WHO Prequalification of In Vitro Diagnostics
PUBLIC REPORT

Product: Monolisa HCV Ag-Ab ULTRA V2
WHO reference number: PQDx 0229-031-00

Monolisa HCV Ag-Ab ULTRA V2 with product codes **72561 and 72562**, manufactured by **Bio-Rad**, **CE-marked regulatory version**, was accepted for the WHO list of prequalified in vitro diagnostics and was listed on 24 January 2020.

Summary of WHO Prequalification Assessment for Monolisa HCV Ag-Ab ULTRA V2

	Date	Outcome
PQ listing	24 January 2020	listed
Dossier review	N/A	MR
Site inspection of quality management system	8-10 November 2021	MR
Product performance evaluation	1st quarter of 2017	MR

MR: Meets requirements.
N/A: Not applicable.

Report amendments and/or product changes

This public report has since been amended. Amendments may have arisen because of changes to the prequalified product for which WHO has been notified and has undertaken a review. Amendments to the report are summarized in the following table, and details of each amendment are provided below.

Version	Summary of amendment	Date of report amendment
2.0	1. Packaging/Labelling updates for the Monolisa HCV Ag-Ab ULTRA V2 codes 72561-72562 are due to the IVDR Certification obtained on July 20th, 2023, according to the requirements of the new Regulation (EU) 2017/746 on In vitro Diagnostic Medical Devices and compliance with the update of the classification of the active substance of ProClin 300 in EU CLP regulation (application of UN-GHS) for effect on aquatic life. There is no change in device design, specifications, or intended use/ indications. There is no change to material, safety, or performance data.	20 August 2024.

	2. The shelf-life of the product was changed from 12 to 18 months.	

Intended use:

According to the claim of intended use purpose from Bio-Rad, "*The Monolisa HCV Ag-Ab ULTRA V2 assay is a semi-quantitative enzyme immunoassay kit for the detection of Hepatitis C Virus (HCV) core antigen and antibodies in human serum or plasma specimens. This kit can be used for the screening of blood donations and as an aid in the diagnosis of hepatitis C infection.*
The Monolisa HCV Ag-Ab ULTRA V2 assay can be used manually or on automated systems".

Assay description:

According to the claim of assay description from Bio-Rad, "*The Monolisa HCV Ag-Ab ULTRA V2 assay is a semi-quantitative enzyme immunoassay kit based on the principle of the sandwich technique for the detection of HCV antigen and the indirect technique for the detection of anti-HCV antibodies in human serum or plasma specimens.*
The solid phase is coated with:
• Purified HCV antigens: Two recombinant proteins from the non-structural region (NS3 and NS4) and a peptide from the structural region (core) of the hepatitis C virus,
• Monoclonal antibody against the core hepatitis C antigen.
The conjugates are based on the use of:
• Biotinylated monoclonal mouse antibody against the hepatitis C core. This monoclonal antibody does not react against the core peptide used in the solid phase (Conjugate 1).
• Mixture of peroxidase-labeled mouse anti-human IgG antibodies and peroxidase-labeled streptavidin (Conjugate 2).
The assay procedure is as follows:
1. Specimens, controls and Conjugate 1 are pipetted into the wells of the microplate.
• If antibodies to HCV are present, they will bind to the antigen coated on the solid phase.
• If hepatitis C core antigen is present, this antigen will be bound by the monoclonal antibodies coated on the solid phase and the biotinylated monoclonal antibodies against the core hepatitis C antigen (Conjugate 1).
2. After incubation at 37°C for 90 minutes and a washing step, Conjugate 2 containing peroxidase-labeled anti-human IgG antibodies and peroxidase-labeled streptavidin are added to each well of the microplate. If human IgG is present, having reacted with the coated antigen on the solid phase, the anti-human IgG conjugate binds to the human antibodies. The conjugated peroxidase/streptavidin binds to the biotin of conjugate 1 if an HCV core antigen is present in the specimen.
3. After 30 minutes of incubation at 37°C, the unbound enzymatic conjugate is removed by another washing step and the presence of the antigen-antibody-peroxidase complexes are detected by adding the substrate.
4. After 30 minutes of incubation at room temperature (+18 - 30°C) and once the reaction has been stopped, the spectrophotometer reading is performed at 450/620-700 nm. The

absorbance measured for a specimen allows detection of the presence or absence of HCV antibodies and/or core antigen of hepatitis C in the specimen. The colour intensity is proportional to the quantity of HCV antibodies and/or the hepatitis C core antigen bound on the solid phase."

Test kit contents:

Component	**96 tests (product code 72561)**	**480 tests (product code 72562)**
R1 MICROPLATE: 12 strips of 8 wells each, coated with monoclonal anti-capsid antibody of the VHC, purified recombinant hepatitis C antigens (NS3, NS4) and a HCV capsid peptide	1 plate	5 plates
R2 CONCENTRATED WASHING SOLUTION (20X): Tris NaCl buffer pH 7.4 Preservative: ProClin 300 (0.04%)	1 vial × 70 ml	1 vial × 235 ml
R3 NEGATIVE CONTROL: Tris HCl Buffer, containing BSA (Bovine Serum Albumin); Preservative: ProClin 300 (0.1%)	1 vial × 1 ml	1 vial × 1 ml
R4 POSITIVE CONTROL: Human serum containing antibodies to HCV, negative for HBs antigen and for anti HIV-1 and anti HIV-2 antibodies diluted in a Tris HCl buffer containing BSA, and photochemically inactivated. Preservative: ProClin 300 (0.1%)	1 vial × 1.5 ml	1 vial × 3 ml
R5a ANTIGEN POSITIVE CONTROL: Antigen positive control synthetic containing a lyophilized capsid peptide.	1 vial × *q.s. ad* 1 ml	1 vial × *q.s. ad* 1 ml
R5b ANTIGEN DILUENT: Distilled water containing a preservative: ProClin 300 (0.5 %)	1 vial × 1 ml	1 vial × 1 ml
R6 CONJUGATE 1: Mouse biotinilated monoclonal antibodies against capsid HCV antigen. Purple coloured Preservative: Sodium azide (< 0.1%), Cosmocil CQ (0.025%)	1 vial × 15 ml	2 vials × 30 ml
R7 CONJUGATE 2: Mouse antibodies directed against human IgG/peroxidase and streptavidin/peroxidase. Green colour. Preservative: ProClin 300 (0.5 %)	1 vial × 15 ml	2 vials × 30 ml

R8 SUBSTRATE BUFFER: Citric acid and sodium acetate solution, pH 4.0, containing H2O2 (0.015%) and dimethyl sulfoxide (DMSO) 4%	1 vial × 60 ml	2 vials × 60 ml
R9 CHROMOGEN - TMB SOLUTION (11X): Solution containing 3.3', 5.5' tetramethylbenzidine (TMB)	1 vial × 5 ml	2 vials × 5 ml
R10 STOPPING SOLUTION: Sulphuric acid solution (H_2SO_4 1N)	1 vial × 28 ml	3 vials × 28 ml

NOTE: The IFU is no longer included in the kits but is now only available online on the following website: www.downloads.biorad.com.

Items required but not provided:

Item
Consumables: • Distilled water • Sodium hypochlorite (household bleach) and sodium bicarbonate. • Absorbent paper • Adhesive films • Disposable gloves • Disposable tubes
Durables: • Safety glasses • Graduated cylinders of 10 ml, 200 ml and 1,000 ml
Equipment: • Calibrated automatic or semiautomatic, adjustable or preset pipettes or multipipettes to measure and dispense 50 µl, 80 µl, 100 µl, 200 µl and 1 ml • Vortex mixer • Automatic, semi-automatic or manual microplate washing system • Water-bath, or equivalent microplate incubator, thermostatically set at 37°C ± 1°C (*) • Container for biohazardous waste • Microplate reader equipped with 450, 490 nm and 620-700 nm filters (*) *(*) Consult manufacturer for detailed information about the equipment recommended by our technical department.*

Storage:
The test kit must be stored at 2-8°C.

Shelf-life upon manufacture:
18 months.

Warnings/limitations:
Please refer to the current version of the instructions for use.

Prioritization for prequalification
Based on the established eligibility criteria, Monolisa HCV Ag-Ab ULTRA V2 was given priority for WHO prequalification assessment.

Product dossier assessment

In accordance with the WHO procedure for abbreviated prequalification assessment, Bio-Rad was not required to submit a product dossier for Monolisa HCV Ag-Ab ULTRA V2 as per the "Instructions for compilation of a product dossier" (PQDx_018 v1). Notwithstanding, certain aspects of the product dossier previously submitted for stringent regulatory review were reviewed by an assessor during the site inspection.

However, a technical review of the instructions for use (IFU) was made, and it was noted that human specimens utilised as positive and negative control specimens had not been screened by state-of-the-art methods (nucleic acid detection assays). Bio-Rad is required to introduce screening using more sensitive methods to ensure that the use of the control material represents a minimum risk to users.

In addition, the results of testing for analytical sensitivity were inappropriately aggregated, giving a potentially incorrect impression of the performance of the assay. Bio-Rad has committed to providing the table below, comprised appropriately of the disaggregated data, in the next version of the instructions for use. The intended use of the product was not clearly documented in the IFU to state the clinical indication and use of the test, the testing population for which the intended use and function is for, the intended use setting and the intended users. On test limitations, to include other suitable methods for screening and diagnosis of HCV viremic infection.

Commitments for prequalification:

1. Bio-Rad to revise the IFU to include a table of results of analytical specificity, intended use statement and other methods for screening and diagnosis of HCV viraemic infection as stated above. This will be implemented in the next revision of the IFU by 31 October 2023. The commitments regarding the analytical specificity, inclusion of other screening and diagnosis methods of HCV viremic infection, and diagnostic sensitivity disaggregated by specimen type were included in the IFU version 0001350 - 2022/03. These commitments were closed. However, the intended use purpose has yet to be amended to include the clinical indication, intended use function, the testing population, the intended use setting, and the intended users. The manufacturer is required to amend the intended use purpose in the next revision of the IFU.

2. Bio-Rad to implement requirements of Technical Specification Series for submission to WHO Prequalification-8 (TSS-8)- Immunoassays to detection hepatitis C antibody and/or antigen by 24 January 2023. The submission of the gap analysis is pending.

Manufacturing site inspection

In accordance with the WHO procedure for abbreviated prequalification assessment, a shortened inspection with fewer inspectors was conducted at the site(s) of manufacture of Monolisa HCV Ag-Ab ULTRA V2 (3, bd Raymond Poincaré, 92430, Marne La Coquette, France on 4-6 April 2018 and Route de Cassel, 59114, Steenvoorde, France on 8-10 November 2021), as per the "*Information for manufacturers on prequalification inspection procedures for the sites of manufacture of diagnostics*" (PQDx_014 v4).
The inspections found that the manufacturer had an acceptable quality management system and acceptable manufacturing practices in place that ensured the consistent manufacture of a product of adequate quality.

The manufacturer's responses to the nonconformities found at the time of the inspection of the Marne La Coquette site were accepted on 9 October 2018. The manufacturer's responses to the nonconformities found at the time of the inspection of the Marne La Coquette site were accepted on 9 October 2018.

A field safety notice (FSCA 03-17 IDD) was issued and came to WHO's notice via the United Kingdom Medicines and Healthcare Products Regulatory Agency (MHRA) related to lowered optical density (OD) readings for the entire microplate, typically towards the end of the product shelf-life. The reported issue could be related to the R6 reagent (Conjugate 1 – Mouse biotinylated monoclonal antibodies against capsid HCV antigen). Bio-rad's correction was to issue certain lots with reduced shelf-life. Bio-Rad's corrective action was to implement additional controls for the selection of the IgG mouse selected in the R6 reagent used in the manufacturing process. WHO has decided that a re-inspection will be necessary to determine that the corrective action has addressed the root cause of the issue.

Based on the inspection team's review of the manufacturer's systems for the Management of Nonconformities and Corrective Actions, as well as the proposed and implemented corrective actions related to the above-referenced field safety corrective actions, the inspection team has concluded that: The manufacturer has proposed and implemented corrective actions (with the outstanding commitments noted) that could reasonably be expected to minimise the risk of the repeat of the failure that led to the above-mentioned field safety corrective action.
Based on the site inspection and corrective action plan review, the quality management system for Monolisa HCV Ag-Ab ULTRA V2 meets WHO prequalification requirements.

Product performance evaluation

Monolisa HCV Ag-Ab ULTRA V2 (Bio-Rad) was evaluated at the National Reference Laboratory, Melbourne, Australia, on behalf of WHO in the 1st quarter of 2017 using serum and plasma specimens. From this evaluation, we drew the following conclusions:

Monolisa HCV Ag-Ab ULTRA V2 (Bio-Rad) is a qualitative enzyme immunoassay for the detection of antibodies to HCV and HCV capsid antigen in human serum and plasma. A volume of 50µl of specimen is needed to perform the assay. This type of assay requires laboratory equipment and cannot be performed in laboratories with limited facilities. Reading of the results must be performed with a spectrophotometer.

In this limited performance evaluation on a panel of 483 specimens characterized using a reference algorithm (Murex anti-HCV (version 4.0) [DiaSorin South Africa Ltd.] and Monolisa anti-HCV Plus ; followed by CHIRON RIBA HCV 3.0 Strip Immunoblot Assay or MP Diagnostics HCV Blot 3.0 on initially reactive specimens), we found an initial sensitivity of 100% (95% CI: 97.1% – 99.9%) and an initial specificity of 100% (95% CI: 98.5% – 100%) compared to the reference results. In this study, 0% of the results were recorded as indeterminate. Lot to lot variation was in the acceptable range for all ten dilution panels.

For four seroconversion panels, Monolisa HCV Ag-Ab ULTRA V2 detected on average 0 specimens earlier than the benchmark assay (Murex Anti-HCV (version 4.0)). For the mixed titer panel (ref 0810-0175, SeraCare), Monolisa HCV Ag-Ab ULTRA V2 correctly classified all 16 specimens. For the low titer panel (ref 0810-0192, SeraCare), Monolisa HCV Ag-Ab ULTRA V2 correctly classified all but one of the 11 specimens.

The invalid rate in this evaluation was 0%.

Labelling

1. **Labels**
2. **Instructions for use**

1.1 MONOLISA HCV Ag-Ab ULTRA V2 96 tests - Cat# 72561 Labels

LABELS

I-BOX

1- Text printed on the box

Bio-Rad
3, Boulevard Raymond Poincaré
92430 Marnes-la-Coquette France
Tel. : +33 (0) 1 47 95 60 00
Fax : +33 (0) 1 47 41 91 33
www.bio-rad.com

2- Box labels

Monolisa HCV Ag-Ab ULTRA V2

REF **72561** Σ **96**

R1	1 x 1	Microplate	**R6**	1 x 15 ml	Conjugate 1
R2	1 x 70 ml	Concentrated washing solution (20X)*	**R7**	1 x 15 ml	Conjugate 2***
R3	1 x 1 ml	Negative control**	**R8**	1 x 60 ml	Substrate buffer
R4	1 x 1.5 ml	Positive control**	**R9**	1 x 5 ml	Chromogen: TMB solution (11X)
R5a	1 x 1 ml *q.s. ad*	Antigen positive control	**R10**	1 x 28 ml	Stopping solution†
R5b	1 x 1 ml	Antigen diluent***			

* ProClin 300 (0.04%) ** ProClin 300 (0.1%) *** ProClin 300 (0.5%) † 1N H_2SO_4

16010813

Made in France

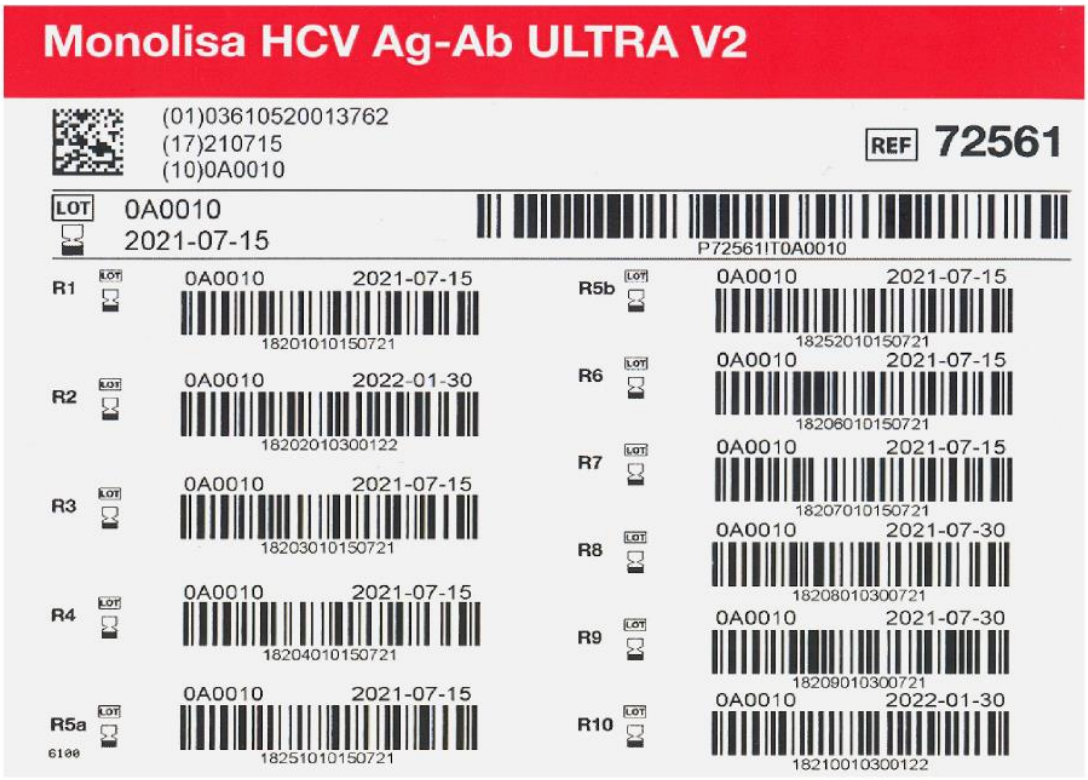
0001350
downloads.bio-rad.com
+ 800 135 79 135

IVD

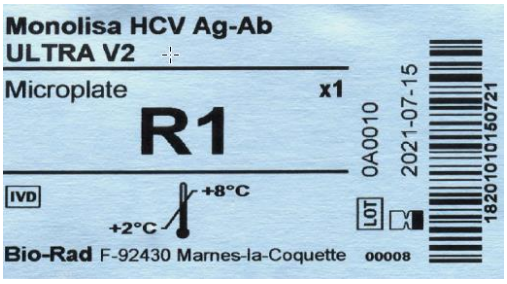
CE 0459

+2°C +8°C

H314 - H317 - H412
P280
P305+P351+P338
P303+P361+P353
P333+P313
P273 - P501

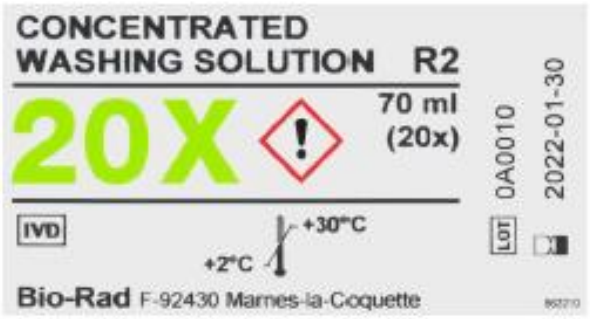


II-REAGENT LABELS




Monolisa HCV Ag-Ab
ULTRA V2
Conjugate 1 15 ml
R6
IVD
+2°C
+8°C
LOT 0A0010
2021-07-15
18206010150721
16010814
Bio-Rad F-92430 Marnes-la-Coquette


Monolisa HCV Ag-Ab
ULTRA V2
Conjugate 2 15 ml
R7
IVD
+2°C
+8°C
LOT 0A0010
2021-07-15
18207010150721
16010840
Bio-Rad F-92430 Marnes-la-Coquette


CONCENTRATED
WASHING SOLUTION R2
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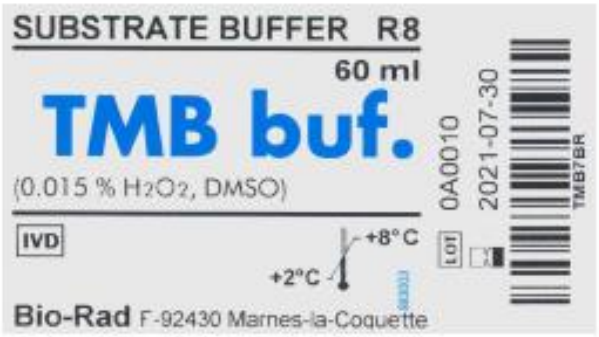
70 ml
(20x)
IVD
+2°C
+30°C
LOT 0A0010
2022-01-30
Bio-Rad F-92430 Marnes-la-Coquette


SUBSTRATE BUFFER R8
60 ml
TMB buf.
(0.015 % H2O2, DMSO)
IVD
+2°C
+8°C
LOT 0A0010
2021-07-30
TMB7BR
Bio-Rad F-92430 Marnes-la-Coquette


CHROMOGEN : TMB SOLUTION R9
5 ml
TMB 11X
IVD
+2°C
+8°C
LOT 0A0010
2021-07-30
Bio-Rad F-92430 Marnes-la-Coquette


STOPPING SOLUTION R10
28 ml
1N
(H2SO4 1N)
IVD
+2°C
+8°C
LOT 0A0010
2022-01-30
STP1BR
Bio-Rad F-92430 Marnes-la-Coquette

1.2 MONOLISA HCV Ag-Ab ULTRA V2 480 tests - Cat# 72562 Labels

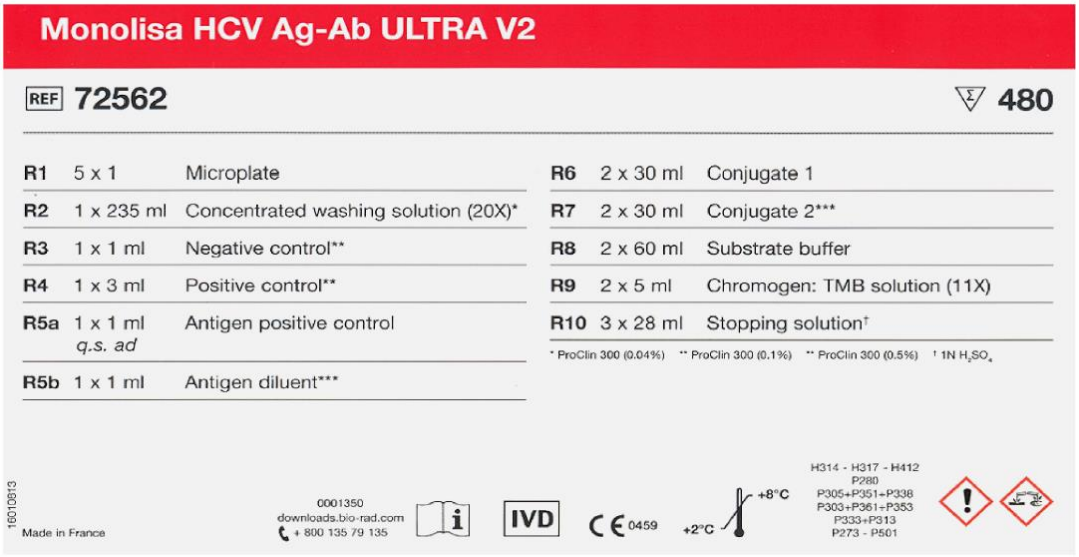
LABELS

I-BOX

1- Text printed on the box

Bio-Rad
3, Boulevard Raymond Poincaré
92430 Marnes-la-Coquette France
Tel. : +33 (0) 1 47 95 60 00
Fax : +33 (0) 1 47 41 91 33

2. Box Labels



Monolisa HCV Ag-Ab ULTRA V2

REF **72562** Σ **480**

R1	5 x 1	Microplate	**R6**	2 x 30 ml	Conjugate 1
R2	1 x 235 ml	Concentrated washing solution (20X)*	**R7**	2 x 30 ml	Conjugate 2***
R3	1 x 1 ml	Negative control**	**R8**	2 x 60 ml	Substrate buffer
R4	1 x 3 ml	Positive control**	**R9**	2 x 5 ml	Chromogen: TMB solution (11X)
R5a	1 x 1 ml *q.s. ad*	Antigen positive control	**R10**	3 x 28 ml	Stopping solution†
R5b	1 x 1 ml	Antigen diluent***			

* ProClin 300 (0.04%) ** ProClin 300 (0.1%) *** ProClin 300 (0.5%) † 1N H_2SO_4

1601013

Made in France

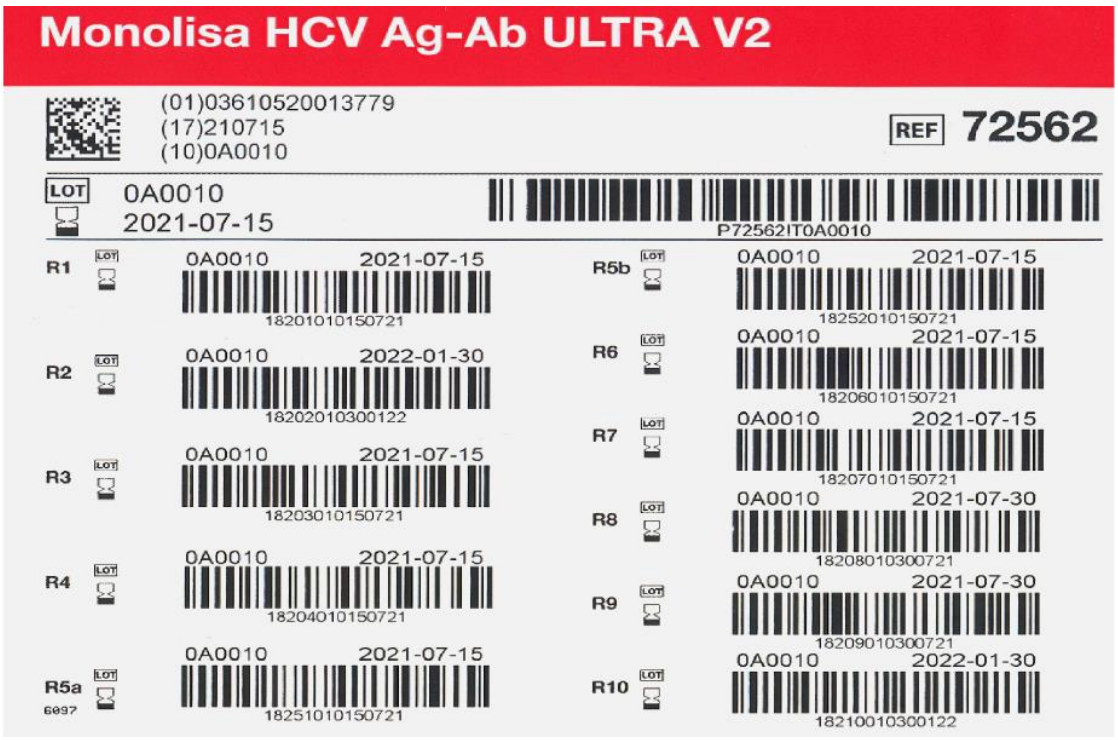
0001350
downloads.bio-rad.com
+ 800 135 79 135

IVD

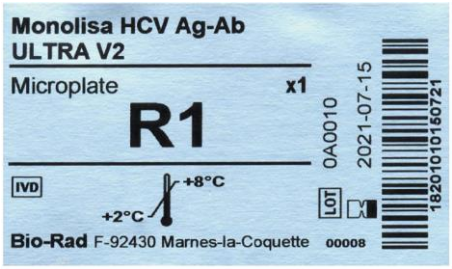
CE 0459

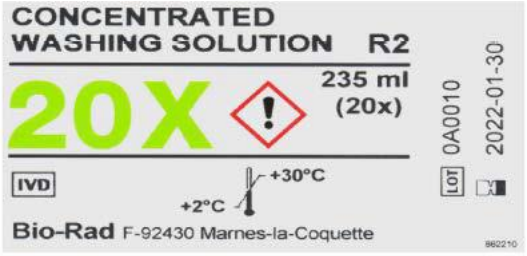
+2°C +8°C

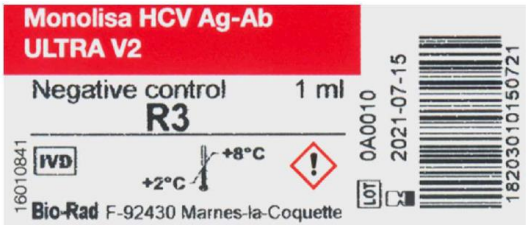
H314 - H317 - H412
P280
P305+P351+P338
P303+P361+P353
P333+P313
P273 - P501



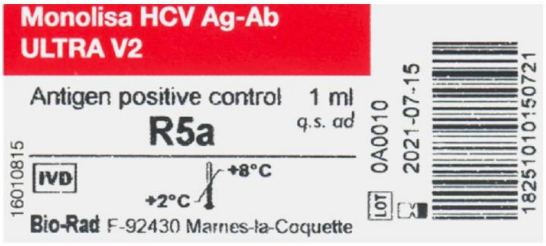
II- REAGENT LABELS

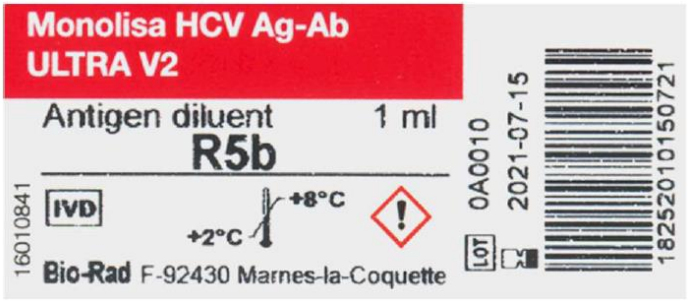


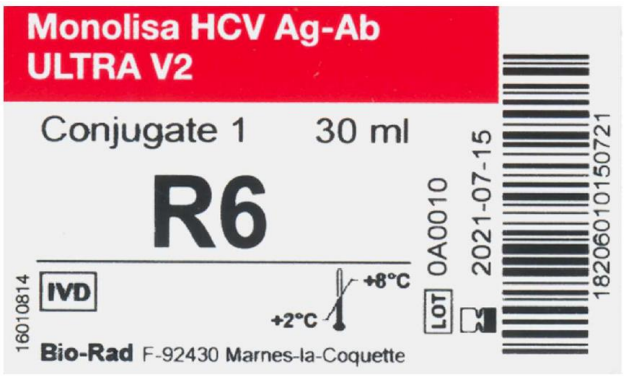


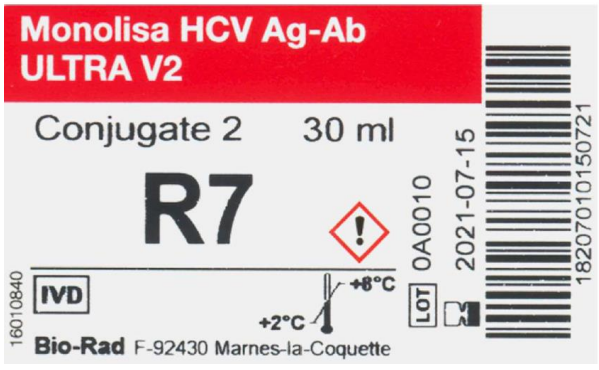



Monolisa HCV Ag-Ab
ULTRA V2
Positive control 3 ml
R4
IVD
+2°C
+8°C
Bio-Rad F-92430 Marnes-la-Coquette
16010841
LOT
0A0010
2021-07-15
18204010150721

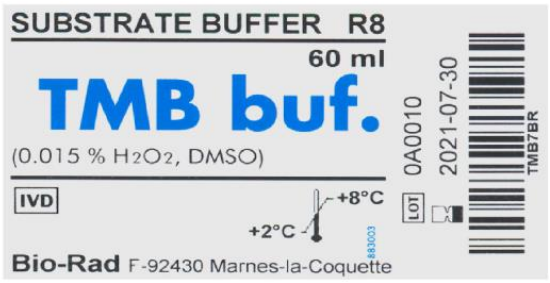

Monolisa HCV Ag-Ab
ULTRA V2
Antigen positive control 1 ml
q.s. ad
R5a
IVD
+2°C
+8°C
Bio-Rad F-92430 Marnes-la-Coquette
16010815
LOT
0A0010
2021-07-15
18251010150721


Monolisa HCV Ag-Ab
ULTRA V2
Antigen diluent 1 ml
R5b
IVD
+2°C
+8°C
Bio-Rad F-92430 Marnes-la-Coquette
16010841
LOT
0A0010
2021-07-15
18252010150721


Monolisa HCV Ag-Ab
ULTRA V2
Conjugate 1 30 ml
R6
IVD
+2°C
+8°C
Bio-Rad F-92430 Marnes-la-Coquette
16010814
LOT
0A0010
2021-07-15
18206010150721


Monolisa HCV Ag-Ab
ULTRA V2
Conjugate 2 30 ml
R7
IVD
+2°C
+8°C
Bio-Rad F-92430 Marnes-la-Coquette
16010840
LOT
0A0010
2021-07-15
18207010150721


CHROMOGEN : TMB SOLUTION R9
5 ml
TMB 11X
IVD
+8°C
+2°C
Bio-Rad F-92430 Marnes-la-Coquette
LOT
0A0010
2021-07-30
862213


SUBSTRATE BUFFER R8
60 ml
TMB buf.
(0.015 % H2O2, DMSO)
IVD
+8°C
+2°C
Bio-Rad F-92430 Marnes-la-Coquette
LOT
0A0010
2021-07-30
TMB7BR


STOPPING SOLUTION R10
28 ml
1N
(H2SO4 1N)
IVD
+8°C
+2°C
Bio-Rad F-92430 Marnes-la-Coquette
LOT
0A0010
2022-01-30
STP1BR
862211

2. Instructions for use[1]

[1] English version of the IFU was the one that was assessed by WHO. It is the responsibility of the manufacturer to ensure correct translation into other languages.

Monolisa HCV Ag-Ab ULTRA V2

1 plate - ∑ 96 REF 72561

5 plates - ∑ 480 REF 72562

SEMI-QUANTITATIVE ENZYME IMMUNOASSAY KIT FOR THE DETECTION OF THE HEPATITIS C ANTIGEN AND ANTIBODIES IN HUMAN SERUM OR PLASMA SPECIMENS

IVD CE 0459

0001350 - 2022/03

IFU compliant with Regulation (EU) 2017/746.

Major changes to the previous version are shaded gray. A gray title indicates significant changes in the content of the chapter. Please read carefully.

For the European Union (Regulation 2017/746/EU), the Summary of Safety and Performances of this device is available via EUDAMED public access https://ec.europa.eu/tools/eudamed.

BIO-RAD

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1 INTENDED USE

The Monolisa HCV Ag-Ab ULTRA V2 assay is a semi-quantitative enzyme immunoassay kit for the detection of Hepatitis C Virus (HCV) core antigen and antibodies in human serum or plasma specimens. This kit can be used for the screening of blood donations and as an aid in the diagnosis of hepatitis C infection.

The Monolisa HCV Ag-Ab ULTRA V2 assay can be used manually or on automated systems.

2 SUMMARY AND EXPLANATION OF THE TEST

The Hepatitis C Virus (HCV) is an enveloped RNA positive-sense virus (9.5 kb) belonging to the Flaviviridae family, of which seven major genotypes were identified. HCV is recognized as being the main cause of non-A and non-B viral hepatitis[1;2;3].

The disease severity is variable and can range from a mild illness for a few weeks (acute HCV) to a chronic and life-long serious illness, which can progress to cirrhosis or liver cancer. Although still expensive, efficient treatments exist thought and can cure it. No vaccine exists[4].

In 2021, WHO estimated that globally, 58 million people were living with chronic hepatitis C, with about 1.5 million new infections per year[5].

The hepatitis C virus is a bloodborne virus and most infection occur through exposure to blood from unsafe injection practices, unsafe health care, unscreened blood transfusions, injection drug use and sexual practices that lead to exposure to blood[6].

Evidence of HCV infection can be obtained through testing to screen for HCV antigens and/or antibodies in serum or plasma specimen and/or RNA[7;8]. In comparison to assays screening for anti-HCV antibodies alone, the use of a combined screening assay for both anti-HCV antibodies and the HCV core antigen can reduce the serological window period and improve detection of the infection[9;10;11;12;13].

3 PRINCIPLES OF THE PROCEDURE

The Monolisa HCV Ag-Ab ULTRA V2 assay is a semi-quantitative enzyme immunoassay kit based on the principle of the sandwich technique for the detection of HCV antigen and the indirect technique for the detection of anti-HCV antibodies in human serum or plasma specimens.

The solid phase is coated with:

- Purified HCV antigens: Two recombinant proteins from the non-structural region (NS3 and NS4) and a peptide from the structural region (core) of the hepatitis C virus,
- Monoclonal antibody against the core hepatitis C antigen.

The conjugates are based on the use of:

- Biotinylated monoclonal mouse antibody against the hepatitis C core. This monoclonal antibody does not react against the core peptide used in the solid phase (Conjugate 1).
- Mixture of peroxidase-labeled mouse anti-human IgG antibodies and peroxidase-labeled streptavidin (Conjugate 2).

The assay procedure is as follows:

1. Specimens, controls and Conjugate 1 are pipetted into the wells of the microplate.
    - If antibodies to HCV are present, they will bind to the antigen coated on the solid phase.
    - If hepatitis C core antigen is present, this antigen will be bound by the monoclonal antibodies coated on the solid phase and the biotinylated monoclonal antibodies against the core hepatitis C antigen (Conjugate 1).
2. After incubation at 37°C for 90 minutes and a washing step, Conjugate 2 containing peroxidase-labeled anti-human IgG antibodies and peroxidase-labeled streptavidin are added to each well of the microplate. If human IgG is present, having reacted with the coated antigen on the solid phase, the anti-human IgG conjugate binds to the human antibodies. The conjugated peroxidase/streptavidin binds to the biotin of conjugate 1 if a HCV core antigen is present in the specimen.

3. After 30 minutes of incubation at 37°C, the unbound enzymatic conjugate is removed by another washing step and the presence of the antigen-antibody-peroxidase complexes are detected by adding the substrate.
4. After 30 minutes of incubation at room temperature (+18 - 30°C) and once the reaction has been stopped, the spectrophotometer reading is performed at 450/620-700 nm. The absorbance measured for a specimen allows detection of the presence or absence of HCV antibodies and/or core antigen of hepatitis C in the specimen. The colour intensity is proportional to the quantity of HCV antibodies and/or the hepatitis C core antigen bound on the solid phase.

4 REAGENTS

4.1 Description

Identification on label		Description	Presentation/Preparation	
			72561	72562
R1	**Microplate**	**Microplate** 12 strips of 8 wells coated with monoclonal anti-core antibody of the HCV, purified recombinant hepatitis C antigens (NS3, NS4) and a HCV core peptide. *Specific ID number = 93*	1 plate **Ready to use**	5 plates **Ready to use**
R2	**Concentrated Washing Solution (20X)**	**Concentrated washing solution (20X)** Tris NaCl Buffer pH 7.4 Preservative: ProClin 300 - 0.04%	1 vial 70 mL **To be diluted**	1 vial 235 mL **To be diluted**
R3	**Negative control**	**Negative control** Tris HCl Buffer, containing BSA (Bovine Serum Albumin) Preservative: ProClin 300 - 0.1%	1 vial 1 mL **Ready to use**	1 vial 1 mL **Ready to use**
R4	**Positive control**	**Positive control** Human serum containing antibodies to HCV, negative for HBs antigen and for anti HIV-1 and anti HIV-2 antibodies, diluted in a Tris HCl buffer containing BSA, and photochemically inactivated. Preservative: ProClin 300 - 0.1%	1 vial 1.5 mL **Ready to use**	1 vial 3 mL **Ready to use**
R5a	**Antigen positive control**	**Antigen positive control** Synthetic antigen positive control containing a lyophilized core peptide.	1 vial *q.s. ad* 1 mL **To be reconstituted**	1 vial *q.s. ad* 1 mL **To be reconstituted**
R5b	**Diluent of R5a**	**Diluent of R5a** Distilled water containing a preservative: ProClin 300 - 0.5 %	1 vial 1 mL **To be reconstituted**	1 vial 1 mL **To be reconstituted**
R6	**Conjugate 1**	**Conjugate 1** Mouse biotinylated monoclonal antibodies against core HCV antigen. Purple coloured. Preservative: Sodium azide - < 0.1%, Cosmocil CQ - 0.025%	1 vial 15 mL **Ready to use**	2 vials 2 x 30 mL **Ready to use**
R7	**Conjugate 2**	**Conjugate 2** Mouse antibodies directed against human IgG / peroxidase and streptavidin / peroxidase. Green coloured. Preservative: ProClin 300 - 0.5 %	1 vial 15 mL **Ready to use**	2 vials 2 x 30 mL **Ready to use**
R8	**Substrate buffer**	**Substrate buffer** Citric acid and sodium acetate solution pH 4.0, containing H_2O_2 (0.015%) and dimethyl sulfoxide DMSO (4%)	1 vial 60 mL **To be reconstituted**	2 vials 2 x 60 mL **To be reconstituted**
R9	**Chromogen: TMB solution (11X)**	**Chromogen: TMB solution (11X)** Solution containing 3.3', 5.5' tetramethylbenzidine (TMB)	1 vial 5 mL **To be diluted**	2 vials 2 x 5 mL **To be diluted**
R10	**Stopping solution**	**Stopping solution** Sulphuric acid solution (H_2SO_4 1N)	1 vial 28 mL **Ready to use**	3 vials 3 x 28 mL **Ready to use**

4.2 Storage and handling requirements

This kit must be stored at +2-8°C.
Reagents can be used until the expiry date shown on the package even after being opened (unless otherwise instructed).

After opening, uncontaminated R2, R3, R4, R6, R7, R8, R9 and R10 reagents stored at +2-8°C can be used up to the expiry date shown on the label.

Identification	Conservation
R1	After opening the vacuum-sealed pouch, store the microwell strips at +2-8°C for up to 30 days in their original pouch with desiccant and resealed with tape.
R2	The diluted washing solution can be stored at +2-30°C for 2 weeks. The concentrated washing solution (R2) can be stored at +2-30°C until the expiry date, even once opened.
R5a + R5b	After reconstitution, the working antigen positive control solution (R5a + R5b) can be stored for 1 month at +2-8°C and 2 months at -20°C (up to 5 freezing/thawing cycles after freezing at -20°C).
R8 + R9	After reconstitution, the reagent stored in the dark can be used within 6 hours at room temperature (+18-30°C).

5 WARNING AND PRECAUTIONS

For *in vitro* diagnostic use.

Device for professional users in a laboratory environment only.

For a patient/user/third party in the European Union and in countries with identical regulatory regimes (Regulation 2017/746/EU on In vitro Diagnostic Medical Devices); if, during the use of this device or as a result of its use, a serious incident occurs, please report it to the manufacturer and to your national Competent Authority.

5.1 Health and safety precautions

- This test kit should be handled only by qualified personnel trained in laboratory procedures and familiar with the potential hazards. Wear appropriate protective clothing, gloves and eye/face protection and handle appropriately in accordance with Good Laboratory Practices.

- The test kit contains human blood components. No known test method can offer complete assurance that infectious agents are absent. Therefore, all human blood derivatives, reagents and human specimens should be handled as if capable of transmitting infectious disease, following the recommended Universal Precautions for bloodborne pathogens as defined by local, regional and national regulations.

- Biological spills: Human source material spills should be treated as potentially infectious.
  Spills not containing acid should be immediately decontaminated, including the spill area, materials and any contaminated surfaces or equipment, with an appropriate chemical disinfectant that is effective for the potential biohazards (commonly a 1:10 dilution of household bleach, 70-80% Ethanol or Isopropanol, an iodophor (such as 0.5% Wescodyne Plus, etc.), and wiped dry.
  Spills containing acid should be appropriately absorbed (wiped up) or neutralized, the area flushed with water and wiped dry. Materials used to absorb the spill may require biohazardous waste disposal. The area should be decontaminated with chemical disinfectants.

NOTE: Do not place solutions containing bleach into the autoclave!

- Dispose of all specimens and materials used to perform the test as though they contain an infectious agent. Laboratory, chemical, or biohazardous wastes must be handled and discarded in accordance with all local, regional, and national regulations.

- For hazard and precautionary statements in this test kit, please refer to the H and P codes on the labels and the information provided at the end of this instruction for use. The Safety Data Sheet is available on www.bio-rad.com.

- This product contains trace amounts of a component which is identified as a substance causing sensitisation but does not require labeling as hazardous.

- This product contains trace amounts of a component which is identified as endocrine disruptor but does not require labeling as hazardous.

5.2 Precautions related to the procedure

5.2.1 Preparing

The reliability of the results depends on the correct implementation of the following Good Laboratory Practices:

- Do not use the kit if the packaging of any component is damaged.
- Do not use expired reagents.
- Before use, wait for 30 minutes for the reagents to stabilize at room temperature (+18-30°C).
- Carefully reconstitute the reagents, avoiding any contamination.
- The use of disposable material is preferred. If using glassware, wash thoroughly and rinse with deionized water.
- Do not mix or use reagents from different lots within a test run.
- Do not allow the microplate to dry between the end of the washing process and reagent dispense.
- The name of the assay and a specific identification number for the test are printed on the frame of each microplate. This specific identification number is also stated on each strip.

  Monolisa HCV Ag-Ab ULTRA V2: Specific ID number = 93

- Verify the specific identification number before use. If the identification number is missing, or different from the stated number corresponding to the assay to be tested, the strip should not be used.

REMARK: For the washing solution (R2, label identification: 20X coloured green), peroxidase substrate buffer (R8, label identification: TMB buffer, coloured blue), chromogen (R9, label identification: TMB 11X coloured purple) and stopping solution (R10, label identification: 1N coloured red), it is possible to use other lots than those contained in the kit, provided the same lot is used within a given test run. These reagents can be used with some of our company's other products. Contact our technical service for detailed information.

- The development solution or the conjugate working solution must be prepared in a clean plastic or glass container. Single-use plastic containers are recommended. When using reusable plastic containers, they can be cleaned by soaking overnight in distilled water or washing solution. When using glass containers, they can be washed with 1N HCl and rinsed thoroughly with distilled water and dried.
- The development solution must be stored in the dark.
- The enzyme reaction is very sensitive to metal ions. Consequently, do not allow any metal element to come into contact with the various conjugate or substrate solutions.
- The development solution (R8 Substrate buffer + R9 Chromogen TMB solution (11X)) must be coloured pink. If this pink colour changes within a few minutes of reconstitution, this indicates that the reagent cannot be used and must be replaced.
- Never use the same container to dilute conjugate and development solution.

5.2.2 Processing

Adherence to the instructions for use is necessary to ensure proper performance of this product.

- Do not change the assay procedure.
- Each run of this assay must proceed to completion without interruption after it has been started. A delay shorter than 5 minutes between two steps is acceptable.

- Check the pipettes and other equipment for accuracy and correct operation.
- Never use the same container to dispense conjugate and development solutions.
- Do not carry out the test in the presence of reactive vapours (acid, alkaline, aldehyde vapors) or dust that could alter the enzymatic activity of the conjugate.
- Use a new dispense tip for each specimen.
- Well washing is a critical step in this procedure: follow the recommended number of washing cycles and make sure that all wells are completely filled and completely emptied. Incorrect washing may lead to inaccurate results.
- Carefully follow the washing procedures described to obtain optimum test performance. With some instruments, it may be necessary to optimize the washing procedure (increase the number of wash steps and/or volume of wash buffer for each cycle) to obtain an acceptable level of background for the negative specimen.
- The spectrophotometric verification of specimen or reagent dispense only shows the presence of specimen or reagent in the wells. The use of this verification does not exclude compliance with Good Laboratory Pppractices.
- The spectrophotometric verification of specimen or reagent dispense does not allow the accuracy of the dispensed volumes to be verified. The rate of wrong answers with this method is closely linked to the accuracy of the system used (a cumulated coefficient of variation of dispensing and reading greater than 10% significantly decreases the quality of the verification).
- Contact your local sales representative for adaptations and special procedures.

6 SPECIMENS

Collect a blood specimen according to current practices.

The test should be performed on native undiluted serum or plasma collected on EDTA, Sodium citrate or ACD-based anticoagulants.

Testing on plasma specimens collected on lithium heparin as anticoagulant is not recommended. A lower signal was observed on HCV antigen positive specimens when this anticoagulant was used.

Separate the serum or plasma from the clot or red cells as soon as possible to avoid any hemolysis. Extensive hemolysis may affect test performance. Specimens containing aggregates must be clarified by centrifugation prior to testing. Suspended fibrin particles or aggregates may yield false-positive results.

Specimens containing up to 120 g/L albumin, 3600 ng/mL biotin and 200 mg/L bilirubin, lipemic specimens containing up to the equivalent of 33 g/L triolein (triglyceride), and hemolyzed specimens containing up to 2 g/L hemoglobin do not affect the results. However, using hyperlipemic or hyperhemolyzed serum or plasma specimens is not recommended.

The specimens can be stored at +2-8°C if screening is performed within 7 days of collection, or they may be stored at -20°C for several months. Do not repeat more than 3 freeze/thaw cycles. The specimens must be thawed at room temperature (+18-30°C). Homogenizing specimens by inverting before use is recommended.

Heating specimens is not recommended because this could significantly reduce detection of the HCV antigen.

If specimens are shipped, pack them in accordance with regulations for the transportation of etiological agents, preferably frozen.

7 PROCEDURE

7.1 Materials required but not provided

- Distilled water
- Sodium hypochlorite (household bleach) and sodium bicarbonate
- Absorbent paper
- Disposable gloves
- Adhesive film
- Safety glasses

- Disposable tubes
- Automatic or semiautomatic, adjustable or preset pipettes or multichannel pipettes to measure and dispense 50 µL, 80 µL, 100 µL, 200 µL and 1 mL
- Graduated cylinders of 10 mL, 200 mL and 1,000 mL capacity
- Vortex mixer
- Automatic (EVOLIS or EVOLIS *Twin Plus* Bio-Rad systems*) or semi-automatic processor
- Manual microplate washer
- Water-bath, or equivalent microplate incubator, thermostatically set at +37°C ± 1°C*
- Microplate reader equipped with 450 nm, 490 nm and 620-700 nm filters*
- Container for biohazardous waste
- Clean plastic or glass containers for preparation of the development solution

(*) Consult your local Bio-Rad representative for detailed information about the equipment recommended by our technical department.

7.2 Reagent preparation

7.2.1 Ready-to-use reagents

Reagent 1 (R1): Microplate
Each support frame containing 12 strips is packed in a sealed pouch. Cut the pouch using scissors 0.5 to 1 cm above the seal. Open the bag and take out the frame. Put the unused strips back into the pouch with desiccant. Close the pouch carefully and put it back into storage at +2-8°C.

Reagent 3 (R3): Negative control

Reagent 4 (R4): Positive control

Reagent 6 (R6): Conjugate 1
Homogenize by inverting before use.

Reagent 7 (R7): Conjugate 2
Homogenize by inverting before use.

Reagent 10 (R10): Stopping solution

7.2.2 Reagents to reconstitute

Reagent 2 (R2): Concentrated washing solution (20X)

- Dilute 1:20 in distilled water to obtain the ready-to-use washing solution.
- Prepare 800 mL for one plate of 12 strips.
- Store the diluted washing solution at +2-30°C for a maximum of 2 weeks.

Reagent 5a (R5a) + Reagent 5b (R5b): Working positive control antigen solution

- Pour the content of the R5b diluent in the lyophilized Ag R5a vial. Recap the vial and let it stand for 10 minutes at room temperature (+18-30°C) shaking and inverting the vial from time to time to enhance dissolution.

Reagent 8 (R8) + Reagent 9 (R9): Enzyme development solution

- Dilute the chromogen (R9) 1:11 in the Substrate buffer (R8) (e.g. 1 mL reagent R9 + 10 mL of R8 reagent).
- 10 mL are necessary and sufficient to treat 12 strips. Homogenize.
- Store the development solution in the dark at room temperature (+18-30°C) for a maximum of 6 hours.

7.3 Assay procedure

Strictly follow the procedure and Good Laboratory Practice.

Use the negative (R3), positive (R4) and working positive antigen solution (R5a +R5b) controls for each series of tests in order to validate the test quality.

1. Carefully define the specimen dispense and identification plan.

2. Prepare the diluted washing solution (R2) and the working positive control antigen solution (R5a + R5b) (refer to *§* 7.2.2).

3. Take the support frame and the necessary number of strips (R1) out of the protective pouch. Put the unused strips back in the pouch with desiccant. Close the pouch with tape and put it back into storage at +2-8°C.

4. Dispense in the following order without prior washing of the plate:
   - 100 µL of conjugate 1 (R6) in each well then
   - 50 µL of negative control (R3) in well A1,
   - 50 µL of positive control (R4) in wells B1, C1, D1,
   - 50 µL of the working positive control antigen solution (R5a + R5b) in well E1,
   - 50 µL of the first specimen in well F1,
   - 50 µL of the second specimen in G1, etc.

   Homogenize the mixture with at least 3 aspirations or with a microplate shaker for 5 seconds. If the specimen dispense takes over 10 minutes, it is recommended to dispense the negative and positive controls after the specimens.

   Depending on the system used, the position of controls or the dispense sequence may be modified.

REMARK: *After the specimen dispense, the wells containing specimens (or controls) turns from purple to blue. It is possible to verify the presence of the (specimens + conjugate 1) in the wells by spectrophotometric reading at 620 nm (refer to § 7.7).*

5. When possible (if a manual procedure is used), cover the microplate with new adhesive film.

6. Incubate the microplate for 90 minutes (± 5 min) at +37°C ± 1°C.

7. If a manual procedure is used, remove the adhesive film. Aspirate the contents of all wells into a container for biohazardous waste (containing sodium hypochlorite). Add a minimum of 370 µL of washing solution to each well. Aspirate again. Repeat this procedure a minimum of five times. The residual volume must be less than 10 µL (if necessary, dry the plate by turning it upside down on absorbent paper). If an automatic washer is used, consult your local Bio-Rad representative for detailed information.

8. Quickly dispense 100 µL of conjugate 2 (R7) into each plate well.

REMARK: The conjugate is coloured green. It is possible to verify the presence of conjugate in the wells by spectrophotometric reading at 620 nm (refer to § 7.7).

9. When possible (if a manual procedure is used), cover the microplate with new adhesive film.

10. Incubate the microplate for 30 minutes (± 5 min) at +37°C ± 1°C.

11. If a manual procedure is used, remove the adhesive film. Aspirate the contents of all wells into a container for biohazardous waste (containing sodium hypochlorite). Add a minimum of 370 µL of washing solution to each well. Aspirate again. Repeat this procedure a minimum of five times. The residual volume must be less than 10 µL (if necessary, dry the plate by turning it upside down on absorbent paper). If an automatic washer is used, consult your local Bio-Rad representative for detailed information.

12. Prepare the enzymatic development solution (reagents R8 + R9).

13. Quickly dispense 80 µL of the prepared enzymatic development solution (R8 + R9) into all wells. Allow the reaction to develop in the dark for 30 minutes (± 5 min) at room temperature (+18-30°C). Do not use adhesive film during this incubation.

REMARK: The dispense of the development solution, which is coloured pink, can be visually checked. There is a clear difference in colour between an empty well and a well containing the pink substrate solution (refer to § 7.7)

14. Add 100 µL of stopping solution (R10) using the same sequence and rate of dispense as for the development solution.

REMARK: The dispense of the colourless stopping solution can be visually checked at this stage. The substrate coluor, pink (for negative specimens) or blue (for positive specimens), fades from the wells, which become colorless (for negative specimens) or yellow (for positive specimens) after adding the stopping solution.

15. Carefully wipe the bottom of each plate. Wait at least 4 minutes after adding the stopping solution and within 30 minutes of stopping the reaction, read the optical density at 450/620-700 nm using a plate reader.
16. Check for concordance between the spectrophotometric and visual readings and against the plate and specimen dispense and identification plan.

7.4 Quality control

Use negative (R3), positive (R4) and working positive antigen solution (R5a +R5b) controls in each series of tests in order to validate the test quality (refer to § 7.5)

7.5 Test validation criteria

This test is validated if the conditions below are met:

1) For the negative control (R3):

The measured absorbance value must be less than 60% of the cut-off value (CO):

OD (Optical Density) < CO x 0.6

2) For the antibodies positive control (R4):

0.800 ≤ Mean OD R4 ≤ 2.700

If one of the positive control R4 individual values differs by more than 30% from the mean value, disregard the value and carry out the calculation again with the two remaining positive controls.

3) For the antigen positive control solution (R5a + R5b):

OD > 0.500

7.6 Calculation / Interpretation of the results

The cut-off is determined with the positive control (R4):

Calculate the mean measured optical density (OD) value for the positive control (R4):

$$\text{Mean OD R4} = \frac{\text{OD (B1)} + \text{OD (C1)} + \text{OD (D1)}}{3}$$

Calculate the cut-off value:

$$\text{CO} = \frac{\text{Mean OD R4}}{5}$$

The presence or absence of anti-HCV antibodies and/or HCV core antigen is determined by comparing the measured absorbance for each specimen to the calculated cut-off value.

The following ratio is calculated for each specimen:

Ratio = OD of the specimen / CO value

Specimens with an optical density lower than the cut-off value (ratio < 1) are considered to be negative for the Monolisa HCV Ag-Ab ULTRA V2 assay.

Results just below the cut-off value (0.9 < ratio < 1.0) should, however, be interpreted with caution. It is advisable to retest the corresponding specimens in duplicate if the systems and laboratory procedures permit.

Specimens with an optical density greater than or equal to the cut-off value (ratio ≥ 1) are considered to be initially positive by the Monolisa HCV Ag-Ab ULTRA V2 assay. They should be retested in duplicate before final interpretation.

If, after retesting, the ratio value of at least one of the 2 duplicates is greater than or equal to 1, the initial result is repeatable and the specimen is declared positive for the Monolisa HCV Ag-Ab ULTRA V2 assay. If the ratio value of the 2 duplicates is less than 1, the initial result is non-repeatable and the specimen is declared negative.

Specimens which have been retested twice and found negative for the Monolisa HCV Ag-Ab ULTRA V2 assay but with one value close to the cut-off value (ratio between 0.9 and 1.0) should be considered with care. It is advisable to retest the patient with another method or retest another specimen.

In the case of very low optical density for tested specimens (negative OD) and when the presence of specimens as well as of reagents has been checked, the results can be interpreted as negative.

Confirming the positive specimens following the current national recommendations and algorithms is recommended.

7.7 Spectrophotometric verification of pipetting

Specimen and Conjugate 1 (R6) pipetting verification

It is possible to verify the presence of specimen + conjugate 1 (R6) in the wells by automatic reading at 620 nm. A well with specimen and conjugate 1 must have an optical density greater than 0.800.

REMARK: After specimen addition, conjugate 1 (R6) turns from purple to blue.

Conjugate 2 (R7) pipetting verification

Conjugate 2 (R7) is coloured green.

The presence of conjugate 2 (R7) in the wells can be controlled by automatic reading at 620 nm: The OD value of each well must be greater than 0.300 (a value lower than this normally indicates an incorrect dispense of the conjugate).

Development solution pipetting verification

The development solution (R8 + R9) is colored pink.

The presence of the pink development solution in the wells can be checked by automatic reading at 490 nm. A well with development solution must have an optical density greater than 0.100 (a lower OD indicates an incorrect dispense of the development solution). There is a significant colour change for the empty wells from uncoloured to pink after the addition of the development solution.

8 TEST LIMITATIONS

Due to the diverse immunological responses of patients infected by the hepatitis C virus (especially during seroconversions), some differences of detection can be observed between tests, depending on the type of antigenic proteins used. A negative result during a screening test does not therefore exclude the possibility of exposure to or infection by the hepatitis C virus.

Any ELISA technique may produce false positive reactions.

It is recommended to check the specificity of the reaction of any sample found to be a repeatable positive, according to the interpretation criteria of the Monolisa HCV Ag-Ab ULTRA V2 kit, using an ELISA anti-HCV antibody screening test or an immunoblot anti-HCV antibody detection test to confirm the presence of anti-HCV antibodies and / or quantitative / qualitative NAT for detection of HCV RNA or HCV core antigen assay to diagnose viraemic infection[14].

According to the literature, HCV carriers undergoing immunosuppression treatment or coinfected with HIV may have particularly low antibody levels, below the detection limit of the HCV tests[15;16].

The use of the Monolisa HCV Ag-Ab ULTRA V2 test is not approved for pools of specimens or diluted specimens.

Fine particles could be seen exceptionally in the conjugate 1 (R6), their presence in any case not altering the quality of the reagent.

9 PERFORMANCE CHARACTERISTICS

9.1 Analytical performance characteristics

All analytical studies were carried out at the Bio-Rad Research & Development laboratory.

9.1.1 Precision measurement

Repeatability and intermediate precision were studied for the Monolisa HCV Ag-Ab ULTRA V2 assay using a panel constituted of negative specimens, HCV antigen and anti-HCV antibody positive specimens at different amounts. This panel was tested for repeatability in 30 replicates during the same run and for intermediate precision in duplicate over a period of 20 days with 2 different runs per day.

Means, standard deviations (SD) and coefficients of variation (CV) of the ratios were calculated.

9.1.1.1 Repeatability

Table I: Repeatability results (ratio)

Panel member	Specimen ID	N	Mean ratio	SD	CV%
#1	**Negative HCV**	30	0.23	0.024	**10.4**
#2	**Low positive HCV Ag**	30	1.21	0.048	**4.0**
#3	**Low positive HCV Ag**	30	1.43	0.053	**3.7**
#4	**High positive HCV Ag**	30	7.18	0.166	**2.3**
#5	**Low positive HCV Ab**	30	1.42	0.046	**3.2**
#6	**Low positive HCV Ab**	30	1.35	0.083	**6.1**
#7	**High positive HCV Ab**	30	6.73	0.153	**2.3**

The CVs obtained on the positive specimens are less than or equal to 10%.

9.1.1.2 Intermediate precision

Table II: Intermediate precision results (ratio)

Panel member	Specimen ID	N	Mean ratio	Within-assay		Between-run/ operator		Between-day		Total Precision	
				SD	CV%	SD	CV%	SD	CV%	SD	CV%
#1	**Negative HCV**	80	0.22	0.017	**7.5**	0.028	**12.5**	0.029	**12.7**	0.043	**19.4**
#2	**Low positive HCV Ag**	80	2.80	0.143	**5.1**	0.277	**9.9**	0.283	**10.1**	0.421	**15.0**
#3	**Low positive HCV Ag**	80	1.56	0.124	**7.9**	0.129	**8.2**	0.083	**5.3**	0.197	**12.6**
#4	**High positive HCV Ag**	68**	6.69	0.500	**7.5**	0.621	**9.3**	0.557	**8.3**	0.973	**14.5**
#5	**Low positive HCV Ab**	80	1.57	0.062	**3.9**	0.125	**8.0**	0*	**N/A**	0.140	**8.9**
#6	**Low positive HCV Ab**	80	1.75	0.075	**4.3**	0.164	**9.3**	0*	**N/A**	0.181	**10.3**
#7	**High positive HCV Ab**	80	7.69	0.285	**3.7**	0.531	**6.9**	0*	**N/A**	0.603	**7.8**

** negative value for variance component was estimated at 0*
*** 3 days not tested due to lack of specimen volume*

The CVs obtained on the positive specimens are less than or equal to 15%.

9.1.2 Analytical sensitivity

The analytical sensitivity of the Monolisa HCV Ag-Ab ULTRA V2 assay was estimated using the 1st WHO International Standard for Hepatitis C Virus (HCV) core antigen - PEI code 129096/12.

The analytical sensitivity was found at 1587 IU/ml with a 95% confidence interval of [1533 – 1644 IU/mL].

9.1.3 Analytical specificity

9.1.3.1 Cross-reactivity study

365 potentially interfering specimens were tested with the Monolisa HCV Ag-Ab ULTRA V2 assay (specimens from patients positive for HIV, HTLV, HAV, HBV, CMV, HSV, VZV, EBV, Rubella, measles, mumps, toxoplasmosis, Syphilis, Chagas, Dengue, Flu influenzae, HAMA, Rheumatoïd factor, Myeloma, ANA, SMA, pregnant women, multiparous women, dialysis patients, patients with cirrhosis, patients with chronic renal failure).

Two specimens were found repeatably positive with the Monolisa HCV Ag-Ab ULTRA V2 assay (one anti-*Toxoplasma gondii* IgM and one Myeloma).

The specificity on this target population is 99.5% (363/365) with a 95% confidence interval of [98.0% - 99.9%].

Table: Reactivity of the Monolisa HCV Ag-Ab ULTRA V2 in specimens from individuals with medical conditions unrelated to HCV infection, and in specimens containing potentially interfering substances.

Conditions	N	Monolisa HCV Ag-Ab ULTRA V2		
		Non reactive	Positive IR	Positive RR
Anti-HIV antibodies (HIV-1, HIV-2)	10	10	0	0
Anti-HTLV I/II antibodies	10	10	0	0
Anti-CMV IgG antibodies	5	5	0	0
Anti-CMV IgM antibodies	**36**	**35**	**1**	**0**
Anti-EBV IgG antibodies	5	5	0	0
Anti-EBV IgM antibodies	5	5	0	0
Anti-HSV-1 IgG antibodies	5	5	0	0
Anti-HSV-1 IgM antibodies	5	5	0	0
Anti-VZV IgG antibodies	5	5	0	0
Anti-VZV IgM antibodies	5	5	0	0
Anti-Mumps IgG antibodies	5	5	0	0
Anti-Mumps IgM antibodies	5	5	0	0
Anti-Measles IgG antibodies	5	5	0	0
Anti-Measles IgM antibodies	5	5	0	0
Anti-Rubella IgG antibodies	5	5	0	0
Anti-Rubella IgM antibodies	5	5	0	0
Anti-*Toxoplasma gondii* IgG antibodies	5	5	0	0
Anti-*Toxoplasma gondii* IgM antibodies	**45**	**44**	**1**	**1**
HBs antigen (Hepatitis B)	10	10	0	0
Anti-HBs antibodies (Hepatitis B)	10	10	0	0
Anti-HAV total antibodies (Hepatitis A)	5	5	0	0
Anti-HAV IgM antibodies (Hepatitis A)	5	5	0	0
Anti-*Treponema pallidum* antibodies (Syphilis)	10	10	0	0
Anti-Dengue antibodies	10	10	0	0
Anti-Chagas antibodies	10	10	0	0
Anti-Flu influenzae antibodies	10	10	0	0
Rheumatoid factors	12	12	0	0
Anti-Mouse antibodies (HAMA)	20	20	0	0
Anti-Nuclear Antibodies (ANA)	10	10	0	0
Anti-Smooth Muscle Antibodies (SMA)	10	10	0	0
Multiparous women	10	10	0	0
Pregnant women	10	10	0	0
Patients with non-infectious cirrhosis	4	4	0	0
Myeloma	**21**	**20**	**1**	**1**
Dialysed patients	6	6	0	0
Patients with chronic renal failure	10	10	0	0
Patients with non-infectious cirrhosis	11	11	0	0
Total	**365**	**362**	**3**	**2**

9.1.4 Hook effect

3 high anti-HCV antibody positive specimens and 2 high HCV antigen positive specimens were tested neat and at different 2-fold dilutions.

Whatever the studied specimens, no negative result was observed on non-diluted specimens and no hook effect was observed during the dilution of the 5 specimens.

No hook effect is observed on the Monolisa HCV Ag-Ab ULTRA V2 assay by testing 3 high anti-HCV antibody positive and 2 high HCV antigen positive specimens.

9.2 Clinical performance characteristics

The clinical performance of the Monolisa HCV Ag-Ab ULTRA V2 assay was assessed during prospective and retrospective studies at 4 sites on specimens obtained from a population of random blood donors, hospitalized patients with acute and chronic hepatitis C virus infection and patients with clinical signs unrelated to hepatitis C virus infection.

Specificity studies on blood donor specimens were performed at two French blood banks. A specificity study on patient specimens was performed at a French hospital laboratory and sensitivity studies were assessed either at the French hospital laboratory or at the Bio-Rad site on patient specimens, seroconversion panels and positive specimens from vendors.

9.2.1 Diagnostic specificity

Specificity on non-selected blood donors:

A total of 5180 fresh specimens from blood donors collected prospectively in 2 different sites was studied. The specimens were either sera (3178) or EDTA K2 plasma (2002). All these specimens were screened with the CE-marked HCV assays used routinely for HCV antibody and HCV RNA screening.

At the 1st site, among the 2641 specimens, 3 specimens found indeterminate with the reference screening assay were discarded from calculation. On the 2638 serum specimens analyzed, 2636 were negative in first intention and 2 specimens were found repeatedly reactive positive.

The specificity RR (Repeat Reactive) on this site is 99.9% (2636/2638) with a 95% Confidence Interval of [99.7% - 100.0%].

At the 2nd site, on the 2539 specimens, 2538 were found negative in first intention and 1 specimen was found repeatedly reactive.

The specificity RR (Repeat Reactive) on this site is 99.96% (2538/2539) with a 95% Confidence Interval of [99.8% - 100.0%].

Specificity on blood donors	Site	Total Number of specimens	Negative	Initial Reactive (IR)	False Repeat Reactive (RR)	Specificity RR (%) 95% CI
Serum	Site 1	2641*	2636	2	2	**99.91% (3172/3175) [99.72% – 99.98%]**
	Site 2	537	536	1	1	
EDTA K2 plasma	Site 2	2002	2002	0	0	**100% (2002/2002) [99.82% – 100.0%]**
Total 5180 blood donors	Sites 1+2	5180*	5174	3	3	**99.94% (5174/5177) [99.83% – 99.99%]**

** 3 indeterminate specimens with reference test were withdrawn*

The total specificity (RR) on the blood donor population is equal to 99.9% (5174/5177) with a 95% confidence interval of [99.8% – 100.0%].

Specificity on hospitalized patients:

A total of 512 prospective specimens from the routine of the French hospital laboratory was tested in parallel with the Monolisa HCV Ag-Ab ULTRA V2 assay and a CE-marked anti-HCV assay.

Among them, 10 specimens found positive by both assays and confirmed positive with a third CE-marked anti-HCV assay, were discarded from the calculation.

One specimen found negative with both CE-marked anti-HCV assays, negative by PCR, was found repeat reactive with Monolisa HCV Ag-Ab ULTRA V2 assay.

The specificity on hospitalized patient specimens was 99.8% (501/502) with a 95% Confidence Interval of [98.9% – 100.0%].

9.2.2 Diagnostic sensitivity

Sensitivity on HCV positive specimens:

- At the French hospital laboratory, 300 retrospective specimens, positive for HCV RNA and genotyped were tested. All specimens were positive with the Monolisa HCV Ag-Ab ULTRA V2 assay.

- At the Bio-Rad site, 250 frozen specimens (100 specimens from patients with chronic hepatitis, 35 specimens from SFTS 1997 panel, 115 positive specimens from vendors) were tested with the Monolisa HCV Ag-Ab ULTRA V2 assay. All specimens were positive with the Monolisa HCV Ag-Ab ULTRA V2 assay.

The overall diagnostic sensitivity was 100% (575/575) with a 95% Confidence Interval of [99.4% - 100.0%].

Freshly drawn (≤ 24h) specimens (French hospital):

25 fresh positive specimens drawn less than 24 hours before testing, were tested with the Monolisa HCV Ag-Ab ULTRA V2 assay. All specimens were positive.

The sensitivity of the Monolisa HCV Ag-Ab ULTRA V2 assay on fresh specimens (≤24H) was 100% (25/25).

Sensitivity on genotyped specimens:

Among the 575 positive specimens tested, 481 specimens were genotyped representing all HCV genotypes (genotypes 1 to 6). All specimens were positive with the Monolisa HCV Ag-Ab ULTRA V2 assay.

Genotypes	***1*** *(1, 1a, 1b, 1a/b)*	***2*** *(2 2a/c, 2a, 2b, 2b/3*	***3*** *(3, 3a, 3b, 3c)*	***4*** *(4, 4a, 4a/c, 4a/c/d, 4c, 4e, 4h, 4n, 4r)*	***5*** *(5, 5a)*	***6*** *(6, 6a, 6a/b, 6n)*	***Total***
N	241	56	107	63	8	6	481

The sensitivity of the Monolisa HCV Ag-Ab ULTRA V2 assay on genotyped specimens was 100% (481/481) with a 95% confidence interval of [99.2%-100.0%].

Sensitivity on seroconversion panels:

39 seroconversion panels (10 core profiles, 10 NS3 profiles and 19 multiples profiles (Core/NS3 or NS3/NS4 or Core/NS3/NS4 or Core/NS3/NS4/NS5)) were tested with the Monolisa HCV Ag-Ab ULTRA V2 assay and compared with a CE-marked HCV Ag / Ab assay and with a CE-marked anti-HCV assay. Earliness of detection has been measured for all panels.

Among the 39 seroconversion panels, 1 on 10 “Core” panels was not detected by Monolisa HCV Ag-Ab ULTRA V2. 3 panels were not detected by the combined Ag-Ab assay and 1 panel was not detected with the anti-HCV assay.

Out of the 38 panels detected by Monolisa HCV Ag-Ab ULTRA V2, 5 had an earlier detection, 27 had an equivalent detection and 6 had a later detection compared to the HCV Ag-Ab assay. In comparison with an anti-HCV antibody test, 28 panels had an earlier detection, 9 had an equivalent detection and 1 had a later detection.

The results were found to be at the state of the art.

	Monolisa HCV Ag-Ab ULTRA V2 *versus* HCV Ag-Ab assay	**Monolisa HCV Ag-Ab ULTRA V2 *versus* Anti-HCV assay**
Number of panels	**38**	**38**
Earlier detection	5	28
Equivalent detection	27	9
Later detection	6	1

Sensitivity on HCV Ag positive specimens:

The sensitivity on HCV Ag positive specimens was performed on 42 specimens (40 specimens from 14 seroconversion panels and 2 specimens from a commercial panel) identified as HCV RNA positive and anti-HCV negative and compared to a CE marked HCV Ag -Ab assay.

Among the 42 selected specimens, 8 specimens were negative with Monolisa HCV Ag-Ab Ultra V2 and among them, 6 specimens were also negative with a CE-marked HCV Ag-Ab assay.

The 2 specimens negative with the Bio-Rad assay and positive with the other assay were re-tested with a new lot of Monolisa HCV Ag-Ab ULTRA V2. One specimen was low positive when retested.

Compared to the PCR status, the sensitivity of the Monolisa HCV Ag-Ab ULTRA V2 assay was 80.9% (34/42) with a 95% confidence interval of [65.9 %– 91.4%] or 83.3% (35/42) with a 95% confidence interval of [68.6 %– 93.0%] after retesting.

Sensitivity on genotyped specimens:

All 42 specimens analyzed for sensitivity were genotyped, covering 21 genotype 1, 12 genotype 2 and 9 genotype 3. The 8 negative specimens were 4 genotype 1, 2 genotype 2 and 2 genotype 3.

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(BG)

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Причинява тежки изгаряния на кожата и сериозно увреждане на очите. Може да причини алергична кожна реакция. Вреден за водните организми, с дълготраен ефект.
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(CZ)

Nebezpečí
Způsobuje těžké poleptání kůže a poškození očí. Může vyvolat alergickou kožní reakci. Škodlivý pro vodní organismy, s dlouhodobými účinky.
Používejte ochranné rukavice/ochranný oděv/ochranné brýle/obličejový štít. PŘI ZASAŽENÍ OČÍ: Několik minut opatrně vyplachujte vodou. Vyjměte kontaktní čočky, jsou-li nasazeny a pokud je lze vyjmout snadno. Pokračujte ve vyplachování. PŘI STYKU S KŮŽÍ (nebo s vlasy): Veškeré kontaminované části oděvu okamžitě svlékněte. Opláchněte kůži vodou/osprchujte. Při podráždění kůže nebo vyrážce: Vyhledejte lékařskou pomoc/ošetření. Zabraňte uvolnění do životního prostředí. Obsah/nádobu likvidujte v souladu s místními/regionálními/národními/mezinárodními předpisy.

(DE)

Gefahr
Verursacht schwere Verätzungen der Haut und schwere Augenschäden. Kann allergische Hautreaktionen verursachen. Schädlich für Wasserorganismen, mit langfristiger Wirkung.
Schutzhandschuhe/Schutzkleidung/Augenschutz/Gesichtsschutz tragen. BEI KONTAKT MIT DEN AUGEN: Einige Minuten lang behutsam mit Wasser spülen. Vorhandene Kontaktlinsen nach Möglichkeit entfernen. Weiter spülen. BEI KONTAKT MIT DER HAUT (oder dem Haar): Alle beschmutzten, getränkten Kleidungsstücke sofort ausziehen. Haut mit Wasser abwaschen/duschen. Bei Hautreizung oder -ausschlag: Ärztlichen Rat einholen/ärztliche Hilfe hinzuziehen. Freisetzung in die Umwelt vermeiden. Entsorgung des Inhalts / des Behälters gemäß den örtlichen / regionalen / nationalen/ internationalen Vorschriften.

(DK)

Fare
Forårsager svære forbrændinger af huden og øjenskader. Kan forårsage allergisk hudreaktion. Skadelig for vandlevende organismer, med langvarige virkninger.
Bær beskyttelseshandsker/beskyttelsestøj/øjenbeskyttelse/ansigtsbeskyttelse VED KONTAKT MED ØJNENE: Skyl forsigtigt med vand i flere minutter. Fjern eventuelle kontaktlinser, hvis dette kan gøres let. Fortsæt skylning. VED KONTAKT MED HUDEN (eller håret): Tilsmudset tøj tages straks af/fjernes. Skyl/brus huden med vand. Ved hudirritation eller udslet: Søg lægehjælp. Undgå udledning til miljøet. Bortskaffelse af indholdet/beholderen i henhold til de lokale/regionale/nationale/internationale forskrifter.

(EE)

Ettevaatust
Põhjustab rasket nahasöövitust ja silmakahjustusi. Võib põhjustada allergilist nahareaktsiooni. Ohtlik veeorganismidele, pikaajaline toime.
Kanda kaitsekindaid/kaitserõivastust/kaitseprille/kaitsemaski. SILMA SATTUMISE KORRAL: loputada mitme minuti jooksul ettevaatlikult veega. Eemaldada kontaktläätsed, kui neid kasutatakse ja kui neid on kerge eemaldada. Loputada veel kord. NAHALE (või juustele) SATTUMISE KORRAL: võtta viivitamata kõik saastunud rõivad seljast. Loputada nahka veega/loputada duši all. Nahaärrituse või _obe korral: pöörduda arsti poole. Vältida sattumist keskkonda. Sisu/konteineri käitlus vastavuses kohalike/regionaalsete/rahvuslike/rahvusvaheliste nõuetega.

(EN)

Danger
Causes severe skin burns and eye damage. May cause an allergic skin reaction. Harmful to aquatic life with long lasting effects.
Wear protective gloves/protective clothing/eye protection/face protection. IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing. IF ON SKIN (or hair): Remove/Take off immediately all contaminated clothing. Rinse skin with water/shower. If skin irritation or rash occurs: Get medical advice/attention. Avoid release to the environment. Dispose of contents/ container in accordance with local/regional/national/international regulations.

(ES)

Peligro
Provoca quemaduras graves en la piel y lesiones oculares graves. Puede provocar una reacción alérgica en la piel. Nocivo para los organismos acuáticos, con efectos nocivos duraderos.
Llevar guantes que aíslen del frío/gafas/máscara. EN CASO DE CONTACTO CON LOS OJOS: Aclarar cuidadosamente con agua durante varios minutos. Quitar las lentes de contacto, si lleva y resulta fácil. Seguir aclarando. EN CASO DE CONTACTO CON LA PIEL (o el pelo): Quitarse inmediatamente las prendas contaminadas. Aclararse la piel con agua o ducharse. En caso de irritación o erupción cutánea: Consultar a un médico. Evitar su liberación al medio ambiente. Eliminar el contenido o el recipiente conforme a la reglamentación local/regional/nacional/internacional.

(FI)

Vaara
Voimakkaasti ihoa syövyttävää ja silmiä vaurioittavaa. Voi aiheuttaa allergisen ihoreaktion. Haitallista vesieliöille, pitkäaikaisia haittavaikutuksia.
Käytä suojakäsineitä/suojavaatetusta/silmiensuojainta/kasvonsuojainta. JOS KEMIKAALIA JOUTUU SILMIIN: Huuhdo huolellisesti vedellä usean minuutin ajan. Poista piilolinssit, _edical voi tehdä helposti. Jatka huuhtomista. JOS KEMIKAALIA JOUTUU IHOLLE (tai hiuksiin): Riisu saastunut vaatetus välittömästi. Huuhdo/suihkuta iho vedellä. Jos ilmenee ihoärsytystä tai ihottumaa: Hakeudu lääkäriin. Vältettävä päästämistä ympäristöön. Säilytä säiliö(t) noudattaen paikallisia/alueellisia/kansallisia/ kansainvälisiä määräyksiä.

(FR)

Danger
Provoque des brûlures de la peau et des lésions oculaires graves. Peut provoquer une allergie cutanée. Nocif pour les organismes aquatiques, entraîne des effets néfastes à long terme.
Porter des gants de protection/des vêtements de protection/un équipement de protection des yeux/du visage. EN CAS DE CONTACT AVEC LES YEUX: rincer avec précaution à l'eau pendant plusieurs minutes. Enlever les lentilles de contact si la victime en porte et si elles peuvent être facilement enlevées. Continuer à rincer. EN CAS DE CONTACT AVEC LA PEAU (ou les cheveux): enlever immédiatement les vêtements contaminés. Rincer la peau à l'eau/se doucher. En cas d'irritation ou d'éruption cutanée: consulter un médecin. Éviter le rejet dans l'environnement. Éliminer le contenu/récipient conformément à la réglementation locale/régionale/nationale/internationale.

(GR)

Κίνδυνος
Προκαλεί σοβαρά δερματικά εγκαύματα και οφθαλμικές βλάβες. Μπορεί να προκαλέσει αλλεργική δερματική αντίδραση. Επιβλαβές για τους υδρόβιους οργανισμούς, με μακροχρόνιες επιπτώσεις.
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(HR)

Opasnost
Uzrokuje teške opekline kože i ozljede oka. Može izazvati alergijsku reakciju na koži. Štetno za vodeni okoliš s dugotrajnim učincima.
Nositi zaštitne rukavice/zaštitnu odijelo/zaštitu za oči/zaštitu za lice. U SLUČAJU DODIRA S OČIMA: oprezno ispirati vodom nekoliko minuta. Ukloniti kontaktne leće ukoliko ih nosite i ako se one lako uklanjaju. Nastaviti ispiranje. U SLUČAJU DODIRA S KOŽOM (ili kosom): odmah ukloniti/skinuti svu zaganenu odjeću. Isprati kožu vodom/ tuširanjem. U slučaju nadražaja ili osipa na koži: zatražiti savjet/pomoć liječnika. Izbjegavati ispuštanje u okoliš. Odložite sadržaje /spremnike u skladu s lokalnim/ regionalnim/nacionalni/međunarodnim odredbama.

(HU)

Veszély
Súlyos égési sérülést és szemkárosodást okoz. Allergiás bőrreakciót válthat ki. Ártalmas a vízi élővilágra, hosszan tartó károsodást okoz.
Védőkesztyű/védőruha/szemvédő/arcvédő használata kötelező. SZEMBE KERÜLÉS esetén: Több percig tartó óvatos öblítés vízzel. Adott esetben a kontaktlencsék eltávolítása, ha könnyen megoldható. Az öblítés folytatása. HA BŐRRE (vagy hajra) KERÜL: Az összes szennyezett ruhadarabot azonnal el kell távolítani/le kell vetni. A bőrt le kell öblíteni vízzel/zuhanyozás. Bőrirritáció vagy kiütések megjelenése esetén: orvosi ellátást kell kérni. Kerülni kell az anyagnak a környezetbe való kijutását. Az edény tartalmát / a tartályt a helyi/regionális/nemzeti/nemzetközi szabályozásoknak megfelelően kell hulladékként elhelyezni.

(IT)

Pericolo
Provoca gravi ustioni cutanee e gravi lesioni oculari. Può provocare una reazione allergica cutanea. Nocivo per gli organismi acquatici con effetti di lunga durata.
Indossare guanti/indumenti protettivi/Proteggere gli occhi/il viso. IN CASO DI CONTATTO CON GLI OCCHI: sciacquare accuratamente per parecchi minuti. Togliere le eventuali lenti a contatto se è agevole farlo. Continuare a sciacquare. IN CASO DI CONTATTO CON LA PELLE (o con i capelli): togliersi di dosso immediatamente tutti gli indumenti contaminati. Sciacquare la pelle/fare una doccia. In caso di irritazione o eruzione della pelle: consultare un medico. Non disperdere nell'ambiente. Smaltire il prodotto/recipiente in conformità con le disposizioni locali / regionali / nazionali / internazionali.

(LT)

Pavojinga
Smarkiai nudegina odą ir pažeidžia akis. Gali sukelti alerginę odos reakciją. Kenksminga vandens organizmams, sukelia ilgalaikius pakitimus.
Mūvėti apsaugines pirštines/dėvėti apsauginius drabužius/naudoti akių (veido) apsaugos priemones. PATEKUS Į AKIS: Kelias minutes atsargiai plauti vandeniu. Išimti kontaktinius lęšius, jeigu jie yra ir jeigu lengvai galima tai padaryti. Toliau plauti akis. PATEKUS ANT ODOS (arba plaukų): Nedelsiant nuvilkti/pašalinti visus užterštus drabužius. Odą nuplauti vandeniu/čiurkšle. Jeigu sudirginama oda arba ją išberia: kreiptis į gydytoją. Saugoti, kad nepatektų į aplinką. Turinį/talpą išpilti (išmesti) - šalinti pagal vietines / regionines / nacionalines / tarptautines taisykles.

(LV)

Briesmas
Smarkiai nudegina odą ir pažeidžia akis. Gali sukelti alerginę odos reakciją. Kenksminga vandens organizmams, sukelia ilgalaikius pakitimus.
Mūvėti apsaugines pirštines/dėvėti apsauginius drabužius/naudoti akių (veido) apsaugos priemones. PATEKUS Į AKIS: Kelias minutes atsargiai plauti vandeniu. Išimti kontaktinius lęšius, jeigu jie yra ir jeigu lengvai galima tai padaryti. Toliau plauti akis. PATEKUS ANT ODOS (arba plaukų): Nedelsiant nuvilkti/pašalinti visus užterštus drabužius. Odą nuplauti vandeniu/čiurkšle. Jeigu sudirginama oda arba ją išberia: kreiptis į gydytoją. Saugoti, kad nepatektų į aplinką. Turinį/talpą išpilti (išmesti) - šalinti pagal vietines / regionines / nacionalines / tarptautines taisykles.

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