

SUMMARY OF SAFETY AND EFFECTIVNESS INFORMATION

I. Identification of Submitter and Contact, and Date of Preparation

A. Submitter and Owner of the 510(k):

Otsuka Pharmaceutical Co., Ltd.
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Osaka , 540-0021 Japan

B. Official Correspondent:

James W. Harris, Ph.D.
Director of Regulatory Compliance
Otsuka America Pharmaceuticals, Inc.
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Rockville, MD 20850-3238

Telephone and Telefax Numbers:

Telephone 301-527-4719
Telefax 301-721-7119

C. Date of Preparation:

March 29, 1999

II. Name of the Device

A. Trade/Proprietary Name:

RLP-Cholesterol Immunoseparation Assay (RLP-Cholesterol Assay)

B. Common/Usual Name:

Remnant Lipoprotein Cholesterol Test System

C. Classification Name:

21 C.F.R. 862.1475 Lipoprotein test system

III. Predicate Device(s)

The Titan Gel Lipoprotein Electrophoresis System (K833611), and the REP Cholesterol Profile-15 Kit (K935162).

IV. Description of the Device

The RLP-Cholesterol Assay uses two mouse monoclonal antibodies (Mab) to isolate remnant lipoproteins. The first one (JI-H) is raised against human apo B-100. This Mab recognizes an epitope near the apo B-51 region to remove lipoproteins containing apo B-100, such as LDL, Lp(a) and nascent VLDL. The second one (H-12) is raised against human apo A-I. This Mab removes lipoproteins containing apo A-I, such as HDL. The monoclonal antibodies are conjugated to sepharose-4B beads and to separate bound lipoproteins from the remnant lipoproteins that remain in the unbound fraction. Cholesterol in the unbound fraction (RLP-C) is then quantified by an enzymatic assay. The remnant lipoproteins isolated by the RLP-Cholesterol Assay have the same physical, chemical and biological properties as the β -VLDL isolated from patients with familial type III hyperlipoproteinemia, indicating that the RLP-Cholesterol Assay has isolated the distinctive remnants that are rich with β -VLDL.

V. Intended Use and Indication

The intended use of the RLP-Cholesterol Assay is:

To separate and measure lipoproteins in order to further characterize the specific type of lipid disorder existing in patients with high levels of cholesterol and triglycerides, *i.e.*, in patients with hyperlipoproteinemia.

The specific indication [identified as the "intended use" on the device's labeling, as required by 21 C.F.R. § 809.10(a)(2)] is:

For use in the quantitative determination of cholesterol contained in remnant lipoproteins in human serum or plasma. The test results are used in combination with total serum triglyceride measurements to diagnose familial type III hyperlipoproteinemia in patients with elevated serum total cholesterol and triglyceride concentrations. .

The predicate devices are the Titan Gel Lipoprotein Electrophoresis System (Titan Gel), and the REP Cholesterol Profile-15 Kit (REP Kit). The RLP-Cholesterol Assay and the predicate devices do not have identical indication statements, known as "intended use" on the devices' labeling.

The indication statement for the Titan Gel is:

For the separation and quantitation of plasma lipoproteins by agarose gel electrophoresis.

The indication statement for the REP Kit is:

For use in the quantitative determination of cholesterol and cholesterol esters in the lipoproteins of serum using the REP agarose electrophoresis system. The system is intended for the assessment of cholesterol content of the high density lipoproteins (HDL), low density lipoproteins (LDL), and very low density lipoproteins (VLDL).

To fully assess the indication of certain *in vitro* devices, however, it is important to look at other parts of the labeling. For example, the device labeling for the Titan Gel provides an overview of the Fredrickson System for classifying or “typing” hyperlipoproteinemia and a discussion of why an accurate determination of type is clinically important. Later, the device labeling provides the interpretation of the results according to the Fredrickson System, which includes a description on how to recognize β -VLDL and diagnose type III hyperlipoproteinemia. Although the “Summary” section of the REP Kit emphasizes the relationship between lipoproteins and coronary heart disease, it also states that “Electrophoresis ...provides a visual display useful in detecting unusual or variant patterns (of lipoproteins).” Typically, such information is used to diagnose a patient’s type of hyperlipoproteinemia.

Although the indication statements in this instance are somewhat different, the intended uses of the devices remain the same; namely, each device is intended to separate and measure lipoproteins to further characterize the specific type of lipid disorder in patients with hyperlipoproteinemia.

VI. Technological Characteristics Compared to the Predicates

The RLP-Cholesterol Assay has different technological characteristics than the Titan Gel and the REP Kit although its technological characteristics are similar to other devices within its type.

The Titan Gel and the REP Kit use agarose gel electrophoresis to separate and measure lipoproteins, including HDL, LDL, VLDL and β -VLDL.

The RLP-Cholesterol Assay relies upon immunoseparation principles to isolate remnant lipoproteins, including β -VLDL. After immunoseparation, cholesterol content of the remnant lipoproteins in the unbound fraction is assayed by an enzymatic spectrophotometric assay.

The different characteristics of the RLP-Cholesterol Assay do not raise new types of safety or effectiveness questions compared to the predicate devices. The applicable safety or effectiveness questions apply to lipoprotein tests in general, including those already cleared by FDA. The RLP-Cholesterol Assay uses established diagnostic technologies and the primary question is whether these devices accurately separate and measure lipoprotein fractions to diagnose the lipoprotein disorder.

VII. Nonclinical Tests

Otsuka performed standard laboratory methods to evaluate the technological performance characteristics of the RLP-Cholesterol Assay to ensure that it is suitable for use in commercial laboratories. These standard methods were performed to describe the detection limit of the test, its linear range, within-run imprecision, run-to-run imprecision, and total imprecision.

The detection limit of the assay was 3.1 mg/dL, and its linear range was 3.1 to 90 mg/dL. The within-run imprecision was 5.0% at 4.82 mg/dL and 3.4% at 24.87 mg/dL. The between-run imprecision was 10.9% at 4.82 mg/dL and 5.7% at 24.87 mg/dL. The imprecision of the assay was comparable to other devices of the same type. The assay produced consistent results from lot-to-lot, and from laboratory-to-laboratory. Common substances, that is, hemoglobin (up to 500 mg/dL, bilirubin (up to 20 mg/dL), ascorbic acid (up to 3 mg/dL) and glucose (up to 1200 mg/dL), did not interfere with the assay.

VIII. Clinical Studies

Otsuka also conducted three clinical studies to demonstrate that its RLP-Cholesterol Assay is substantially equivalent to the predicate devices. These studies were: the Reference Range Study, the Type IIb, III and IV Study, and the Clinical Utility Study. The Reference Range Study and the Type IIb, III and IV Study provide critical information to demonstrate the performance of the RLP-Cholesterol Assay. The Clinical Utility Study provides additional supporting information.

A. Reference Range Study

The study enrolled 729 healthy volunteers who provided informed consent. Approximately 120 males and 120 females were enrolled into each of the three age groups (18 – 34, 35-54 and ≥ 55 years old). Subjects may have been normolipidemic or hyperlipidemic. The 95th percentile for the RLP-C to total TG ratio was calculated and used as the basis to establish a cut-off value.

The mean fasting and random RLP-C to total serum TG ratios were 0.05 ± 0.02 and 0.06 ± 0.02 , respectively. The 95th percentile from subjects, fasting or random samples, was 0.08. However, 95th percentiles of 0.09 were observed in some relatively large subgroups of subjects.

Considering the differences in some subgroups, a value of ≥ 0.10 was selected as the cut-off for the RLP-C to total serum TG ratio.

B. Type IIb, III and IV Study

This study evaluated the performance of the RLP-Cholesterol Assay to one of the predicate devices (REP Kit) and to the laboratory reference method (ultracentrifugation).

This clinical study, which utilized a matched case-control study design, was conducted at two centers specializing in familial lipid disorders.

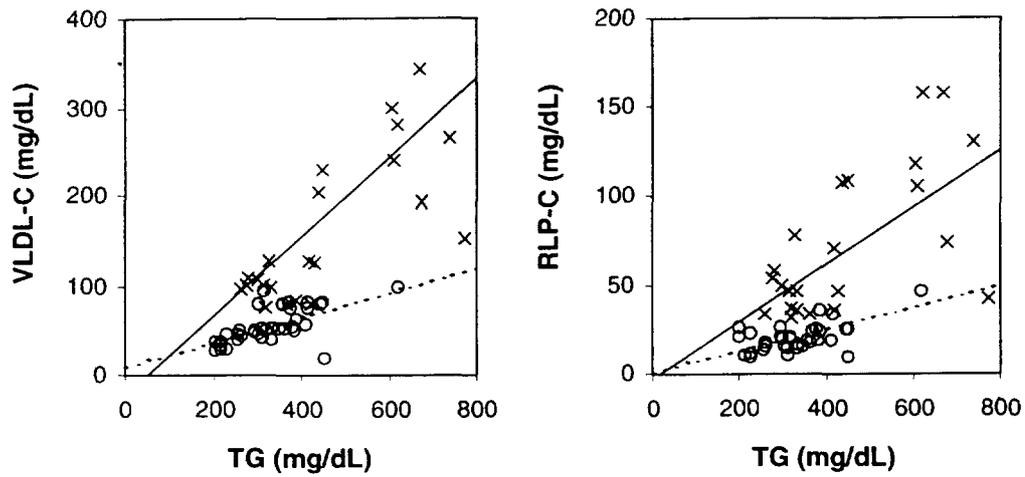
The study design allowed Otsuka: (1) to enroll a sufficient number of subjects with familial type III hyperlipoproteinemia, even in light of the rarity of the genetic disorder (1 to 10 in 10,000 in the general population); and, (2) to compare the performance of the new device with the predicate device and ultracentrifugation in diagnosing type III hyperlipoproteinemia from other types of hyperlipoproteinemia with similar lipid profiles. Subjects with type IIb, III, and IV hyperlipoproteinemia are clinically indistinguishable based upon their cholesterol and TG levels.

Sixty-two subjects enrolled in the study met the inclusion/exclusion criteria and had total serum TG levels between 200 and 800 mg/dL. Of the 62 subjects, 24 had type III hyperlipoproteinemia; 38 had type IIb or IV hyperlipoproteinemia.

Lipoproteins measured by the RLP-Cholesterol Assay (RLP-C values) and by ultracentrifugation (VLDL-C values) were highly correlated (Pearson $r = 0.96$). The relationship was similar among subjects with type III hyperlipoproteinemia and subjects without this disorder.

At all TG concentrations, the RLP-C and VLDL-C concentrations were significantly higher in type III subjects than in non type IV subjects, as shown in the figure below. This finding reflects the accumulation of remnant lipoproteins in type III subjects

Linear Relationship between VLDL-C (left), RLP-C (right) and TG in type III (crosses) and non-type III Subjects (open circles)



The solid lines represent the linear regression line for the type III samples; the dotted lines represent the linear regression lines for the non-Type IV samples

Consistent with previous reports, type III subjects had significantly higher RLP-C to total TG, and VLDL-C to total TG, ratios. The mean RLP-C to total TG ratio in type III subjects was 0.16 versus 0.06 in non-type III subjects. For the reference method, the mean VLDL-C to total TG ratio in type III subjects was 0.34 versus 0.17 in non-type III subjects.

The ability of the RLP-Cholesterol Assay, the predicate device, and the laboratory reference method (ultracentrifugation) to diagnose type III hyperlipoproteinemia was compared. These analyses included only type III and non-type III subjects who had fasting total cholesterol concentration > 200 mg/dL and total serum TG concentration between 200 and 800 mg/dL. These subjects resemble the target population for the use of RLP-C total TG ratio.

Of the 20 type III subjects, 19 (95.0%) had an RLP-C to total TG ratios ≥ 0.10 ; 16 had a VLDL-C to total TG ratios ≥ 0.30 , and 20 had β -VLDL present. The only type III subject who had an RLP-C to total TG ratio < 0.10 also had the VLDL-C to total TG ratio < 0.30. In comparison, all 31 non-type III subjects were negative for β -VLDL; 29 (93.5%) had the RLP-C to total TG ratio < 0.10; and 30 (96.8%) had the VLDL-C to total TG ratio < 0.30.

In total, the RLP-Cholesterol Assay properly diagnosed 48 of the 51 subjects (94.1%) versus the laboratory reference method, which properly diagnosed 46 of the 51 subjects (90.2%). The predicate device properly diagnosed 51 subjects (100.0%).

These results demonstrate that the RLP-C to total TG ratio performed at least as well as the laboratory reference method and similarly to the predicate device in the diagnosis of type III hyperlipoproteinemia. The predicate device in this case requires the isolation of serum lipoproteins by ultracentrifugation to confirm a diagnosis of type III hyperlipoproteinemia. The predicate device does not require this complex and labor-intensive additional step to diagnose either type IIb or IV hyperlipoproteinemia. This demonstrates the difficulty in diagnosing type IV hyperlipoproteinemia, and highlights the need for new methods which do not rely upon ultracentrifugation because of its limited availability in laboratories. Thus, with this device, the diagnosis of type III hyperlipoproteinemia will become more widely available in clinical practice.

C. Clinical Utility Study

The study provided additional supportive information about the effectiveness of the RLP-Cholesterol Assay. Unlike the Type IIb, III and IV Study described above; this study did not select subjects based upon type of hyperlipoproteinemia. Instead, it selected healthy subjects, subjects with coronary artery disease, and subjects with diabetes. Of the 724 subjects were enrolled in the study, 140 of them were hyperlipidemic (serum total cholesterol and TG concentrations > 200 mg/dL). Of the 140 hyperlipidemic subjects, the overall agreement between the RLP-C to TG ratio and the VLDL-C to TG ratio was 98.6%.

There were two hyperlipidemic subjects who had familial type III hyperlipoproteinemia in the study. Both these two subjects had an RLP-C to total TG ratio ≥ 0.10 but only one had the VLDL-C to total TG ratio ≥ 0.30 .

IX. Overall Conclusions

The performance data clearly demonstrate that the RLP-Cholesterol Assay is substantially equivalent to the predicate devices. Two clinical studies with different study designs and study populations demonstrate that the RLP-Cholesterol Assay performed as well as the laboratory reference method and is similar to the predicate devices in the diagnosis of type III hyperlipoproteinemia.



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SEP 18 2002

Otsuka Pharmaceutical Co., Ltd.
c/o Mr. James Harris, Ph.D.
Otsuka America Pharmaceutical, Inc.
2440 Research Blvd.
Rockville, Maryland 20850

Re: K991083
Trade Name: RLP Cholesterol Immunoseparation Assay
Regulatory Class: I reserved Product Code: CHH
Regulatory Class: I Product Code: JHO
Dated: June 21, 1999
Received: June 21, 1999

Dear Mr. Harris:

This SE Letter corrects SE Letter dated August 20, 1999. It corrects the Product Code under Class I which read JHD to JHO.

We have reviewed your Section 510(k) notification of intent to market the device referenced above and we have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

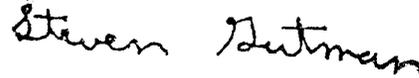
If your device is classified (see above) into either class II (Special Controls) or class III (Premarket Approval), it may be subject to such additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 895. A substantially equivalent determination assumes compliance with the Current Good Manufacturing Practice requirements, as set forth in the Quality System Regulation (QS) for Medical Devices: General regulation (21 CFR Part 820) and that, through periodic QS inspections, the Food and Drug Administration (FDA) will verify such assumptions. Failure to comply with the GMP regulation may result in regulatory action. In addition, FDA may publish further announcements concerning your device in the Federal Register. Please note: this response to your premarket notification submission does not affect any obligation you might have under sections 531 through 542 of the Act for devices under the Electronic Product Radiation Control provisions, or other Federal laws or regulations.

Under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88), this device may require a CLIA complexity categorization. To determine if it does, you should contact the Centers for Disease Control and Prevention (CDC) at (770) 488-7655.

This letter will allow you to begin marketing your device as described in your 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific advice for your device on our labeling regulation (21 CFR Part 801 and additionally 809.10 for in vitro diagnostic devices), please contact the Office of Compliance at (301) 594-4588. Additionally, for questions on the promotion and advertising of your device, please contact the Office of Compliance at (301) 594-4639. Also, please note the regulation entitled, "Misbranding by reference to premarket notification"(21 CFR 807.97). Other general information on your responsibilities under the Act may be obtained from the Division of Small Manufacturers Assistance at its toll-free number (800) 638-2041 or (301) 443-6597, or at its internet address "<http://www.fda.gov/cdrh/dsma/dsmamain.html>".

Sincerely yours,

A handwritten signature in black ink that reads "Steven Gutman". The signature is written in a cursive style.

Steven I. Gutman, M.D, M.B.A.
Director
Division of Clinical
Laboratory Devices
Office of Device Evaluation
Center for Devices and
Radiological Health

Indications for Use

510(k) Number (if known):

Device Name: RLP-Cholesterol Immunoseparation Assay

Indications for Use:

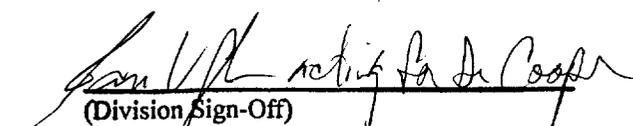
The RLP-Cholesterol Assay is intended for use in the quantitative determination of cholesterol contained in remnant lipoproteins in human serum or plasma. The test results are used in combination with total serum triglyceride measurements to aid in the diagnosis of familial type III hyperlipoproteinemia in patients with serum total cholesterol concentration \geq 200 mg/dL and triglyceride concentrations between 200 and 800 mg/dL.

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use

OR Over-The-Counter Use

(Per 21 CFR 801.109)


(Division Sign-Off)

Division of Clinical Laboratory Devices

510(k) Number

K991083