Measurement of Ribavirin Using High-Performance Liquid Chromatography With Ultraviolet Detection (HPLC-UV) (Reference 2013.02.005)

Notice of Assessment

December 2013
1 GENERAL INFORMATION
1.1 Requestor: CHUM
1.2 Application Sent to MSSS: August 28, 2012
1.3 Application Received by INESSS: July 1, 2013
1.4 Notice Issued: October 31, 2013

Note:
This notice is based on the scientific and commercial information (submitted by the requestor[s]) and on a complementary review of the literature according to the data available at the time that this test was assessed by INESSS.

2 TECHNOLOGY, COMPANY, AND LICENCE(S)
2.1 Name of the Technology
High-performance liquid chromatography with ultraviolet detection (HPLC-UV).

2.2 Brief Description of the Technology, and Technical and Clinical Specifications
Ribavirin is a pharmacological agent used primarily for the long-term treatment of hepatitis C. Its accumulation in erythrocytes leads to hemolytic anemia. Therapeutic drug monitoring for ribavirin involves measuring ribavirin in plasma or serum. Moreover, measurements in whole blood are used in studies to validate other methods.

For the safety of laboratory personnel, pre-treatment with heat may be applied to deactivate hepatitis C virus (HCV) potentially present in the sample. Various methods may be used to extract ribavirin molecules, including solid-phase extraction on phenylboronic acid columns [Homma et al., 1999]. The purified fraction is then analyzed using HPLC.

HPLC-UV enables the separation and detection of ribavirin molecules to obtain a unique chromatographic profile. The results obtained are quantitative.
2.3 Company or Developer

The test is performed using an "in-house" method. The measurement of ribavirin is carried out using plasma or serum from the collected sample. The main steps in the protocol are the following:

- Solid-phase extraction on a phenylboronic acid cartridge (following the addition of an internal control: 3-methylcytidine):
  - addition of sample to the cartridge under alkaline conditions;
  - water-wash
  - elution of sample under acidic conditions.
- Eluate analysis using reversed-phase HPLC-UV.

Threshold values are the following:

- Therapeutic: 2.0 mcg/mL to 2.5 mcg/mL
- Toxic: > 2.5 mcg/mL.

Other authors report higher threshold values.

2.4 Licence: Not applicable.

2.5 Patent, If Any: Not applicable.

2.6 Approval Status (Health Canada, FDA)

Not applicable. The requestor uses an in-house method for the test, as well as internal quality control (group of patients).

2.7 Weighted Value: 17.9.

3 CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

3.1 Targeted Patient Group

The test is used for the therapeutic drug monitoring of ribavirin in patients with hepatitis C.

3.2 Targeted Disease(s)

Hepatitis C Virus Infection

Hepatitis C virus C (HCV) infects the liver, causing hepatitis, cirrhosis or liver cancer. This type of infection can cause death. The World Health Organization (WHO) estimates HCV prevalence at 2% to 3% of the world’s population [ASPC, 2012], which represents at least 150 million to 170 million infected people [WHO, 2013; Morello et al., 2007; Chan et al., 2009]. In 2007, the prevalence of HCV in Canada was estimated at 0.8%, with approximately 21% of cases unaware of their infection. In 2009, the prevalence was 33.7 cases per 100,000 population, based on the Canadian Notifiable Disease Surveillance System (CNDSS) [ASPC, 2012]. The majority (61%) of HCV cases in Canada are among people who inject drugs [ASPC, 2012]. Moreover, in a significant portion (at least 20%) of cases, there is coinfection with the human immunodeficiency virus (HIV) [INSPQ, 2011]. The mortality rate for viral hepatitis (all types) in 2009 was 1 per 100,000 [Statistics Canada, 2012].

1. Based on the information provided by the requestor.
In Quebec, the incidence rate for cases reported in 2011 was 17.1 per 100,000 people, or 1,356 new cases. Incidence rates dropped from 50.2 to 17.1 between 2000 and 2011, a decrease of 66% (data taken from the *Registre des maladies à déclaration obligatoire* [MADO]) [MSSS, 2013].

**Pharmacological Treatment and Adverse Effects**

Ribavirin, a synthetic guanosine nucleoside analog [Solas et al., 2011; Stanke-Labesque et al., 2009; Morello et al., 2007], is an antiviral agent with broad-spectrum activity against various DNA and RNA viruses (Loregian et al., 2007) and is used in the treatment of HCV in combination with pegylated interferon alfa [D’Avolio et al., 2012; Gandia et al., 2010]. Ribavirin can be used to treat infections caused by respiratory syncytial virus, influenza A and B viruses, and Lassa fever virus [Loregian et al., 2007]. In Quebec, ribavirin is on the list of exceptional medications covered by the public prescription drug plan (APC, 2013).

The combination of ribavirin and pegylated interferon-alfa is standard treatment for chronic HCV infections [Dominguez et al., 2012; Myers et al., 2012; Chan et al., 2009; Sauvage et al., 2009; Stanke-Labesque et al., 2009; Loregian et al., 2007; Morello et al., 2007]. Half of the patients treated with this combined therapy relapse or do not respond to treatment [Sauvage et al., 2009; Morello et al., 2007]. Indeed, its efficacy depends, among other things, on the HCV genotype [SIGN, 2013]. In patients with HCV genotype 2 or 3 infections, this dual therapy is highly effective, whereas nearly half of patients with HCV genotype 1 do not achieve a sustained virologic response [Stanke-Labesque et al., 2009]. HCV genotype 1 is the most difficult to treat and the most prevalent [Brochot et al., 2010]. The duration of treatment depends mainly on viral genotype, HIV coinfection, rapid virologic response, viral load and treatment tolerance [APC, 2013; Solas et al., 2011; Pinette et al., 2009].

Ribavirin is rapidly absorbed (maximum plasma concentration after 1 to 2 hours). It is rapidly distributed (half-life of approximately 3.7 hours) and eliminated very slowly, mainly through the kidneys. Its elimination half-life is 270 hours to 300 hours [APhC, 2013]. A steady state can be reached after approximately 3 to 4 weeks of treatment [Solas et al., 2011; Sauvage et al. 2009] or after a much longer period [Dominguez et al., 2012]. Ribavirin has high inter-individual pharmacokinetic variability but low intra-individual variability [APhC, 2013; Sauvage et al., 2009; Brochot et al., 2010; Stanke-Labesque et al., 2009].

One of the most common side effects associated with ribavirin use is reversible hemolytic anemia, which is caused by the accumulation of ribavirin in erythrocytes [Brochot et al., 2010; Sauvage et al., 2009; Stanke-Labesque et al., 2009; Loregian et al., 2007; Morello et al., 2007; Homma et al., 1999]. Indeed, once it has entered erythrocytes, ribavirin is converted into phosphorylated metabolites by intracellular phosphorylation. These metabolites decrease intracellular ATP (adenosine triphosphate) levels, resulting in the reduction of erythrocyte integrity, which may be followed by hemolysis [D’Avolio et al., 2012; Solas et al., 2011; Stanke-Labesque et al., 2009; Homma et al., 1999].

**Relevance of Therapeutic Drug Monitoring**

The concentration of ribavirin required for therapeutic efficacy overlaps the toxic concentration threshold and poses a risk of severe anemia. Therefore, the therapeutic range of ribavirin is very narrow [Solas et al., 2011]. Given its high inter-individual pharmacokinetic variability and its low intra-individual variability, as well as the existing correlation between drug concentration and efficacy or

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2. Ribavirin may be administered in combination with interferon alfa (pegylated or non-pegylated) or in triple therapy with boceprevir or telaprevir in the treatment of hepatitis C. Ribavirin monotherapy is not effective [APhC, 2013].

3. A sustained virologic response is defined as maintaining undetectable viral load 24 weeks (6 months) after discontinuation of treatment [Dominguez et al., 2012; Solas et al., 2011].

4. Elimination half-life for repeated doses. For a single dose, the elimination half-life is 44 hours to 49 hours.
toxicity, ribavirin would be a good candidate for therapeutic drug monitoring [Gandia et al., 2010]. However, this correlation was demonstrated in only one study, and a Canadian review cites contradictory data regarding the correlation [Chan et al., 2009].

3.3 Number of Patients Targeted
The requestor foresees approximately 2,000 to 2,200 tests per year.

Over the past five years, the number of patients with chronic hepatitis C treated with ribavirin has remained relatively stable in Quebec, averaging approximately 780 individuals\(^5\) per year (data from the RAMQ).

3.4 Medical Specialties Involved
Medical biochemistry, hematology, hepatology, gastroenterology, and infectious disease.

3.5 Testing Procedure
Blood samples should be collected according to the usual procedures for this type of sampling. Differences in the methods and duration of sample storage were noted between the information provided by the requestor and that found in the literature.

Based on the information provided by the requestor, blood samples can be collected in non-gel collection tubes, in the case of serum, or in tubes containing an anticoagulant such as ethylenediaminetetraacetic acid (EDTA) or heparin, in the case of plasma. The samples are stored at room temperature for at most 2 hours until they are centrifuged. The samples (plasma or serum), separated from cells, may then be refrigerated for one week or frozen for a longer period.

Based on the information from the literature, blood samples (for plasma analysis) should be collected in EDTA or gel separator tubes, as ribavirin concentrations show a lower variability in plasma than in serum [Solas et al., 2011; Stanke-Labesque et al., 2009]. The tubes must be kept on ice for at most 2 hours prior to centrifugation, as the concentration in plasma decreases at higher temperatures over longer periods of time. The plasma can be stored for at least 3 months at -20 °C for further tests [Solas et al., 2011; Stanke-Labesque et al., 2009].

There are no specifications regarding sampling location.

4 TECHNOLOGY BACKGROUND


4.2 Brief Description of the Current Technological Context
Various analytical methods were developed to quantify ribavirin in serum or plasma: bioassay, radioimmunoassay (RIA), capillary electrophoresis, GC-MS, HPLC-UV, HPLC-MS/MS and LC-MS/MS\(^6\) [Solas et al., 2011; Sauvage et al., 2009; Stanke-Labesque et al., 2009; Loregian et al., 2007; Homma et al., 1999].

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\(^5\)This number excludes patients covered by a private insurance plan.

\(^6\) GC-MS: gas chromatography-mass spectrometry.
HPLC-UV: high-performance liquid chromatography-ultraviolet detection.
HPLC-MS-MS: high-performance liquid chromatography-tandem mass spectrometry.
LC-MS-MS: liquid chromatography- tandem mass spectrometry
RIA lacks specificity and cross-reacts with the metabolites of ribavirin, which limits its use for therapeutic drug monitoring. Most HPLC methods show adequate recovery, accuracy, specificity and selectivity [Solas et al., 2011; Stanke-Labesque et al., 2009]. The HPLC-MS/MS and HPLC-UV methods are equivalent in terms of accuracy and precision [Solas et al., 2011; Stanke-Labesque et al., 2009]. The HPLC-MS/MS method has the advantage of high specificity, suitable for simple sample preparation such as protein precipitation, and high sensitivity, suitable for small volumes of plasma [Solas et al., 2011; Stanke-Labesque et al., 2009]. The LC-MS/MS generally requires a smaller sample volume and a shorter extraction procedure than that of HPLC-UV [Sauvage et al., 2009].

HPLC-UV quantification requires a preliminary step involving liquid- or solid-phase extraction. The liquid-liquid extraction method with different solvents (acetonitrile, methanol, ethyl acetate, ether, chloroform, dichloroethane and dichloromethane) shows low recovery and low reproducibility [Loregian et al., 2007]. It could affect the specificity and selectivity of the method. This type of procedure requires an internal control and several solvents, making the whole process laborious and costly [Morello et al., 2007], contrary to claims made by other studies [Solas et al., 2011; Stanke-Labesque et al., 2009].

In contrast, solid-phase extraction on phenylboronic acid columns, which selectively bind to structures containing ribose, allows reproducible and effective sample preparation [Loregian et al., 2007]. It does not require the use of solvents for the preconditioning of cartridges or the extraction of ribavirin [Morello et al., 2007], but, like liquid-phase extraction, it is time-consuming and costly [Solas et al., 2011; Sauvage et al., 2009; Stanke-Labesque et al., 2009].

In short, HPLC-UV is the most commonly used method for the quantification of ribavirin [Sauvage et al., 2009]. It is used to separate and detect ribavirin molecules (or metabolites). However, different extraction techniques may be used for sample preparation prior to testing.

4.3 Brief Description of the Advantages Cited for the New Technology

HPLC-UV is a reliable method. Solid-phase extraction on phenylboronic acid columns allows reproducible and effective sample preparation, although it can be lengthy and costly.

4.4 Cost of Technology and Options: Not assessed.

5 EVIDENCE

5.1 Clinical relevance

5.1.1 Other Tests Replaced: Not applicable.

5.1.2 Diagnostic or Prognostic Value

Mortality: The test ensures the optimal dosage of the drug, which could prevent the potentially deadly consequences of ribavirin-induced hemolytic anemia. No studies have assessed this parameter.

Morbidity and Quality of Life: accurate dosing allows for appropriate treatment, which ensures better control of HCV infection and avoids any worsening of the patient's condition. Ribavirin-induced anemia can increase fatigue and worsen quality of life [Brochot et al., 2010]. In this regard, the test may help in preventing anemia. Relevant quantitative data have not been identified.

Treatment Modifications Based on Test Results: Therapeutic drug monitoring allows the necessary adjustments to be made to ribavirin doses to prevent hematologic toxicity (hemolytic anemia) and to optimize the patient's response to treatment. In some cases, ribavirin treatment may have to be discontinued. The available information is derived from expert opinion. However, one journal article
reports conflicting evidence regarding a correlation between ribavirin concentrations and virologic response or development of toxicity [Chan et al., 2009].

5.1.3 Therapeutic Value
Ribavirin tests ensure adequate therapeutic monitoring of the drug to optimize patient dosage, thus achieving maximum therapeutic response while preventing drug toxicity [Solas et al., 2011; Gandia et al., 2010; Sauvage et al., 2009; Stanke-Labesque et al., 2009; Loregian et al., 2007; Morello et al., 2007]. An erythropoietin treatment may be administered to maintain optimal ribavirin dose levels as well as the efficacy of the drug [Dominguez et al., 2012; Brochot et al., 2010]. In some cases, following test results, a dose reduction or discontinuation of ribavirin treatment may be considered [Solas et al., 2011; Brochot et al., 2010]. A change in medication may then be proposed.

Based on the local data provided by the requestor, an average of 6 samples per patient, or one sample every 2 months, were collected from 2012 to 2013 from 249 patients. From this sampling, 68% of patients treated with ribavirin developed significant anemia and required a dosage adjustment had ribavirin levels higher than 2.5 mcg/mL. The toxic threshold defined, 2.5 mcg/mL, is currently being assessed. The reference range is not definitive.

5.2 Clinical Validity
No data on clinical validity are available from the selected studies.

5.3 Analytical (or Technical) Validity
Data on the analytical validity of HPLC-UV were derived from the results of six studies on the validation of the method. They refer to whole blood, plasma, or serum specimens.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>PRESENCE</th>
<th>ABSENCE</th>
<th>NOT APPLICABLE</th>
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<tbody>
<tr>
<td>Repeatability</td>
<td>x</td>
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<tr>
<td>Reproducibility</td>
<td>x</td>
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<td>Analytical sensitivity</td>
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<td>x</td>
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<tr>
<td>Analytical specificity</td>
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<td></td>
<td>x</td>
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<tr>
<td>Matrix effect</td>
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<td>x</td>
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<tr>
<td>Concordance</td>
<td></td>
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<td>x</td>
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<tr>
<td>Correlation between test and comparator</td>
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<td></td>
<td>x</td>
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<tr>
<td>Other, depending on type of test</td>
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</table>

Repeatability, Reproducibility, and Accuracy
Data on repeatability and reproducibility are shown in Table 1. The test is relatively precise, reproducible and accurate, with coefficients of variation that do not exceed 13%. Moreover, Sauvage et al. (2009) performed interlaboratory assays that calculated relative errors at less than 11% within and among lots, and at less than 17% within a group of patients.
Table 1: Repeatability, Reproducibility, and Accuracy

<table>
<thead>
<tr>
<th>STUDY</th>
<th>METHOD</th>
<th>NUMBER AND TYPE OF SPECIMENS</th>
<th>CONCENTRATION OF RIBAVIRIN† (mcg/mL)</th>
<th>PRECISION</th>
<th>ACCURACY (% BIAS)</th>
</tr>
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<tbody>
<tr>
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<td>INTRA-ASSAY (% CV)</td>
<td>INTER-ASSAY (% CV)</td>
</tr>
<tr>
<td>Homma et al., 1999</td>
<td>HPLC-UV</td>
<td>5 (whole blood)</td>
<td>0.41</td>
<td>10.4</td>
<td>11.7</td>
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<tr>
<td></td>
<td></td>
<td>5 (whole blood)</td>
<td>2.44</td>
<td>3.2</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5 (whole blood)</td>
<td>9.77</td>
<td>5.9</td>
<td>6.0</td>
</tr>
<tr>
<td>Sauvage et al., 2009</td>
<td>HPLC-UV</td>
<td>Intra-assay: 6 Inter-assay: 23 (plasma or serum)</td>
<td>0.1 to 10</td>
<td>&lt; 6.7*</td>
<td>&lt; 6.0*</td>
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<td></td>
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<td>LC-MS/MS (tech. 1) Intra-assay: 5 Inter-assay: 5 (plasma or serum)</td>
<td>0.01 to 5</td>
<td>&lt; 7.8*</td>
<td>&lt; 13.3*</td>
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<td>LC-MS/MS (tech. 2) Intra-assay: 6 Inter-assay: 6 (plasma or serum)</td>
<td>0.1 to 7</td>
<td>&lt; 3.9*</td>
<td>&lt; 10.7*</td>
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<table>
<thead>
<tr>
<th>STUDIES</th>
<th>METHOD</th>
<th>NUMBER AND TYPE OF SPECIMENS</th>
<th>CONCENTRATION OF RIBAVIRIN† (mcg/mL)</th>
<th>PRECISION</th>
<th>ACCURACY (% BIAS)</th>
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<tbody>
<tr>
<td></td>
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<td>INTRA-DAY (% CV)</td>
<td>INTER-DAY (% CV)</td>
</tr>
<tr>
<td>D’Avolio et al., 2013</td>
<td>HPLC-UV</td>
<td>10 (whole blood)</td>
<td>7.5</td>
<td>3.97*</td>
<td>8.07*</td>
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<td></td>
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<td></td>
<td>50</td>
<td>2.93*</td>
<td>3.91*</td>
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<td></td>
<td></td>
<td>100</td>
<td>2.87*</td>
<td>4.63*</td>
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<td></td>
<td></td>
<td></td>
<td>200</td>
<td>3.00*</td>
<td>3.89*</td>
</tr>
<tr>
<td>Loregian et al., 2007</td>
<td>HPLC-UV</td>
<td>Intra-day: 6 times Inter-day: 3 days (plasma)</td>
<td>0.05</td>
<td>4.1</td>
<td>4.3</td>
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<td></td>
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<td>0.2</td>
<td>3.1</td>
<td>2.3</td>
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<td>1</td>
<td>0.7</td>
<td>0.5</td>
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<td></td>
<td>5</td>
<td>0.2</td>
<td>0.7</td>
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<td></td>
<td></td>
<td>10</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Morello et al., 2007</td>
<td>HPLC-UV</td>
<td>n/a (plasma)</td>
<td>0.05</td>
<td>0.9</td>
<td>1.4</td>
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<td></td>
<td></td>
<td>0.5</td>
<td>3.5</td>
<td>1.1</td>
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<td></td>
<td></td>
<td></td>
<td>5</td>
<td>0.9</td>
<td>0.4</td>
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</tbody>
</table>

Abbreviations: CV = coefficient of variation; HPLC-UV = high-performance liquid chromatography-ultraviolet; LC-MS/MS = liquid chromatography tandem mass spectrometry; mcg/mL = micrograms per millilitre; NA = not available.

*Relative standard deviation.
†The units presented in the studies were converted for consistency purposes.
Linearity
The HPLC-UV method yields linear calibration curves. Hence, the method allows the quantification of ribavirin concentrations with a small margin of error compared with calibrated solutions (standards). The selected studies point towards the same conclusion (Table 2).

Table 2: Linearity of Calibration Curves with the HPLC-UV Method

<table>
<thead>
<tr>
<th>STUDY</th>
<th>CONCENTRATION OF RIBAVIRIN (mcg/mL)</th>
<th>CORRELATION COEFFICIENT</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Avolio et al., 2003</td>
<td>0.625 to 320</td>
<td>$r^2 = 0.998$</td>
</tr>
<tr>
<td>Loregian et al., 2007</td>
<td>8 calibration points: 2.5; 5; 12.5; 25; 50; 100; 250; 500</td>
<td>$\geq 0.997$ for all curves</td>
</tr>
<tr>
<td>Homma et al., 1999</td>
<td></td>
<td>$r = 0.9999$</td>
</tr>
<tr>
<td>Morello et al., 2007</td>
<td>0.05; 0.5; 5</td>
<td>$r^2 = 0.997$</td>
</tr>
<tr>
<td>Sauvage et al., 2009</td>
<td>0.125 to 4.550</td>
<td>$r = 0.9996$</td>
</tr>
</tbody>
</table>

Abbreviation: mcg/mL = micrograms per millilitre

Analytical Sensitivity and Specificity, Interference and Recovery
Data on the limit of detection and the limit of quantification (Table 3) provide information on the sensitivity of HPLC-UV testing. As to the method's specificity, no interference was observed. Peaks in ribavirin and in the reference standards were observed at the retention times of 4.8 ± 0.15 min and 10.5 ± 0.15 min, respectively. No interference peaks generated by endogenous substances were observed [D’Avolio et al., 2013].

No significant interference was observed with the antiretroviral drugs [Morello et al., 2007], antiviral agents or antibiotics tested [Loregian et al., 2007].

In most of the studies, the recovery rate was greater than 80%, with the exception of two studies in which the rate was greater than 55% and greater than 63% at concentrations of 0.1 mcg/mL to 10 mcg/mL and 0.41 mcg/mL (1.67 μM), respectively [Sauvage et al., 2009; Homma et al., 1999].
Table 3: Recovery, Limit of Detection and Limit of Quantification

<table>
<thead>
<tr>
<th>STUDY</th>
<th>METHOD</th>
<th>NUMBER OF SPECIMENS</th>
<th>CONCENTRATION OF RIBAVIRIN* (mcg/mL)</th>
<th>RECOVERY (%)</th>
<th>LOD AND LOQ (mcg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Avolio et al., 2013</td>
<td>HPLC-UV</td>
<td>10</td>
<td>7.5 to 200</td>
<td>80.1</td>
<td>LOD: 0.312 LOQ: 0.625 (whole blood)</td>
</tr>
<tr>
<td>Homma et al., 1999</td>
<td>HPLC-UV</td>
<td>5</td>
<td>0.41</td>
<td>63.2</td>
<td>LOD: 0.0195 g/mL (plasma) 0.0488 g/mL (whole blood)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5</td>
<td>2.44</td>
<td>85.9</td>
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<td></td>
<td>5</td>
<td>9.77</td>
<td>90.7</td>
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<tr>
<td>Loregian et al., 2007</td>
<td>HPLC-UV</td>
<td>4</td>
<td>0.05 to 10</td>
<td>90.4</td>
<td>LOQ: 0.05 (plasma)</td>
</tr>
<tr>
<td>Morello et al., 2007</td>
<td>HPLC-UV</td>
<td>NA</td>
<td>0.05</td>
<td>93</td>
<td>LOD: 0.025 LOQ: 0.050 (plasma)</td>
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<td>0.5</td>
<td>91</td>
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<td>5</td>
<td>98</td>
<td></td>
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<tr>
<td>Sauvage et al., 2009</td>
<td>HPLC-UV</td>
<td>5</td>
<td>0.1 to 10</td>
<td>&gt; 55.3</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>LC-MS-MS</td>
<td>3</td>
<td>0.01 to 5</td>
<td>&gt; 92.8</td>
<td>NA</td>
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<td>(tech. 1)</td>
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<td></td>
<td>LC-MS-MS</td>
<td>3</td>
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<td></td>
<td>(tech. 2)</td>
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</tbody>
</table>

Abbreviations: LOD = limit of detection; LOQ = limit of quantification; mcg/mL = micrograms per millilitre; NA = not available.

*The units in these studies were converted for consistency.

5.4 Recommendations for Listing in Other Jurisdictions

Therapeutic drug monitoring for ribavirin has been recommended by French studies [Solas et al., 2011; Brochot et al., 2010; Stanke-Labesque et al., 2009], but a Canadian study (critical review) does not recommend it because of conflicting evidence concerning a correlation between ribavirin concentrations and virologic response or development of toxicity [Chan et al., 2009].

RIBAJUSTE, a multicentre, randomized clinical trial (Phase 3), is currently being conducted in France. It will assess the efficacy and safety of dose adaptation of ribavirin in individuals with HCV genotype 1 compared with standard treatment. This study could help determine whether therapeutic drug monitoring of ribavirin offers an advantage over clinical monitoring of signs and symptoms [Chan et al., 2009; NIH, 2013]. The results of this study are expected in spring of 2014.

6 ANTICIPATED OUTCOMES OF INTRODUCING THE TEST

7. Information obtained from the RIBAJUSTE study.
6.1 Impact on Material and Human Resources
The equipment needed to perform HPLC-UV tests is generally available in laboratories. However, the sample extraction phase prior to testing may vary depending on the protocols used. Therefore, material and human resources should be planned accordingly.

6.2 Economic Consequences of Introducing the Test Into Quebec's Health Care and Social Services System: Not assessed.

6.3 Main Organizational, Ethical, and Other (Social, Legal, Political) Issues: Not assessed.

7 IN BRIEF

7.1 Clinical Relevance
Based on expert opinion, ribavirin tests allow therapeutic drug monitoring to optimize drug dosage while preventing hematologic toxicity. However, there is conflicting evidence concerning a correlation between ribavirin concentrations and virologic response or development of toxicity. Moreover, reference thresholds for therapeutic and toxicity values vary among studies and among individuals.

7.2 Clinical Validity: No data available on clinical validity.

7.3 Analytical Validity
The data on analytical validity depict HPLC-UV as a reliable method (precise, accurate, and reproducible) for the quantification of ribavirin in plasma, serum or whole blood. No significant interference was observed with antiretroviral drugs, antivirals or antibiotics.

7.4 Recommendations for Listing in Other Jurisdictions
Therapeutic monitoring of ribavirin has been recommended in French studies. However, a Canadian review has concluded that, for the time being, there is conflicting and insufficient evidence on the clinical utility and relevance of the test.
8 INESSS NOTICE IN BRIEF

Measurement of Ribavirin Using High-Performance Liquid chromatography With Ultraviolet Detection (HPLC-UV)

<table>
<thead>
<tr>
<th>Status of the Diagnostic Technology</th>
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</thead>
<tbody>
<tr>
<td>☐ Established</td>
</tr>
<tr>
<td>☐ Innovative</td>
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<tr>
<td>☒ Experimental (for research purposes only)</td>
</tr>
<tr>
<td>☐ Replacement for technology:__________which becomes obsolete</td>
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</tbody>
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INESSS Recommendation:

☐ Add test to the Index

☒ Do not add test to the Index

*Despite the available local data, the test’s clinical utility has not yet been determined, especially since the toxicity threshold has not been clearly established. There are no available data on its clinical validity.*

*A review of Canadian literature concluded that therapeutic drug monitoring of ribavirin is not recommended for the time being due to insufficient and conflicting evidence regarding its clinical validity.*

*The RIBAJUSTE clinical trial is currently being conducted in France, and its results are expected in the spring of 2014. It could provide some answers concerning clinical validity.*

☐ Reassess test

Additional Recommendation:

☐ Draw connection with listing of drugs, if companion test

☐ Production of an optimal use guide

☐ Production of indicators, when monitoring is required
REFERENCES


