# Free Valproic Acid Assay (Reference — 2013.03.006)

Notice of Assessment

April 2014

# 1 GENERAL INFORMATION

## 1.1 Requestor

Hôpital Maisonneuve-Rosemont

## 1.2 Application for Review Submitted to MSSS

May 1, 2013

## 1.3 Application Received by INESSS

November 1, 2013

## 1.4 Notice Issued

February 28, 2014

**Note:**
This notice is based on the scientific and commercial information submitted by the requestor 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

Ultrafiltration prior to chemiluminescent microparticle immunoassay (CMIA).

## 2.2 Brief Description of the Technology, and Clinical and Technical Specifications:

The requestor uses ultrafiltration to purify a serum sample prior to determining valproic acid in its free form by chemiluminescent microparticle immunoassay (CMIA).

The goal of ultrafiltration is to purify a sample by preserving only the free fraction[19] of valproic acid, i.e., the non-protein-bound form [Liu et al., 1992; Cramer et al., 1983]. The requestor's method first involves preparing the serum by centrifugation. Next, an aliquot is filtered through a membrane filter with very small diameter pores[20] by a second centrifugation in order to obtain a protein-free ultrafiltrate (information provided by the requestor).

CMIA is an immunoassay for the quantitative measurement of valproic acid in human serum or plasma. Anti-valproic acid–coated paramagnetic microparticles bind to valproic acid found in the sample and to the valproic acid acridinium-labelled conjugate. After washing, pre-trigger and trigger solutions are added.[21] The resulting chemiluminescent reaction is measured as relative light units (RLUs) by the analyzer [Abbott Laboratories, 2009]. There is an inverse relationship between the amount of analyte (valproic acid in the sample) and RLUs. In other words, the greater the amount of analyte, the less intense the light signal.

The reference values used in the requestor's laboratory are 35 to 70 µmol/L for the free fraction and 347 to 693 µmol/L for total valproic acid.

[19] More than 90% of valproic acid binds to plasma proteins (principally albumin) [CPhA, 2013].
[20] The membrane filter is built into a purpose-designed tube.
[21] These solutions s excite the chromophore, in this case acridinium.

### 2.3 Company or Developer

In-house method for ultrafiltration; reagent kit from Abbott Laboratories for the CMIA.

### 2.4 Licence(s)

Not applicable.

### 2.5 Patent, If Any

Not applicable.

### 2.6 Approval Status (Health Canada, FDA)

The reagent kit, ARCHITECT *i*Valproic Acid™, is licensed by Health Canada (No. 1199, May 21, 2009) and by the FDA (No. K090358, August 7, 2009).

### 2.7 Weighted Value

38.0.

## 3 CLINICAL INDICATIONS, PRACTICE SETTINGS, AND TESTING PROCEDURES

### 3.1 Targeted Patient Group

Patients treated with valproic acid who present signs and symptoms of toxicity despite normal concentrations of total valproic acid or who need treatment monitoring because of hypoproteinemia (including hypoalbuminemia), kidney or liver failure, or hepatitis, and pediatric patients treated with valproic acid.

### 3.2 Targeted Disease(s)

**Epilepsy and its treatment**

Epilepsy is the second most common neurological disease after migraine. Its estimated prevalence varies between 0.5% and 1% in the Western population [Forsgren *et al.*, 2005]. It is characterized by recurring seizures caused by excessive brain activity.

Valproic acid is an anticonvulsant indicated for use as sole or adjunctive therapy in the treatment of simple or complex absence seizures,[22] and is useful for treating primary generalized or tonic-clonic seizures [CPhA, 2013], bipolar disorders and migraine prophylaxis [DeVane, 2003; Warner et al., 1998]. Valproic acid was first used clinically in 1964 [Liu et al., 1992]. It has been available in France since 1967 and in the United States since 1978 [Bentué-Ferrer et al., 2010]. In Quebec, it has been included in the List of Medications and covered by Public Prescription Drug Insurance Plan since at least 1998.[23]

The safety and efficacy of valproic acid in treating elderly patients 65 years of age or older with epilepsy or mania have not been evaluated. For children under the age of 2 years, this drug should be used with extreme caution and only as a sole agent. Administration of valproic acid is contraindicated for patients with hepatic disease or significant hepatic insufficiency, patients with known urea cycle disorders, and for patients with known hypersensitivity to the drug. Serious

[22] Simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2 to 15 seconds), accompanied by certain generalized epileptiform discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present [CPhA, 2013].

[23] Institut national d'excellence en santé et en services sociaux (INESSS), Extrait d'avis au Ministre : Acide valproïque [website]. Assessment published July 1, 1998. Available at www.inesss.qc.ca/activites/evaluation-des-medicaments/evaluation-des-medicaments/extrait-davis-au-ministre/toutes-les-marques-1.html.

precautions may also be observed because of the risk of hepatotoxicity, teratogenicity[24] and pancreatitis. The most common adverse effects of valproic acid are gastrointestinal (nausea, vomiting, and indigestion) as well as d and tremor [CPhA, 2013].

**Pharmacokinetics and dosing**

Valproic acid is rapidly absorbed after oral administration. Administration with food does not affect total absorption. Peak serum concentration occurs approximately 1 to 4 hours after an oral dose [CPhA, 2013]. Steady state is reached in 2 to 4 days [Warner et al., 1998]. Valproic acid is strongly bound (90%) to human plasma proteins (principally albumin). Due to the saturable plasma protein binding, the relationship between dose and total valproate concentration[25] is nonlinear, i.e., concentration does not increase proportionally with the dose, but rather increases to a lesser extent. However, the kinetics of unbound drug (not bound to proteins) is linear. Valproate is metabolized almost entirely by the liver. While valproic acid and its metabolites are mostly eliminated in urine, very little unmetabolized parent drug is excreted in urine. The serum half-life[26] ranges from 6 to 16 hours [CPhA, 2013].

Various drug-drug interactions potentially influence valproic acid pharmacokinetics and *vice versa* [CPhA, 2013]. For example, carbapenem antibiotics can reduce serum valproic acid concentrations to sub-therapeutic levels [CPhA, 2013; Bentué-Ferrer et al., 2010]. Increasing valproic acid dose may not be sufficient to overcome this interaction. If co-administration is essential, serum valproic acid concentrations should be monitored daily [CPhA, 2013].
Renal insufficiency is associated with an increase in the unbound fraction of valproate. Monitoring of total concentration in patients with renal insufficiency may be misleading, since total concentration may appear to be normal while unbound concentration may be substantially elevated [CPhA, 2013]. Determining the unbound fraction can therefore be helpful, even essential, for certain patients.

Determining unbound valproic acid could be used in the therapeutic monitoring of patients with epilepsy being treated with this drug in particular clinical situations, inter alia: for signs and symptoms of toxicity despite normal total valproic acid concentrations; for therapeutic monitoring in the presence of hypoproteinemia (including hypoalbuminemia), kidney or liver insufficiency, or hepatitis; and for pediatric patients (information provided by the requestor).

## 3.3 Number of Patients Targeted

Approximately 100 tests per year for the next three years (information provided by the requestor).

In the Index, test 30601 for valproic acid is not specific to its free form. Its weighted value is 4.6 with no mention of the technology used. During the 2012-2013 fiscal year, 70,500 valproic acid tests were performed. For the 2013-2014 fiscal year (up until September 21, 2013), 35,015 tests have been performed (information provided by the MSSS).

## 3.4 Medical Specialities and Other Professions Involved

Neurology, biochemistry, hepatology, nephrology, pediatrics.

[24] In administering valproic acid to pregnant women or women of childbearing age , benefits of its use should be weighed against the risk of injury to the fetus [CPhA, 2013].
[25] Valproate is a salt of valproic acid.
[26] One study mentioned that the elimination half-life is between 11 and 20 hours [Bentué-Ferrer et al., 2010].

### 3.5 Testing Procedure

Serum sampling by the usual blood collection procedures for this type of sample. Citrate and oxalate anticoagulant tube types are to be avoided when assaying either free or total valproic acid because they substantially decrease the total concentration of valproic acid [Warner et al., 1998]. Repeated samples should be drawn at a consistent time of day because of the circadian rhythm effect [Warner et al., 1998]. There are no specifications as to the place of collection.

## 4 TECHNOLOGY BACKGROUND

### 4.1 Nature of the Diagnostic Technology

Unique test.

### 4.2 Brief Description of the Current Technological Context

Ultrafiltration is often used in sample preparation to isolate free valproic acid prior to its quantification [Pham et al., 2012; Falahat-Pisheh et al., 2007; Liu et al., 1992; Abadin et al., 1991; Haidukewych, 1985; Cramer et al., 1983]. Various methods can be used to determine free valproic acid, inter alia: gas chromatography (GC) [Falahat-Pisheh et al., 2007], high-performance liquid chromatography (HPLC) [Liu et al., 1992], capillary electrophoresis with contactless conductivity detection [Pham et al., 2012], fluorescence polarization immunoassay (FPIA) [Bentué-Ferrer et al., 2010; Haidukewych, 1985], enzyme immunoassay (EIA, including enzyme multiplied immunoassay test [EMIT]) [Bentué-Ferrer et al., 2010; Liu et al., 1992; Haidukewych, 1985], chemiluminescent immunoassay [Bentué-Ferrer et al., 2010], or other immunoassays [Inamdar et al., 2004].

Several kits using various immunoassay techniques (e.g., FPIA, CMIA, EMIT, CEDIA, immunochemistry or other tests) are licensed by Health Canada (see Appendix). These kits are sold by no fewer than six different manufacturers and can be used on different analyzers.

The test assessed here requires ultrafiltration prior to chemiluminescent microparticle immunoassay (CMIA). The assay is based on competition between the targeted analyte and the chromophore-labelled conjugate.

### 4.3 Brief Description of the Advantages Cited for the New Technology

Sample preparation by ultrafiltration takes much less time than other techniques for the same step, such as solid phase extraction. Using the CMIA reagent kit also reduces the time required for the test, compared with the more time-consuming HPLC test.[27]

The requestor's laboratory is participating in an internal quality control program and in an external quality control program of the College of American Pathologists (CAP), *Z-A Therapeutic Drug Monitoring*.

### 4.4 Cost of Technology and Options

The reagent kit is used with the Architect i2000SR System™ from Abbott Laboratories. This analyzer has a priority function for assaying "urgent" samples. The analyser can also test for other analytes by CMIA with the same buffer or trigger solutions and simultaneously perform regular biochemistry tests [Abbott Laboratories, 2014 and 2009].

[27] An HPLC assay also requires a sample preparation step such as extraction, solvent evaporation or derivatization by means of a fluorescent-labelling reagent [Liu et al., 1992]. Derivatization is a technique used in chemistry to transform a compound into a product with a similar chemical structure called a "derivative."

In addition to the purchase of reagents and the immunoassay apparatus, costs will also include the equipment needed for ultrafiltration, a prerequisite for the test.

# 5 EVIDENCE

## 5.1 Clinical Relevance

### 5.1.1 Diagnostic or Prognostic Value

No study has demonstrated a relationship between serum or plasma measurement of free valproic acid and mortality, morbidity, or quality of life.

### 5.1.2 Therapeutic Value

While a good correlation has not been established between daily dose, total serum valproate concentration, and therapeutic effect, therapeutic valproate serum concentrations[28] for most patients with epilepsy range from 50 to 100 µg/mL [CPhA, 2013]. This therapeutic range equates with molar concentrations of 346 to 693 µmol/L [Bentué-Ferrer et al., 2010; Parent et al., 1993].

Free valproic acid assay is more effective than total valproic acid assay in adjusting dosage regimens [Gomez Bellver et al., 1993; Abadin et al., 1991, Levy, 1980], especially if high doses are administered [Gomez Bellver et al., 1993], because total concentrations can lead to erroneous interpretations. Indeed, valproic acid has a high degree of plasma protein binding, which can become saturated at the plasma concentrations of a normal dose. Valproic acid is therefore characterized by a nonlinear concentration-dose relationship [Levy, 1980], i.e., the plasma protein binding is nonlinear [DeVane, 2003], and the free fraction is not constant across the dosing interval [Gomez Bellver et al., 1993]. Furthermore, plasma clearance depends on protein binding[29] [Haroldson et al., 2000; Gomez Bellver et al., 1993]. Only the unbound drug is metabolized [Warner et al., 1998]. Thus, this can lead to drug toxicity [Dasgupta, 2002].

No recent studies indicate whether therapeutic monitoring of free valproic acid is routinely performed. Older studies (prior to 2003) indicate otherwise [Dasgupta, 2002; Warner et al., 1998; Haidukewych and Rodin, 1982].

There is scant literature on reference values for the free fraction of valproic acid in serum. One study reports a therapeutic range from 5 to 15 µg/mL;[30] this range matches that for total concentration,i.e., 50 to 100 µg/mL [De Maat et al., 2011]. The reference values used in the requestor's laboratory are 35 to 70 µmol/L (or 5 to 10 µg/mL[31]) for free valproic acid. Pharmacological therapeutic monitoring of free valproic acid has been studied by a few authors [Bentué-Ferrer et al., 2010; Haidukewych and Rodin, 1982; Levy, 1980]. None of the studies provide data on clinical benefit, although they all state the value of monitoring in particular clinical situations. The Société Française de Pharmacologie et de Thérapeutique recommends pharmacological therapeutic monitoring of valproic acid (valproate) in specific physiological conditions (pregnancy, childhood), in combination therapy, and in cases of treatment failure, suspected adverse effects, and therapy noncompliance [Bentué-Ferrer et al., 2010]. However, systematic monitoring is not encouraged. The article does not specify, however, whether this recommendation applies to the free form of the drug. The study by Haidukewych and Rodin

[28] One study reports a therapeutic serum range from 50 to 120 µg/mL, or 347 to 833 µmol/L [Warner et al., 1998]. Another study reports therapeutic total valproate plasma concentrations between 50 and 100 µg/mL [Haidukewych and Rodin, 1982].
[29] Clearance is limited by the concentration of free valproic acid in the blood [Haroldson et al., 2000].
[30] By manual calculation, these values equate to molar concentrations of 35 to 104 µmol/L.
[31] Values obtained by manual calculation using a molecular weight of 144.2114 g/mol for valproic acid.

[1982] concludes that determining the free form in patients presenting adverse effects is useful. The study by Levy [1980] suggests monitoring the free form in clinical situations when there is suspicion of intra- or inter-individual variability in protein binding, such that monitoring the total concentration of valproic acid would be inadequate.

A systematic review by the Cochrane Collaboration, published in 2007 and updated in 2010, reported the results of only one randomized study that met that review's inclusion criteria. This study does not distinguish the effects of each antiepileptic drug. The review authors conclude there is no clear evidence to support routine pharmacological therapeutic monitoring of antiepileptic drugs. However, this does not exclude the clinical usefulness of this monitoring in some cases of polytherapy or in special situations, although evidence is lacking [Tomson et al., 2007].

## 5.2 Clinical Validity

No studies on clinical validity were identified.

## 5.3 Analytical (or Technical) Validity

The analytical validity of CMIA is presented in the monograph for the ARCHITECT *i*Valproic Acid™ system [Abbott Laboratories, 2009]. The data provided are indicative, and the results obtained can vary from one laboratory to another. No other studies on the validity of this kit were identified. A sample preparation method such as ultrafiltration is required prior to using this kit in order to assay only the free fraction of valproic acid. The same kit can be used to measure total valproic acid.

### 5.3.1 Repeatability and Reproducibility

Repeatability of measurements (intra-assay, n = 80): coefficient of variation < 5% for concentrations between 20 and 150 µg/mL.

Reproducibility of measurement: Coefficient of variation ≤ 5% for concentrations between 20 and 150 µg/mL. Controls at three levels with four serum panels were assayed in duplicate on three instruments using three lots of reagent at two separate times per day for 20 days.

### 5.3.2 Analytical Sensitivity and Linearity

Analytical sensitivity is defined as the lower limit of detection, which is 0.51 µg/mL. However, the kit is designed to have a limit of 2 µg/mL. The measurement range of the assay, verified by linearity studies, is 2 to 150 µg/mL. A therapeutic range of 50 to 100 µg/mL has been suggested for valproic acid.

### 5.3.3 Analytical Specificity, Interference, and Recovery

The mean recovery rate for serum ranges from 94% to 105%, and for plasma, from 98% to 103%. The specificity of the assay kit was determined by studying the cross-reactivity of compounds whose chemical structure or concurrent usage could cause potential interference. Cross-reactivity (≥ 6%) was observed in serum samples with valproic acid concentrations between 50 and 100 µg/mL with the following compounds: 4-ene-valproic acid, 2-propyl-4-pentenoic acid, 3-keto-valproic acid, and 2-propyl-2-pentenoic acid. Other substances interfere with the recovery rate: acetylcysteine, acetylsalicylic acid and ibuprofen. Compounds that may interfere with recovery include triglycerides, hemoglobin, bilirubin, and proteins. These lists are not exhaustive; additional information can be obtained from the manufacturer.

#### 5.3.4 Correlation Between Test and Comparator

The FPIA method (fluorescence polarization immunoassay using an AxSYM Valproic Acid™ system by the same manufacturer) was compared with the CMIA method, using a Passing-Bablock regression (correlation coefficient 0.986). This means that both methods have very similar results.

### 5.4 Recommendations from Other Organizations

No assessment reports or clinical practice guidelines with recommendations for monitoring the free form of valproic acid in epilepsy treatment were identified.

The clinical practice guidelines of the National Institute for Health and Clinical Excellence (NICE) and of the Scottish Intercollegiate Guidelines Network (SIGN) recommend against routine monitoring of antiepileptic drug concentrations [NICE 2013; SIGN, 2005 and 2003]. Monitoring may be indicated if there are concerns about medical compliance, toxicity [SIGN, 2003], or drug interaction, and in specific clinical conditions such as status epilepticus, organ failure, and certain situations in pregnancy [NICE, 2013]. However, these guidelines do not specifically mention monitoring free valproic acid.

## 6 ANTICIPATED OUTCOMES OF INTRODUCING THE TEST

### 6.1 Impact on Material and Human Resources

The prerequisite ultrafiltration of the sample and the use of the CMIA reagent kit are expected to have a negligible impact on material and human resources given the expected annual volume (about 100 tests annually).

### 6.2 Economic Consequences of Introducing 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

The free valproic acid assay would be useful in adjusting dosage regiments in order to avoid drug toxicity, because total serum concentrations of the drug can lead to misinterpretations in particular clinical situations. However, few studies specify the therapeutic range for the free form and establish its clinical utility.

### 7.2 Clinical Validity

No studies on clinical validity were identified.

### 7.3 Analytical Validity

The analytical validity of the technique is taken from the CMIA kit monograph. No other studies on the validity of this kit were identified.

### 7.4 Recommendations from Other Organizations

No identified organization recommends free valproic acid assays for the therapeutic monitoring of the drug in patients with epilepsy.

## 8 INESSS NOTICE IN BRIEF

# Free Valproic Acid Assay

**Status of the Diagnostic Technology**

☒ Established
☐ Innovative
☐ Experimental (for research purposes only)
☐ Replacement for technology_____, which becomes obsolete

**INESSS Recommendation**

☐ Include test in the Index
☒ Do not include test in the Index
*Clinical benefit is not proven and no data on clinical validity was identified.*
*Little correlation between measured concentration and clinical status.*
☐ Reassess test

**Additional Recommendation**

☐ Draw connection with listing of drugs, if companion test
☐ Produce an optimal use manual
☐ Identify indicators, when monitoring is required

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# APPENDIX A

**List of devices using immunological methods licensed by Health Canada** (based on MDALL data[32])

**Key word**: valpro
Date and time consulted: January 20, 2014, at 12:45 p.m.

**Table A1: 28 Results Found**

| DEVICE NAME | LICENCE NO. | MANUFACTURER |
|---|---|---|
| ADVIA 1200 CHEMISTRY SYSTEM - VALPROIC ACID (VPA) ASSAY | 67070 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| ADVIA 1200 CHEMISTRY SYSTEM - VALPROIC ACID 2 (VPA 2) ASSAY | 67070 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| ADVIA CENTAUR CP SYSTEM - VALPROIC ACID (VALP)ASSAY | 69989 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| ADVIA CENTAUR SYSTEM - VALPROIC | 10057 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| ADVIA CENTAUR XP SYSTEM - VALPROIC ACID (VALP)ASSAY | 72572 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| ADVIA CENTAUR SYSTEM - VALPROIC 2 (VPA 2)ASSAY | 234 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| ADVIA CHEMISTRY SYSTEM - VALPROIC ACID (VPA) ASSAY | 234 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| ARCHITECT I SYSTEM - VALPROIC ACID ASSAY | 1199 | ABBOTT LABORATORIES DIAGNOSTIC DIVISION |
| AXSYM SYSTEM - VALPROIC ACID ASSAY | 63184 | ABBOTT LABORATORIES DIAGNOSTIC DIVISION |
| CEDIA TDM ASSAY - VALPROIC ACID | 62390 | MICROGENICS CORPORATION |
| COBAS INTEGRA VALPROIC ACID (VALP) | 76865 | ROCHE DIAGNOSTICS GMBH |
| COBAS INTEGRA VALPROIC ACID FOR COBAS C SYSTEMS | 76865 | ROCHE DIAGNOSTICS GMBH |
| DIMENSION CLINICAL CHEMISTRY SYSTEM - VALPROIC ACID FLEX REAGENT CARTRIDGE | 2232 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| DIMENSION EXL SYSTEM - VALPROIC ACID (VALP) ASSAY | 78489 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| DIMENSION VISTA SYSTEM - VALPROIC ACID | 73261 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| DIMENSION XPAND SYSTEM - VALPROIC ACID (VALP) ASSAY | 30615 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| EMIT VALPROIC ACID ASSAY | 7927 | SIEMENS HEALTHCARE DIAGNOSTICS INC. |
| HITACHI ONLINE TDM VALPROIC ACID | 76865 | ROCHE DIAGNOSTICS GMBH |
| HITACHI ONLINE TDM VALPROIC ACID (HIT.911, 912, 917 AND MOD. P) | 76865 | ROCHE DIAGNOSTICS GMBH |
| IMMAGE IMMUNOCHEMISTRY SYSTEMS VALPROCIC ACID (VPA) REAGENT | 7323 | BECKMAN COULTER, INC. |
| IMMULITE 1000 SYSTEM - VALPROIC ASSAY ACID | 63176 | SIEMENS HEALTHCARE DIAGNOSTICS PRODUCTS LIMITED |

[32] Available at: webprod5.hc-sc.gc.ca/mdll-limh/prepareSearch-preparerRecherche.do?type=active&lang=eng.

| DEVICE NAME | LICENCE NO. | MANUFACTURER |
|---|---|---|
| IMMULITE 2000 SYSTEM - VALPROIC ACID ASSAY | 29184 | SIEMENS HEALTHCARE DIAGNOSTICS PRODUCTS LIMITED |
| IMMULITE SYSTEM - VALPROIC ACID ASSAY | 922 | SIEMENS HEALTHCARE DIAGNOSTICS PRODUCTS LIMITED |
| MULTIGENT AEROSET/C8000 VALPROIC ACID ASSAY | 64481 | MICROGENICS CORPORATION |
| ROCHE HITACHI - VALPROIC ACID | 712 | ROCHE DIAGNOSTICS GMBH |
| SYNCHRON SYSTEMS VALPROIC ACID (VPA) REAGENT | 10355 | BECKMAN COULTER, INC. |
| VALP2 (ONLINE VALPROIC ACID) FOR COBAS C SYSTEMS | 76865 | ROCHE DIAGNOSTICS GMBH |
| VALPROIC ACID IMMUNOASSAY FOR HITACHI 717 | 65016 | RANDOX LABORATORIES LTD. |