properly stored at 2-8°C between two successive 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 vial allows at least 15 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.

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 analyzer prior to loading the control vials on board. For details, refer to the analyzer operator's manual.

7. QUALITY CONTROLS

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® Biotrin Parvovirus B19 IgG Plus controls are intended to monitor for substantial reagent failure. Whenever controls lie outside the expected ranges provided on the certificate of analysis, calibration should be repeated and controls and samples retested. If control values obtained after successful calibration lie repeatedly outside the expected ranges, the test should be repeated using an unopened control vial. Do not report patient results until control results are within expected ranges.

Strict adherence to the instructions of the LIAISON® Biotrin Control Parvovirus B19 IgG Plus are necessary to obtain reliable results.

8. LIMITATIONS

Control values for assays other than LIAISON® Biotrin Parvovirus B19 IgG Plus assay have not been established.

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