Title:	"PHASE III CLINICAL STUDY TO EVALUATE THE THERAPEUTIC EFFICACY IN MEXICAN PATIENTS WITH DYSLIPIDEMIA THROUGH THE ORAL ROUTE USE OF L-CARNITINE + ATORVASTATIN COMPARED WITH ATORVASTATIN."
Investigational product:	Atorvastatin 10mg/Carnitine 500mg
Posology indications:	Dyslipidemias of the total hypercholesterolemia type, LDL lipoprotein hypercholesterolemia, hypoalphalipoproteinemia, hypertriglyceridemia.
Type of study:	Phase III clinical assay, experimental randomized with two other multi-center, longitudinal treatment groups, to evaluate the therapeutic efficacy in the dyslipidemias of Mexican adults.
Code of study:	**GMX-001-2017**
Clinical phase of study:	Phase III Study
Sponsor:	Valeant Pharmaceuticals International. Calzada de Tlalpan 2021 Col Parque San Andrés México D.F. C.P. 04040
Elaboration and Coordination:	Dr. Ventura Aguirre Rojas. Medical and Regulatory Director for Mexico and Latin America, Valeant Pharmaceuticals International Dr. Francisco Javier Figueroa Vallejo. Coordinator of Clinical Studies for Mexico and Latin America, Valeant Pharmaceuticals International
Elaboration date:	August 3, 2017.
Version Number:	02.
Amendment Number :	0.

CONFIDENTIALITY AGREEMENT

The information contained in this document, especially the non-published data, is property of Valeant Pharmaceuticals International (or is controlled by it).

This document is provided confidentially to investigator, potential investigator or consultant, for its revision and/or revision by its workgroup, and in the event of revision by the Ethics Institutional Review Board.

It is understood that this information shall not be made known to third parties, without written authorization from Valeant Pharmaceuticals International, with the exception and in the necessary extension to obtain the informed consent of the participants to whom the medicine will be administered.

SIGNATURE PAGE FOR AUTHORIZATION BY THE SPONSOR

Valeant Pharmaceuticals International is committed to perform the study according to what is stipulated in this protocol, in conformity with the existing guidelines of the Regulations for the human research of the General Health Law, COFEPRIS, the Good Clinical Practices (GCP), the Helsinki Declaration and the International Conference on Harmonization (ICH).

Dr. Ventura Aguirre Rojas

Medical and Regulatory Director of Mexico and Latin America

Signature: _____ Date: / /

DD MMM YYYY

Dr. Francisco Javier Figueroa Vallejo

Clinical Research Coordinator of Mexico and Latin America

Signature: _____ Date: / /

DD MMM YYYY

M.C. Cesar Alik Pedrajo Zenteno

Pharmacovigilance Manager of Latin America

Signature: _____ Date: / /

DD MMM YYYY

SIGNATURE PAGE FOR APPROVAL OF PROTOCOL BY THE PRINCIPAL INVESTIGATOR

Complete name (in print): _____

Location of the site for the research: _____

Address (street, number, colony, municipality, state and Z.C.): _____

_____

_____

Fixed Telephone: _____

Mobile Telephone: _____

E-mail: _____

I have read this protocol and I commit myself to carry out the study according to what is stipulated in it, in conformance with prevailing guidelines of the Regulation for human research of the General Health Law, COFEPRIS, Good Clinical Practices (GCP), the Helsinki Declaration and the International Conference for Harmonization (ICH).

Any deviation from this protocol shall be agreed in writing, previous analysis, between the Sponsor and me.

I agree that I or the person designated by me, will inform completely to all participating patients in this study about the pertinent details and purpose of the study before they accept to participate in the study in conformance to what is established in the GCP and in the requirements of the regulatory authorities.

I shall be responsible of preserving the format of informed consent of each patient in the study file and of providing each patient with a faithful copy of the signed original of its informed consent format.

Name and signature: _____

Date: ____/____/____
DD MMM YYYY

Table of Contents

SUMMARY

General objectives:	Evaluate the therapeutic efficacy in Mexican adults with dyslipidemia through the oral route use of L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment. Evaluate the safety of the medicines under study.
Hypothesis:	The combined use of L-carnitine + atorvastatin offers therapeutic superiority with respect to the use of atorvastatin as treatment to reduce the percentage of C-LDL in patients with dyslipidemia. The combination of L-carnitine + atorvastatin shows fewer incidences in the presence of adverse events attributable to the medicine in comparison to the use of atorvastatin as mono-therapy, in the treatment of dyslipidemia patients.
Design:	Phase III clinical assay, experimental randomized with two treatment, multi-centered, longitudinal, to evaluate the therapeutic efficacy in dyslipidemias of Mexican adults.
Material and Methods:	
Sample Size	120 subjects will be included.
Inclusion Criteria	Mexicans between 35 and 75 years of age. Gender indistinct. Patient with abnormal lipid profile considered as serum levels of C-LDL of 100mg/dl or greater obtained by laboratory parameters. Not under pharmacologic treatment to handle their dyslipidemia or accepting to suspend their current treatment and be evaluated for their inclusion in the next 3 weeks starting on the day of the initial evaluation. Women in fertile stage with a safe, hormonal-free family planning method. A safe planning method includes surgical methods in women, intrauterine device that doesn't release progestines and use of preservative in all their sexual relations. Women in fertile stage who don't wish to become pregnant during their participation in the study. Post-menopause women or with hysterectomy history. Have a fixed and/or mobile telephone and accept to receive calls from the site for study processes. Grant their duly informed consent.
Exclusion Criteria	Subject lacking the mental capacity to understand the processes which imply their participation in the study and thus,

	not capable of granting their participation in a voluntary manner. History of hypersensitivity to the medicines being studied. Daily intake of at least 240ml of grape juice or sporadic ingestion of 1 liter. Potentially fertile women without a safe family planning method, who wish to become pregnant during the study, are already pregnant or in lactation period. Having on Globorisk scale for Mexicans, or as an associated risk factor, a high stratification for cardiovascular risk. Basal laboratory values with elevation of ALT 1.5 times larger than the upper limit considered normal according to international units. Basal laboratory values with elevation of CPK not attributable to physical activity. Subjects who are under anti-coagulant treatment, suffer from coagulation disorders, or any circumstance which contraindicates the taking of a blood. History of acute myocardial infarction, unstable angina, some confirmed coronopathy, arrhythmias, congestive cardiac failure or cerebrovascular disease. History of muscular conditions of the genetic type or of rhabdomyolysis in patient or first degree relative. History or diagnose of congenital hepatic disorders, chronic infection by hepatitis virus, hepatitis with fatty liver, alcoholic hepatitis, primary biliary cirrhosis, primary sclerosis, cholangitis or hepatic failure. History or diagnose of congenital renal disorders, chronic renal failure, acute renal damage or nephritic syndrome. History of infection by Human Immunodeficiency Virus. History of Acute or Chronic Pancreatitis. History of the following endocrine diseases: non-controlled Diabetes Mellitus, lipodystrophy, thyroid disorders, Cushing Syndrome and/or Polycystic Ovary Syndrome. Diseases which compromise immunity such as Systemic Lupus Erythematous, Rheumatoid Arthritis, Antiphospholipid Antibodies Syndrome or Psoriasis. Diseases by deposit such as Gaucher Disease, disease by glycogen deposit, Tay-Sachs juvenile disease or Niemann Pick Disease. Diagnose of Kawasaki Disease, Werner Syndrome, intermittent acute Porphyria, Idiopathic Hyperkalemia or Klinefelter Syndrome.

	Suffer from Idiopathic Hyperkalemia, Klinefelter Syndrome, Werner Syndrome, Kawasaki Disease or Porphyria. History of epilepsy. History or diagnose of alcoholism. Intake of more than 20g of alcohol per day. User of marihuana. User of illegal drugs. Intake of medicines with pharmacologic interaction which increase or decrease the efficacy of L-Carnitine and/or atorvastatin or alter the lipids in blood such as: Macrolide antibiotics: Erythromycin, Telithromycin and Clarithromycin. Azole anti-fungi: Ketoconazole, Itraconazole, Fluconazole and Nefazodone. Quercetin, Amiodarone, Aprepitant, Cimetidine, Ciprofloxacin, Cyclosporine, Diltiazem, Imatinib, Echinacea, Enoxacin, Ergotamine, Metronidazole, Mifepristone, Tofisopam, Gestodene, Verapamil, Mibefradil, Fluoxetine, Phenobarbital, Carbamazepine, Phenytoin, Rifampin, Modafinil, Glucocorticoids, Felbamate, Rosiglitazone, Griseofulvin, Pioglitazone, Gemfibrozil, Clofibrate, Fenofibrate, Niacin, Nefazodone, Cholestyramine, Colchicine, Colestipol, Primidone, Topiramate, Troglitazone, Rifabutin, Digoxin, Thiazides, anabolic Steroids, Progestogens, Estrogens, Danazol, Amiodarone, fibric Acid, docosahexaenoic acid, Isotretinoine, Immunosuppressives, protease inhibitors of HIV or of the Hepatitis C Virus, Inhibitors of the co-transport of sodium-glucose, Tamoxifen, Raloxifene, non-selective Beta blockers, biliary acid sequestrants, asparginase, Sirolimus and Interferon. Patients who have been diagnosed with terminal conditions. Patients with recent Cancer diagnose or undergoing any type of therapy for same. Patients who have suffered skin cancer not of the melanoma type and have been cured and haven't been on treatment for at least 1 year before the start of their participation in the study may enter. Patients under lipid lowering treatment and who, because of their clinical condition aren't candidates to the period of lavage or detoxification; or well reject same. Been participating in another clinical trial or having concluded their participation in the 30 days previous to beginning their participation in this study. Any other which, at the Investigator's criteria, puts at risk the safety of the participant and/or interferes with the results of the study.

Medicine	L-Carnitine, Atorvastatin
Dose	L-Carnitine 1 g + Atorvastatin 20 mg daily for 6 months and Atorvastatin 20 mg daily for 6 months
Efficacy criteria:	The efficacy of the combined treatment vs. atorvastatin in mono-therapy for dyslipidemia will be compared, through evaluation of the variability of the biochemical parameters at the start and end of the study.

INTRODUCTION

Cardiovascular diseases constitute the first cause of mortality in Mexico and the world; in 2012 they caused 46% of non-transmissible secondary deaths and 37% in premature deaths in persons under 70 years of age; situations that were potentially reversible with an adequate handling of prevention. For the year 2030 a mortality of 22.2 million persons is projected, according to data from the World Health Organization in 2014. [1]

This overall view sets us on the way to act on the factors that may determine the risk of suffering cardiovascular diseases; for this, primary and secondary prevention strategies have to be used, which modify morbidity and mortality. In this area, dyslipidemias have a wide terrain, for they form part of the modifiable cardiovascular risk factors; being the main identified modifiable factor. [L1] This correction is linked to a cost-effective benefit in population older than 20 years, becoming its prevention and handling a necessity. [2, L1] Besides, a favorable effect has been proven in the diminishing of tension figures secondary to the decrease of figures of fatty acids in serum. [L1, L2]

Furthermore, dyslipidemias have been associated as a risk factor for the acquisition of type 2 Diabetes Mellitus (significant cause of mortality at national and global level) and arthrosclerosis; the latter pathology plays a central role in three of the five main causes of death in Mexico. [L1]

Certain strategies necessary for underscoring the problem of interest have been identified, with an integral focus which rises from the changes in lifestyle; the exception are the dyslipidemias of genetic origin or of primary origin. Another impact strategy is the secondary prevention, done in populations with high cardiovascular risk; with a predominantly clinical focus, aimed at early detection and opportune treatment of the dyslipidemias to avoid a disease by alteration of fatty acids. The outline of nutritional and pharmacologic treatment of patients with dyslipidemias is based on the serum levels of lipids, in function of the cardiovascular risk level and certain particular recommendations, [2] being able to continue with this pairing of treatment as a manner of keeping the lipids level below the limited parameters according to the established cardiovascular risk level.

The statins are a pharmacologic group used in the correction of serum levels of lipids which are found altered in dyslipidemias, available since 1987, broadly described and well-tolerated. [3] Their use is recommendable in the primary and

secondary prevention of the dyslipidemias. [2, 4]

Identified secondary reactions have been attributed to them that in special situations limit their use. [5] But at the same time, with the previous identification of the factors that make the patients prone to suffering these reactions and due to their low frequency, they keep on being used and are the most adequate management to treat the dyslipidemias, with an approach to benefit in the decrease of the cardiovascular risk. [6]

Even so, in this protocol the possibility of finding a therapeutic alternative with a greater efficacy and a better safety profile is proposed, adding the L-carnitine, which counts with a repertory of evidence that sustains the safety and therapeutic efficacy in dyslipidemia patients. [7]

In this study, the necessary elements to sustain the performance of the study in a Mexican population will be approached in an integral manner with an objective focus. To lead to the efficacious comprehension of the study protocol definition and abbreviations are included, which will be set in the posterior section. In the theoretical frame the basic concepts of the alterations of lipids in Mexicans will be explained; besides, the argumentation of dyslipidemias will be led based on the antecedents and the therapy used as an interrogative derived from previous studies, indicating the relation of the themes, sub-themes or variables.

It is transcendent to know the magnitude, relevance and impact of the interrogative in study, how a therapy adequate to the patient who courses with dyslipidemias may have a new expectative of treatment that is efficacious and safe, for which the necessary argumentation is recurred to situate the necessity of the study.

In the proposed hypothesis the postulate of proving the therapeutic efficacy of L-carnitine + atorvastatin in comparison to atorvastatin arises, for which overall and specific objectives are proposed that Valeant Pharmaceuticals International through their department of Clinical Research considers of special interest in this protocol study. Nonetheless, there exist premises of the study, which will be considered in compliance in temporality and convenience of Valeant Pharmaceuticals International during the study, not being a primordial part of study object but that, may include the generation of new investigations focused on the therapeutics of dyslipidemias and associated factors for the benefit of the Mexican population.

The methodology used describes the procedures and tools that will help in the fulfillment of the research, following a structure of logical ordination for a study of experimental nature with clinical object, through the collection of data from the adequate sources. A study of the therapeutic efficacy of the product under research for dyslipidemias is proposed, with exploratory goals and longitudinal interventions and random assignation of treatments blind to the observer; localizing this study as a clinical assay of therapeutic superiority. The criteria for the selection of patients are focused on allocating for the population that has the condition a treatment that has therapeutic benefits and foresees the incidence of adverse events related with the investigational product and the active control, as well as the foreseeables not related with the investigational product. In the progression of the protocol the methods for data gathering and the analysis processing of same are described.

In this document is included a chronogram that mentions the times to follow previous to the inclusion of the participants, during and posterior to the conclusion of their participation in the study; besides the processes that will be carried out with the documentation generated during and after the study.

This protocol forms part of the Clincal Trials of Valeant Pharmaceuticals International, a responsible pharmaceutical company, concerned for watching the autonomy, beneficence and justice of the subjects of investigation; for which it was developed and was designed to proceed in the most ethical way possible in the handling of the participants and the documentation generated from these, having as a reference for their compliance the criteria established in the Helsinki Declaration, the Guides of Good Clinical Practices and others stipulated by the International Conference for Harmonization (ICH), not leaving aside what's contained in local regulations.

Since this protocol is designed to be carried out in Mexican population, it is written so that its content and the processes stemming from it in the investigation comply according to the Normativity and existing requirements by the Federal Commission for the Protection of Sanitary Risks (COFEPRIS). At the same time, it shall develop in concordance to the Mexican Official Norms, NOM-012-SSA3-2012 that establishes the criteria for the execution of human research projects for health in human beings, NOM- 004-SSA3-2012 of the clinical file, The Regulation of the general health law in matters of human research, General Health Law DOF 27-01-2017, Regulations of the Federal Commission for the Protection against Health Risks; making use of these of an enunciate character but not limitative, for there could be recourse to another existing normativity in favor of the adequate execution of the Clinical Study.

1. DEFINITIONS

Physical Activity: the motor acts performed by persons, as part of their daily and/or programmed (exercise) activities.

Anorexia: no food ingestion.

Apolipoproteins: proteins of the lipoprotein surface that, besides providing stability to the lipid particles, direct their metabolic destiny.

Rheumatoid Arthritis: chronic inflammatory disease, self-immune and systemic of unknown etiology; its main target organ is the synovial membrane.

Arthrosclerosis: is a disease that initially affects the intima of distribution arteries, with endothelial damage and inflammation, which is characterized by deposits of lipids and proliferation of fibrous tissue, with capacity to obstruct the vessel's lumen either by growth of the plaque or by rupture and thrombosis. It is the most frequent complication of the association of Diabetes, Arterial Hypertension and Hypercholesterolemia, with an exponential increase when associated to smoking.

Audit: A systematic and independent exam of the activities and documents related with the study to determine if the evaluated activities were executed and the data was registered, analyzed and reported with accuracy in accordance to the protocol, standard procedures of operation of the sponsor, Guidelines of Good Clinical Practices and the applicable regulatory requirements.

Fasting: the abstinence of caloric ingestion, for a determinate period of time. For the determination of lipids it will have to be from 9 to 12 hours.

Cases with known diagnose of dyslipidemia under treatment: the set of people with known diagnose of dyslipidemias which course with controlled levels of triglycerides, total cholesterol, C-HDL, C-no HDL or C-LDL in response to the treatment or continue uncontrolled despite treatment.

Cholesterol: the steroid molecule, formed by four hydro carbonated rings plus an aliphatic chain of eight carbon atoms in the C-17 and one OH in the C-3 of the A ring. Although from the chemical point of view it is an alcohol, it possesses physical properties similar to those of a lipid.

Cholesterol HDL (C-HDL, High Density Lipoprotein): is the concentration of cholesterol contained in the high-density lipoproteins. The HDL participates in the reverse transport of cholesterol, that is, from the tissues to the liver for their excretion or recycling. They are lipoproteins that contain Apo A-I and float at larger densities compared with the lipoproteins that contain the Apo B, due to their high protein content. For this they are known as high-density lipoproteins.

Cholesterol LDL (C-LDL, Low Density Lipoprotein): is the concentration of cholesterol contained in the low-density lipoproteins; transport cholesterol to the tissues, its elevation favors the appearance of arthrosclerosis and therefore, of cardiovascular problems.

Cholesterol Not-HDL: is all the cholesterol that isn't transported by the Cholesterol HDL and is potentially atherogenic. The use of non-HDL cholesterol (C-Non-HDL) as a tool to evaluate the risk of death by cardiovascular disease. The C-Non-HDL is defined as the difference between the total cholesterol value and the cholesterol of the HDL (C-no-HDL= CT - C-HDL), and comprises the fractions of lipoproteins: LDL, IDL, and VLDL, and includes highly atherogenic particles like the remnants of VLDL and Lp (a).

Acute renal damage: is a syndrome characterized by the sudden and sustained decrease of the glomerular filtrate, the diuresis or both and the consequent increase of nitrogenized products in blood.

Diabetes mellitus: is a chronic-degenerative systemic disease of a heterogeneous character, with variable degrees of hereditary predisposition and with the participation of diverse ambient factors, and which is characterized by chronic hypoglycemia due to the deficiency in the production or action of insulin, which affects the intermediate metabolism of carbohydrates, proteins and fats.

Diet: the set of foods that are consumed each day.

Healthy diet: the set of natural and prepared foods which are consumed each day with balance, variety and sufficiency in calories, proteins, carbohydrates, fats, vitamins, fiber and micronutrients, as well as the ingestion of water, to have an adequate corporal nutrition which translates in and adequate nutritional state for the age and gender.

Dyslipidemias: the alteration of the normal concentration of lipids in blood.

Source documents: Documents, data and original registries (for example, hospital registries, clinical sheets, laboratory notes, memoranda, diaries of the subjects or verification lists of evaluation, registries of delivery from pharmacy, data registered by automated instruments, certified copies or transcriptions after being verified as exact copies, micro-files, photographic negatives, magnetic means or microfilm, x-rays, expedients of the subjects and registries preserved in the pharmacy, in the laboratories and in the medical-technical departments involved in the clinical study).

Education for Health: the process of teaching-learning of attitudes in the general population that allows, through the exchange and analysis of the information, to develop abilities and change attitudes with the purpose of inducing behaviors to avoid overweight, obesity, sedentary lifestyle, stress, smoking and the excessive consumption of alcohol, as well as the factors of lifestyle which propitiate the development of dyslipidemias and which are acquired with an attitude contrary to the observance of individual, familiar and collective health.

Peripheral arterial disease: is one of the clinical manifestations of arthrosclerosis characterized by stenosis or obstruction of the arterial lumen due to plaques of atheroma originated in the intima which affects the abdominal aorta and its terminal branches.

Premature cardiovascular disease: the onset of manifestations of cardiovascular disease in men under 55 or women under 65.

Statins: pharmacologic group utilized as a lipid-lowering agent with effect over the inhibition of the enzyme HMG-CoA reductase.

Healthy lifestyles: refers to behaviors that diminish the risk of contracting disease such as: correct feeding, adequate control and treatment of tensions and negative emotions: good exercise, sleep and distraction regime; the control and avoidance in the abuse of substances such as caffeine, nicotine and alcohol; a correct distribution and use of time.

Clinical file: the set of written, graphic and imaging documents or of any other nature, in which the health personnel shall make the registries, annotations and certifications correspondent to their intervention, with arrangement adherence to the sanitary dispositions.

Cerebral vascular event: presence of neurologic symptoms which have an abrupt onset such as headache, nausea, vomit, deterioration of vigil, aphasia or hemiparesis, and which are corroborated with an image study.

Risk factor: the attribute or exposition of a person, population or environment, that are associated to the probability of the occurrence of an event.

Fibrates: pharmacologic group for the treatment of dyslipidemias with action on the receptor of peroxisomal proliferators.

Tumor necrosis factor: is a protein of the group of cytokines released by the cells of the immune system that intervene in the inflammation and the apoptosis.

Unsaturated fats: these are found in foods of vegetable origin like vegetable oils (olive, sunflower or corn oil). Also in dry fruits (nuts, almonds, etc.) and in seeds (sesame, sunflower, flax). These are liquid fats at ambient temperature. According to the number of double links they present, they are classified as:

- Monounsaturated (one sole double link): the most representative is oleic acid present mainly in olive oil and other fats of vegetable origin like seed oils (sunflower seed oil, colza oil). They are also found in nuts, almonds and avocados. The substitution of saturated fats for unsaturated fats in the diet contributes to maintaining normal levels of blood cholesterol. Oleic acid is an unsaturated fat.

- Polyunsaturated (two or more double links): These are essential for our organism because they can't be synthetized and must be supplied through the daily diet to regulate metabolic processes of the cardiovascular, immune and pulmonary systems, among others. They are present in foods of vegetable and animal origin. There exist two families within these: Omega 3 and Omega 6.

Saturated fats: these are found in foods of animal origin like meats, sausages, milk and derivatives (cheese, ice-creams). These are fats that solidify at ambient temperature. They can also be found in oils of vegetable origin like coconut or palm oils (which are consumed through industrial pastries, salty aperitifs and transformed products).

Trans fats: these are unsaturated fats that are formed in the industrial processing of some foods known as hydrogenation, during which they change their configuration and pass from being unsaturated fats to saturated fats, becoming solid fats. They are found in fried foods, snacks, baked products (cakes, rolls, cookies) and prepared foods. The consumption of Trans fat

acids causes in the organism an effect more negative than saturated fats since it increases the levels of C-LDL and triglycerides and also reduces the C-HDL in blood.

Family hypercholesterolemia: is the dyslipidemia associated to a larger risk of arthrosclerosis, is the entity in which the main abnormality is the elevation of C-LDL as consequence of the mutations of the gen of the receptor LDL, of the apoB or of the proprotein gen convertase subtilisin kexin 9 (PcsK9). There are two forms, the heterozygotes and the homozygotes; their transmission may be dominant or recessive autosomal. It is characterized for having levels of total cholesterol greater than 400mg/dL. The corneal arch and the sinewy xanthomas are characteristic of this pathology.

Polygenic Hypercholesterolemia: is the entity in which the elevations of C-LDL are superior to 160 mg/dL and <190mg/dL and characteristically xanthomas aren't present. Diagnose is established when at least one first-degree relative has C-LDL above 160 mg/dL.

Hyperglycemia: elevation of glucose above 100mg/dl.

Combined Family Hyperlipidemia: is the entity which manifests with different phenotypes, with constant fluctuations in the lipid profile, absence of xanthomas, Apo B > percentile 90 demographic, family or personal history of premature ischemic cardiopathy, have a relative with hypertriglyceridemia, a relative with hypercholesterolemia and a relative with both dyslipidemias, association with Metabolic Syndrome.

Systemic arterial hypertension: is a syndrome of multiple etiologies characterized by the persistent elevation of arterial pressure figures ≥ 140/90 ml/Hg.

Endogenous familial hypertriglyceridemia: the entity in which there is triglyceride values greater than 200 mg/dL, with C-LDL normal or low. The levels of C-HDL are diminished and normal levels of Apo B, coexist in patients with type 2 Diabetes.

Hypertriglyceridemia: abnormal elevation of triglycerides in blood, greater than 150mg/dl.

Hypoalphalipoproteinemia: abnormal descent of type HDL cholesterol in blood less than 40mg/dl.

Lipid-lowering agents: the medicines that reduce the lipid levels in blood.

Hypothyroidism: common endocrine disease, caused by and inadequate action of thyroid hormones, mainly by diminishment in their synthesis and secretion and occasionally by peripheral resistance to thyroid hormones.

Corporal mass index (CMI): is the corporal weight divided by the height squared (Kg/m2).

Chronic renal failure: diminishment in renal function, expressed by a glomerular rate of filtration less than 60 ml/min/1.73m^2 or as the presence of renal damage (histologic alterations, albuminuria, proteinuria, alterations of the urinary sediment or alterations in image tests) in a persistent manner during at least 3 months.

Insulin deficiency: deficiency in the secretion of insulin by the pancreas causes hyperglycemia.

Investigator: A person responsible for the conduction of the clinical study at the site where the study is done. If the study is conducted by a group of individuals the investigator is the leader responsible for the group and shall be called main investigator.

Systemic Lupus Erythematous: a disease that is self-immune, inflammatory, chronic and of unknown etiology, which is characterized by the presence of multiple antibodies and a wide spectrum of clinical manifestations in different organs and systems, among which the skin, joints, kidney, lung, central nervous system, serous membranes and other systems stand out.

Myalgia: presence of muscular pain.

Myoglobinuria: presence of myoglobin in urine.

Myonecrosis: death of muscular tissue.

Myositis: presence of muscular inflammation.

Monitoring: The act of supervising the process of a clinical study and assuring that it is conducted, registered and reported according to the protocol, Standard Operative Procedures, Guidelines of Good Clinical Practices and the applicable regulatory requirements.

Obesity: CMI equal to or greater than 30 in adults.

Sponsor: An individual, company, institution or organization responsible of initiating/managing/controlling and/or financing a clinical study.

Placebo: inert substance from a pharmacologic point of view.

Person at risk: a person with one or several factors that could develop a dyslipidemia.

Corporal weight: according to the Corporal Mass Index (Kg/m2), to the next classification: Corporal mass index >18.5 and <24.9 normal weight, Corporal mass index > 25 and < 29.9 overweight, corporal mass index > 30 obesity.

Pre-diabetes: a person with an intermediate metabolic state between normal state and Diabetes. The term pre-diabetes is applied in cases of Abnormal Fasting Glucose (AFG), as well as in cases of Intolerance to Glucose (ITG).

Primary prevention: set of activities done by the health personnel, by the community or by governments to prevent or delay the onset of a determinate condition.

Secondary prevention: activity that tries to delay the recurrence or death by a disease.

Cardiovascular disease: term that refers to al vascular diseases caused by arthrosclerosis.

First attention level: the attention units that constitute the entry to health services; they are primordially oriented to the promotion of health, prevention, detection, diagnose, early treatment and control of most prevalent diseases.

Reactive protein C: circulating plasmatic protein that increases its levels in response to inflammation.

Psoriasis: chronic condition that is inflammatory, systemic, with a genetic etiology and that may be modified by environmental factors. It is characterized by the presence of scales, erythematous patches, papules and plaques that are frequently itchy and often manifest in bone projections.

Chylomicrons: Lipoprotein isolated through ultracentrifugation of plasma, characterized by low density and large diameter.

Rhabdomyolysis: disorder characterized by the de-structuring and posterior necrosis of the skeletal muscle.

Resistance to insulin: is the decrease of the action of this hormone in muscular, hepatic and adipose tissues.

Cardiovascular risk: probability of presenting a death by cardiovascular event within 10 years.

Second level attention: the units that addresses health problems that due to their complexity can't be solved in the first attention level.

Cushing syndrome: Hormonal disorder caused by excess of exposure to cortisol.

Anti-phospholipid antibodies syndrome: pro-thrombotic, self-immune and systemic disease characterized by the association of venous and/or arterial thrombosis, recurrent fetal loss, often accompanied by mild to moderate thrombocytopenia and elevated titles of anti-phospholipid antibodies.

Metabolic syndrome: the set of biochemical, physiological and anthropometric abnormalities, that occur simultaneously and may produce or be linked to the resistance to insulin and/or overweight or central obesity, that increase the risk of developing Diabetes mellitus, cardiovascular disease or both. Its fundamental components are: abdominal obesity, pre-Diabetes or type 2 Diabetes mellitus, arterial hypertension or frontier arterial pressure, dyslipidemia (hypertriglyceridemia and/or low HDL).

Nephritic syndrome: common endocrine disease, caused by inadequate action of the thyroid hormones, mainly by decrease in their synthesis and secretion and occasionally by peripheral resistance to thyroid hormones.

Smoking: is the addiction to tobacco or other products of tobacco.

Triglycerides: are the molecules of glycerol, esterified by three fatty acids. It is the main form of energy storage in the organism. Also called triacylglycerols.

Ubiquinone: also called Coenzyme Q10; is a 1,4-benzoquinona, where the Q refers to the chemical group quinone, and the 10 refers to the number of subunits of the chemical product isoprenyl in its tail.

Tendinous xanthomas: these are the subcutaneous lipid deposits, in form of protuberances, located mainly in the Achilles' tendon or in the tendons of the extensor muscles of the hands, associated to the elevation of serum cholesterol.

Tuberous xanthomas: are the subcutaneous lipid deposits located on knees and elbows, associated to dysbetalipoproteinemia.

2. SYMBOLS AND ABBREVIATIONS

ALT: Alanine aminotransferase

APO B: Apolipoprotein B

APO CII: Apolipoprotein CII

AST: Aspartate aminotransferase

AUC: Area Under the Curve

C-HDL: Cholesterol of high density lipoproteins

C-LDL: Cholesterol of low density lipoproteins

C-No-HDL: Cholesterol no HDL

CPK: Creatinine phosphokinase

CT: Cholesterol total

ENSANUT: Health and Nutrition National Survey

g: Grams

HMG-CoA: Hydroxymethyl-glutaryl-coenzyme A

IL-6: Interleukin 6

IL-1: Interleukin 1

CMI: Corporal Mass Index

CH: Carbohydrates

Kcal: Kilocalorie

Kg/m2: Kilograms per meters (height) squared

LDL: Low-density lipoproteins

MCP-1: Monocyte 1 Chemoattractive lipoproteins

mg: Milligram

mg/day: Milligrams per day

mg/dl: Milligrams per deciliter

mg/kg: Milligrams per kilogram

mmHg: Millimeters of mercury

NCEP: National Cholesterol Education Program

MON: Mexican Official Norm

PCSK9: Proprotein convertase subtilisin/kexin type 9

PPAR: Peroxisomal proliferator receptors

TG: Triglycerides

TNF: -Tumor Necrosis Factor

VLDL: Very Low Density Lipoproteins

%: Percentage

>: Grater than

<: Less than

≥: Greater than or equal to

≤: Less than or equal to

°C: Degrees Centigrade

3. THEORETICAL FRAMEWORK

3.1. Lipids

Lipids are a group of immediate principles, very heterogeneous from the molecular point of view, but they maintain a common characteristic: they are soluble in inorganic solvents and insoluble in an aqueous medium. They participate in diverse organic functions as structures in the cellular wall, energetic deposits, structure of hormones and cellular signaling. According to their composition they are classified in simple lipids and complex lipids. The simple lipids contain only carbon, hydrogen and oxygen; in this group are included fatty acids, acylglycerols, waxes and cholesterol. The complex lipids contain carbon, hydrogen, oxygen and besides phosphorus and/or nitrogen and/or sulphur; some examples are phospholipids and sphingolipids. [8]

Within the lipids of interest in this study are found the Total Cholesterol, high density Cholesterol (HDL), low density Cholesterol (LDL) and triglycerides.

Cholesterol has a molecular structure derived from cyclopentone cholesterol Cyclopentanoperhydrophenanthrene (sterane), with polar head (hydroxyl group) and a-polar tail. It is found present in the cells of vertebrate animals, is an essential component of plasmatic membranes and precursor of lipoproteins, biliary salts, vitamin D and hormones (sexual and corticosteroids). Because of their hydrophobic character, in blood it is transported by lipoproteins and, at cellular level, can be found forming part of the membranes or in the cytoplasm, previous esterification with a fatty acid, for the excess of free cholesterol is toxic for the cell. The accumulation of intracellular esterified cholesterol is harmful to man, favoring the development of arteriosclerotic lesions [9]

More than half of cholesterol is obtained from the diet, known as exogenous cholesterol; the rest is synthetized inside the organism and is known as endogenous cholesterol. It isn’t possible to completely metabolize cholesterol and since its accumulation is deleterious, it isn’t surprising that its homeostasis is subject to complex and fine mechanisms of regulation.

From Cholesterol, proteins are derived that have the name lipoproteins, are subcellular spherical structures evolutionarily developed for the transport of lipids, insoluble in the bloodstream. They are composed by a polar cover and a nucleus; the polar cover contains apolipoproteins, phospholipids and free

cholesterol; in the nucleus are found the hydrophobic elements (esters of cholesterol and triglycerides). Through ultracentrifugation 4 major classes of plasmatic lipoproteins have been isolated that vary in size, density and protein and lipid composition. These are chylomicrons (CM), very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). [10, 11] The VLDL are lipoproteins rich in triglycerides (TG) and cholesterol, are in charge of endogenous transport of lipids from the place of hepatic synthesis to the peripheral tissues. They are considered atherogenic particles, especially those of smaller size. The C-LDL lipoproteins are the final product of the metabolism of the VLDL, and are considered highly atherogenic. [10]

The C-HDL lipoproteins originate in the precursors which come from the liver, intestine and the catabolism of other lipoproteins. They are the protagonists of the reverse transport of cholesterol from the peripheral tissues to the liver for their biliary elimination. Therefore, they are considered as anti-atherogenic particles. [12]

The apolipoproteins are proteins of the lipoprotein surface which besides providing stability to the lipid particles, aid in their metabolic destiny. Denominated with letters of the alphabet, the most important are A, B, C and E. The apolipoproteins A type I and type II (Apo AI and Apo AII), are the most abundant in plasma, are synthetized in the liver and are structural components of the HDL, although they are also found in the chylomicrons. The apolipoproteins B correspond to types 48 and 100 (Apo B48 y Apo B100). The first one is from intestinal synthesis and exclusive of chylomicrons, the second one is from hepatic synthesis and of VLDL and LDL. Besides, the Apo B100 is ligand of the receptor of LDL (LDLR). the apolipoproteins type I, type II and type III (Apo CI, CII and CIII), are present in all particles and are fundamental in the hydrolysis of its triglycerides; finally, the apolipoprotein E is of pervasive synthesis (liver, astrocytes, macrophages, etc.), in not very abundant but is present in all lipoproteins, inclusively in the LDL. [10]

3.2. Dyslipidemias

The abnormal metabolism of lipids (dyslipidemia) plays a crucial role in the onset of cardiovascular disease due to the arthrosclerosis and thrombosis of the wall of arterial vessels. The metabolism of lipids may be altered in different paths, favoring changes in the concentration or function of the plasmatic lipoproteins. When other factors of cardiovascular risk are added to this such as

hypertension, smoking diabetes, metabolic syndrome and chronic inflammation, it predisposes the subject to an early start of atherosclerosis. The dyslipidemia is usually asymptomatic; the majority of patients are identified only during a routine revision or following control for having presented a cardiovascular event. [13]

The common characteristic of dyslipidemias is having abnormal concentrations of serum lipoproteins. Typically, elevated plasmatic concentrations of triglycerides (TG), total cholesterol (TC) are observed, also low levels of lipoproteins derived from high density cholesterol (C-HDL) and prevalence of lipoproteins derived from low density cholesterol (C-LDL). The alteration of the serum profile of lipids in their different lipoprotein fractions leads to an increase in the risk of cardiovascular disease; this being the main cause of mortality secondary to dyslipidemias. Besides, dyslipidemias are the most frequent modifiable cardiovascular risk factor. [2]

The lipoprotein alteration associated to cardiovascular risk is attributed to C-LDL, lipoprotein that has replaced total cholesterol as primary measurement for the risk of atherogenic lipoproteins and remains as the most used measurement as objective of the treatment. [14,15] It has been identified that not only the levels of C-LDL increase the Cardiovascular Risk, but that also proteins rich in TG and lipoprotein remnant are atherogenic; known as Cholesterol No HDL (C-No HDL). [4, 6]

Notwithstanding the aforementioned associations, it is recommendable to measure other lipids in blood for an integral diagnose. These lipids include CT, TG and C-HDL.[14]

There exist detailed descriptions which date back to 1993-1994 in the National Survey of Chronic Diseases where a sample amount of 15,607 adults was available, between 20 and 69 years of age, residents in 417 urban areas of Mexico. Reference values were obtained of TC 182.7 + 40mg/dl, LDL 116.6+ 36mg/dl, HDL 38.3+ 9.5mg/dl and TG 213.4 +158mg/dl, with a larger prevalence of hypertriglyceridemia (42.3%) and hypoalphalipoproteinemia (61%). The TC was found high in 27.1%. [17] There are other precedents that speak of the prevalence of dyslipidemias located among the Mexican population, in the study CARMELA where Mexico was included, showing a prevalence of little more than 50% in persons over 20 years of age. [18]

The most frequent dyslipidemias in Mexicans are the decrease of C-HDL and hypertriglyceridemia; [19] finding figures of up to 58.9% of prevalence for hypoalphalipoproteinemia, which place it as the most predominant dyslipidemia.[20]

In turn, dyslipidemias are classified as primary and secondary; the first group is constituted by disorders characterized by defects in the enzymes, receptors or metabolites that participate in the synthesis and elimination of the lipoproteins; the most frequent is familial hypercholesterolemia, followed by combined familial hyperlipidemia, dysbetalipoproteinemia and familial hypertriglyceridemia.[13] The second group includes the alterations in the lipids, consequence of diseases and use of some drugs. [19,21]

Hereunder are more comments with respect to the primary and secondary factors.

A. Primary

The primary errors of the lipid metabolism include:

a) Familial Endogenous Hypertriglyceridemia.
b) Combined Familial Hyperlipemia (CFH).
c) Familial Hypercholesterolemia (FH).
   i. Classic Familial Hypercholesterolemia (FH1).
   ii. Familial Defective Apo B (FDB).
   iii. Mutations in the PCSK9 gen (Protein Convertase Subtilisin/Kexin type 9; FH3).
   iv. Deficiency of cholesterol 7-a-hydroxylase (CYP7A1).
   v. Recessive Autosomal Hypercholesterolemia (RAH).

a) **Endogenous Familial Hypertriglyceridemia.** Dominant autosomal disorder of variable penetration; some sporadic cases have been described. The defect hasn't been defined yet and it is thought that it could be the presence of common polymorphic variants located in introns of the gene if lipase lipoprotein (LPL), in the promoter of Apo CIII and/or the alleles ε2 and ε4 of the gene Apo E; the presence of these variants may be expressed phenotypically with hypertriglyceridemia when some precipitating factors coexist such as obesity, alcoholism, fat diet, smoking, etc. The interaction gene/environment is therefore very important. A prevalence of 1% has been estimated in the general population and a 5% among the survivors of an acute heart attack. It is considered that the metabolic disorder is due to the increase of the synthesis of VLDL, associated or not to defective lipolysis and some authors postulate that the subjacent pathogenic element is the insulin-resistance. It usually expresses after puberty and courses with hypertriglyceridemia between 200 and 700 mg/dl (phenotype IV), at expense of VLDL of a larger size but not increased in number, so the levels of plasmatic Apo B are located within normality. On the other hand, when the C-HDL is low and the C-LDL is normal or low it is

denominated “phenotype B” (small and dense LDL particles). In homozygotes for the mutation c.433C>T of the gene Apo AV a phenotype V may appear with chylomicronemia in fasting and levels of plasmatic triglycerides superior to 1000 mg/dl. The impact of this disorder over the risk of cardiovascular disease among those who suffer from it is controversial and seems conditioned by the levels of C-HDL and/or the existence of the phenotype B. Some variants of Apo E (E3/3, E4/3 or E4/2), polymorphisms in Apo CIII (SstI, S2, -455T>C, -482C>T, homozygotes -455C) and variants of Apo AV (a5*2/A5*3) confer a larger risk. There are values of triglycerides greater than 200mg/dl, C-LDL normal or low, C-HDL diminished and coexists in patient of type 2 Diabetes. [2, L1]

b) **Combined Familial Hyperlipemia (CFH):** the study of extensive genealogic trees of affected families has led to consider it as a dominant autosomal hereditary disorder with an elevated penetration and heterogeneous and unknown genetic bases, to the point of questioning if it is a sole entity. In this sense, the CFH has been related with some polymorphisms of the gene of LPL. The presence of these polymorphisms leads to a reduction in the activity among 30-50% of the cases. Also, CFH has been related with polymorphisms in the gene Apo CIII. It has prevalence in the population estimated at 1-2%. The pathogenesis is complex and isn’t totally clear either, but its known that there is a hyper flow of free fatty acids to the liver, consequence of bad digestion in the adipose tissue where a low activity of the acylation stimulating proteins (ASP Acyl-Stimulating Protein) has been shown, and of the lipase sensitive to hormones (HSL Hormone Sensitive Lipase). This defect causes an increase in hepatic synthesis of Apo B and a consequent increase in the production of VLDL particles that are of a smaller size than those present in healthy subjects or with Familial Hypertriglyceridemia. In their metabolism these particles produce the highly atherogenic small and dense LDLs (phenotype B). A defective lipolysis may or may not be associated. The affected individuals present dyslipidemia starting from puberty, being characteristic the inter-individual phenotypic variability among members of the same family and inter-individual, throughout life, , as a response to diet modifications, in physical activity or weight, and to exogenous factors (alcohol and/or drugs). Isolated hypercholesterolemia may appear at the expense of LDL or phenotype IIA (less frequent), hypertriglyceridemia (200-500 mg/dl) by increase of VLDL particles

(phenotype IV) or mixed hyperlipemia due to increase in both C-LDL and VLDL (phenotype IIb), characteristic of the disorder. It is frequent that there are low levels of C-HDL and elevated concentrations of Apo B, above the demographic 90 percentile. [2, L1]

c) **Familial Hypercholesterolemia (FH):** We understand as monogenic familial hypercholesterolemia (FH) a set of disorders of lipid metabolism of a hereditary character, characterized by hypercholesterolemia at expense of C-LDL, since an early age in life and an elevated incidence of precocious atherosclerotic cardiovascular disease. To date, 5 hereditary disorders have been identified as cause of familial hypercholesterolemia, the most frequent of them in Mexicans is the classic familial hypercholesterolemia (FH1). [17] Although in other populations it has been observed that the greater prevalence courses with combined familial hypercholesterolemia (disorder of mixed hyperlipidemia and hypertriglyceridemia). [17] In prevalence range it is followed by Apo B defective familial (BDF or FH2), being the most rare that caused by mutations of the gene PCSK9 (Proprotein Convertase Subitilisin/Kexin type 9; HF3), the deficiency of cholesterol 7 to hydroxylase (CYP7A1) or the Recessive Autosomal Hypercholesterolemia (RAH). The elevation of C-LDL is a consequence of mutations of the gene of receptor LDL, of apoB or of the gene PCSK9. [2, 17, 22, L1]

i. **Classic Familial Hypercholesterolemia (FH1):** dominant autosomal hereditary disorder due to mutations in the gene that codifies the receptor of low density lipoproteins (LDLR), located in chromosome 19p13.2, where normally 18 exons codify the 5 dominions of said protein. The defect may affect the synthesis of the receptor, its transport to the cellular surface, the union to lipoproteins, internalization or even its recycling, conditioning the defective elimination of C-LDL particles in blood. [23] This causes levels of TC larger than 300mg/dl, C-LDL larger than 190mg/dl and sinewy xanthomas. [17]

To date, more than 1000 mutations have been described globally. Therefore its distribution is universal, with a prevalence of 1/500 subjects for the heterozygote form and 1/1, 000,000 for the homozygote. The characteristic and pathognomonic clinical trait, although not so frequent is the presence of sinewy and cutaneous

xanthomas. Furthermore, xanthelasmas and corneal arch may appear, although they aren't so specific. Patients with FH have C-LDL values at double or triple of what's observed in the general population, oscillating between 190 and 400 mg/dl; the triglycerides generally show normal values although in some cases they might be elevated. The certainty diagnose approximates the binomial genetic defect-functional alteration, that is, known or new mutation and hypercholesterolemia. There is no unanimity among the international scientific community to determine which should be the unequivocal clinical criteria for the diagnose of FH, although the most widespread are the criteria of the Dutch MEDPED, having estimated for a score of at least 8 points (certainty diagnose), a sensitivity of 41% and a specificity of 88%. [24] Neither is the cutting point of greater sensitivity known to use the determination of C-LDL as the exclusive diagnostic tool, for although its values are greater in subjects with FH than in the general population, the interval overlaps between both populations, especially in young subjects where the sieving of cases of FH would have a greater benefit. The natural history of FH is intimately linked to the development of cardiovascular disease for the main cause of death in these patients is ischemic cardiopathy; 50% of women and 85% of untreated men will suffer a coronary event before age 65 (10% of the cases of ischemic cardiopathy in some countries) therefore, the value and extension of the remaining factors of classic cardiovascular risk isn't comparable to that of the general population. [25]

Classic familial hypercholesterolemia is catalogued as the hyperlipidemia that has the greatest association with Cardiovascular Risk. [19]

ii. **Familial Defective Apo (FDB):** Dominant autosomal defect. Four simple polymorphisms of nucleotides have been recognized (SNPs single nucleotide polymorphisms), in the gene ApoB located in the chromosome 2, associated to functional defects. This genetic defect of the Caucasian race dates back 6000-7000 years and has been linked to the existence of Celtic villages, which at the time dwelled in central Europe. In this line it hasn't been possible to identify it in Japanese or Israelis. In Europe it implies from 2 to 5% of primary hypercholesterolemias with prevalence in

the variable general population that oscillates between 1/500-700, clearly larger in Switzerland (1/210). In Spain, a prevalence of 2.8 cases /100,000 habitants had been estimated after identifying the first family. As a result of the publishing of the first data of the Spanish Registry of Familial Hypercholesterolemia, a prevalence of 1.4% was appreciated among subjects with primary hypercholesterolemia (13/913). [26] The defect provokes a reduction in the elimination of circulating C-LDL particles of 20- 30%. Nonetheless there is a regulation to the increase of reverse transport of cholesterol and of the activity of the C-LDL receptor that determines an increase in hepatic capture of VLDL remnants and a lesser conversion of these to C-LDL. Although in the presence of an adequate environmental and genetic substrate it may result in a clinical syndrome that is indistinguishable from FH, it often presents with a more favorable phenotype: a lesser prevalence of xanthomas and corneal arch, inferior total cholesterol and LDL levels and greater levels of HDL, with a more delayed cardiovascular disease. [27]

iii. **Mutation in the gene PCSK9 (Protein Convertase Subtilisin/Kexin type 9; HF3):** PCSK9 is a serinprotease of hepatic and intestinal location, belonging to the secreting subtilase families that intervene in the homeostasis of cholesterol, favoring the catabolism of LDLR and preventing their recycling in the cellular surface. Therefore, its activity diminishes the amount of LDLR and increases the plasmatic concentrations of C-LDL. The gene that codifies the protein is localized in chromosome 1 (1p32.3) and mutations have been describe in it with opposing functional response, that is, gain or loss of function. [28] Since the year 2003 the mutations with gain in function have been related with the phenotype of FH implying 2-3% of patients clinically diagnosed with FH without mutations detected in the genes LDLR or Apo B. The levels of C-LDL are somewhat lower than in FH1although there is still a high cardiovascular risk that can't be controlled, even with the best response to treatment.[29]

iv. **Deficiency of cholesterol 7-α-hydroxylase (CYP7A1**): Cholesterol 7-α-hydroxylase is an enzyme that belongs to the superfamily of cytochrome P450 that catalyzes the first step in the hepatic synthesis of biliary acids. Polymorphisms in the gene that codifies its synthesis (8q11) have been related with phenotype

of FH following a same pattern of dominant autosomal heredity. In these patients the levels of C-LDL are somewhat lower than in classic FH and there is often Hypertriglyceridemia. The disorder presents predisposition for atherosclerotic cardiovascular disease and cholelithiasis. The poor response to treatment with statins is characteristic. [27]

v. **Recessive Autosomal Hypercholesterolemia (RAH):** is very exceptional, since there exist about 50 described cases. It follows a pattern of recessive **autosomal** heredity, being characteristic in the progenitors the consanguinity and the absence of lipid alterations. The defect resides in mutations of the gene LDLRAP1 (locus 1p35) that codifies an adaptor protein that is necessary for the internalization and posterior recycling of the LDLRs. Mutations with a loss of function provoke a diminishment of LDLR and thus, an increase in plasmatic concentrations of total cholesterol, C-LDL and even triglycerides (VLDL and remnants are eliminated with difficulty). Precocious cardiovascular disease and a good response to statins are characteristic. [30]

B. Secondary

It may appear isolated or associated to a primary dyslipidemia. In a study formed by a cohort of 824 patients referred for dyslipidemia evaluation, it was found that 28% had one or more potential causes of dyslipidemia; the most common causes were alcohol consumption (10%) and non-controlled diabetes mellitus (8%).[31]

a) **Poorly-controlled type 2 Diabetes mellitus:** may course with hypertriglyceridemia due to an increase in the synthesis of VLDL and/or decrease of its catabolism due to a lesser activity of the LPL. A dysbetalipoproteinemia may also be triggered in genetically predisposed subjects (Apo E2/E2) by the accumulation of intermediate density lipoproteinemia (*Intermediate Low Density Lipoproteins,* IDL). In turn, a relation with the diminishment of C-HDL is observed. [32, L3]

b) **Obesity:** is related with the hyper production of VLDL and consequently of C-LDL. Hypertriglyceridemia or mixed dyslipidemia may also appear. [L1]

c) **Anorexia:** on occasions hypercholesterolemia is present. [2, L1]

d) **Hypothyroidism:** there exists an association in presenting elevations in total cholesterol with the presence of hypothyroidism in a 56%; [17] as a consequence of the decrease in hepatic activity of the LDLR an increase of C-LDL is produced (phenotype IIa). A phenotype IIb may also appear due to an accumulation of VLDL. On individuals with isoform Apo E2/2 the existence of hypothyroidism triggers a dysbetalipoproteinemia. Substitute hormonal treatment corrects the associated lipid alterations; otherwise, a subjacent primary dyslipidemia may be suspect. [2, L1]

e) **Cushing Syndrome:** it may produce hypertriglyceridemia caused by an increase in hepatic synthesis of VLDL (phenotype IV) or a mixed hyperlipemia caused by an increase in the conversion of VLDL to C-LDL through activation of the lipoprotein lipase. [L1]

f) **Nephrotic syndrome:** Often, an increase of Total Cholesterol, triglycerides and apolipoprotein B which guards close relation with proteinuria, may be produced. These alterations contribute to the development and progression of cardiovascular disease and renal damage. [33]

g) **Chronic renal failure:** is characterized by the elevation of triglycerides and the presence of low levels of C-HDL, with fewer changes in stages 1 and 2 of chronic renal disease, in serum levels of TC and C-LDL. [34]

h) **Hepatic disorders:** Hepatitis with fatty liver may produce mild hypertriglyceridemia caused by hypo activity of hepatic lipase (HL) and a defect in the elimination of chylomicrons and VLDL. In cholestasis, a decrease of the enzyme lecithin cholesterol acyl transferase (LCAT) with hypercholesterolemia at the expense of lipoproteins (LDL normal or low) is present. Other alterations which are related as secondary causes of dyslipidemias are primary biliary cirrhosis, primary sclerosis cholangitis (associated to ulcerous colitis in 90%) and the malformation of the biliary conducts. [2, L1]

i) **Pancreatic diseases:** acute pancreatitis is found if it results in insulinopenia, hyperglycemia and systemic inflammatory response; due to the secondary decrease of said hormone, important in the metabolic processes of the organism. [2]

j) **Human Immunodeficiency Virus:** patients who have this virus, show inferior levels of CT, C-LDL and C-HDL with hypertriglyceridemia. [35]

k) **Autoimmune diseases:** it has been observed that patients who course with rheumatoid arthritis, systemic lupus erythematous, Antiphospholipid antibodies syndrome and psoriasis have a greater frequency of arthrosclerosis caused by combined hypercholesterolemia and cardiovascular morbidity and mortality rates which are elevated with respect to the population in general. [36]

l) **Other diseases:** it has been reported that in diseases by deposit (Diseases by deposit of glycogen, Gaucher disease, Tay-Sachs juvenile disease and Niemann Pick disease) course with variable abnormalities in the metabolism of lipids.[2, 37] Besides the previous, alterations of lipids are observed in idiopathic Hyperkalemia, Klinefelter Syndrome, Werner Syndrome, Kawasaki Disease and intermittent acute Porfiria. [37]

m) **Recreational drugs:** an alteration in the lipid profile is observed in specific in the increase of triglycerides in subjects who used alcohol and marihuana. [33]

n) **Hormonal pharmacotherapy that may elevate C-LDL:** anabolic steroids, glucocorticoids, progestin and danazol. [33]

o) **Cardiometabolic pharmacotherapy that may elevate C-LDL:** amiodarone, thiazide diuretics, thiazide diuretics, rosiglitazone, fibric acid, docosahexaenoic acid. [33]

p) **Other pharmacotherapies that may elevate C-LDL:** Isotretinoin, Immunosuppressors (Cyclosporine) and inhibitors of the co-transport of sodium-glucose. [33]

q) **Hormonal pharmacotherapy that increases the TG:** oral estrogens, oral contraceptives, glucocorticoids, tamoxifen and raloxifene.[33]

r) **Cardiometabolic pharmacotherapy that increases TG:** Non-selective Beta-blockers, thiazide diuretics and sequestrants of biliary acids.[33]

s) **Antineoplastic pharmacotherapy that increases TG:** L- asparginase and cyclophosphamide. [33]

t) **Other pharmacotherapies that increase TG:** retinoids, inhibitors of protease, immunoactive agents, cyclosporine, sirolimus and interferon. [33]

3.3. Cardiovascular risk factors

Cardiovascular diseases constitute a serious world public health for being the first cause of morbidity-mortality at global level. [1] Besides, this place in the ranking has been maintained for more than 10 years. [38]

Cardiovascular risk is defined as the probability of presenting death by cardiovascular event within 10 years. [39]

A direct relation is seen with arthrosclerosis, progressive pathologic process, related with age and of a marked inflammatory component that affects arteries of medium and large caliber, characterized by the deposit of lipoproteins in the sub endothelial space which form a plaque of atheroma (basic lesion) and for presenting acute complication in the form of cardiovascular accidents (ictus, angina, acute heart attack). [40] The pathologic findings reveal that the vascular intima is filled with caseous cellular detritus, rich in lipids which form plaques; said plaques are surrounded by active macrophages that contain inclusions of lipids and surrounding cells of proliferating stroma. [41]

The development of said disease is promoted by several risk factors, denominated cardiovascular risk factors; some are modifiable and subject to preventive measures, others are not modifiable. [42] Cardiovascular risk is defined as the probability of a clinical event (cardiovascular death) which happens to a person in a period of 10 years. [42]

3.3.1. Non-modifiable Cardiovascular Risk Factors

- Age. In men, being older than 45 years, and in women, being older than 55 years.

- Gender, being born male.
- Race
- History of premature ischemic cardiopathy, in men younger than 55 and in women younger than 65.

3.3.2. Modifiable Cardiovascular Risk Factors

- Dyslipidemia
- Systemic arterial hypertension
- Diabetes Mellitus
- Smoking
- Obesity

In subjects from 20 to 79 years of age who don't have clinical history of associated cardiovascular disease, international guides suggest as a first step measuring the associated cardiovascular risk factors. If they have a minor risk (-7.5%) than 10 years, the factors have to be evaluated every 4 to 6 years. If the patient is between 40 and 79 years old estimate the risk to 10 years in a formal manner. [39]

In the approach of the problem, lipids will be addressed as a favorable factor of cardiovascular risk among other pertinent considerations.

4. APPROACH OF THE PROBLEM

From the results of great epidemiologic studies (Framingham Heart Study, Multiple Risk Factor Intervention Trial (MRFIT), etc.) cardiovascular risk factors (smoking, hypercholesterolemia, diabetes mellitus and/or arterial hypertension) were identified, and finally the binomial arthrosclerosis-cardiovascular accidents is established. Since then, total cholesterol, C- LDL, C-HDL and plasmatic triglycerides have been related in a greater or lesser measure with the development of atherosclerotic cardiovascular disease, representing approximately a 50% of the demographic attributable risk. [43] Thus, the abnormal metabolism of lipids, dyslipidemia, plays a crucial role in the pathogenesis of cardiovascular diseases. This may present alterations in different ways, favoring changes in the concentration or function of the

plasmatic lipoproteins. When other cardiovascular risk factors are added to this, such as systemic arterial hypertension, smoking, diabetes, metabolic syndrome and chronic inflammation, it predisposes the individual to and early onset of arthrosclerosis. [41]

The Mexican population has a high prevalence of deaths in adults caused by cardiovascular events. Data from the year 2015 reported mortality associated to cardiovascular events in adults by reason of 292 cases for every 100,000 habitants; combined with the poor forecast in the quality of life of the survivors, since some shall require long-term health care and their working capacity will be affected in a negative manner. Besides, in our country, it has been possible to reduce only 1% of deaths secondary to cardiovascular disease, compared to a 48% reduction in developed countries. [44]

In our country, the average values of cholesterol present significant differences between the different socio-economic levels of the populations. There is a greater prevalence of hypercholesterolemia in medium and high socio-economic strata, in the population in northern Mexico and a relation with the presentation of this alteration at an older age has been seen. According to a study from 2007, the global prevalence of hypercholesterolemia in Mexico was 23.6%, lower than that reported in the United States of America (39%) and higher than that of Japan; the authors emphasized that this dyslipidemia is determined by two factors: genetic predisposition and diet. [45]

The National Survey of Health and Nutrition (ENSANUT), gathers data throughout Mexico about health and nutrition determinants in each sector of demographic health and makes a comparative between genders. As part of the ENSANUT done in 2006, the values of Total Cholesterol in serum were studied in adult Mexican population with a sample size of 4,040. A prevalence of 43.6% was found for individuals with total cholesterol in serum registries greater than 200mg/dl. [20] This same year, the Mexican Institute of Social Security (IMSS) made a study with a larger sample than that of ENSANUT (20,062 vs. 4,040); the prevalence found was 12.4% for men and 13.8% for women. [46]

In past years, a study was made to know more about the factors of the metabolic syndrome for Latin America; Mexico ventured in said study called CARMELA, from which arose an analysis attuned to the serum profile found in the included population. For this caption 833 men and 889 women were studied (48.4% and 51.6% respectively) from 25 to 64 years of age. The results

gave a media for serum levels of TC of 202.9mg/dl; it was shown that in groups of an older age the blood level of TC was greater (188.5mg/dl in the group of 25-34 years vs. 216.5mg/dl for the group from 55 to 64 years). According to gender, the average values of TC were larger for men with 204.3mg/dl, compared to the media of 201.6mg/dl found in women. For the C-LDL, type of cholesterol whose values are used as cardiovascular risk predictors, the average value was 118.7mg/dl; with this a correlation was found (just like with the TC) in presenting blood levels of C-LDL more elevated in the group of older age (127.2mg/dl vs. 109mg/dl in the population of 25-34 years). C-HDL, known as the type of cholesterol that should present figures greater than 40mg/dl as benefic against the cardiovascular risk, showed average values of 49.2mg/dl. The average values of triglycerides were found at 183.9mg/dl, having a significant increase in the younger age group in comparison with the older age group with 159mg/dl (25-24 years) to 200.6mg/dl (55 to 64 years). [18]

With respect to the question, which is the most frequent dyslipidemia in the adult Mexican population? 2 have been placed as the main ones; the first one is the decrease of HDL type cholesterol and the second one is the increase of triglycerides. [19] The ENSANUT 2006 found that up to 58.9% of the adult Mexican population courses with figures of C-HDL lower than 40mg/dl, entering into the group of those who suffer hypoalphalipoproteinemia. [20] There are studies that indicate that 24.3% of the Mexican population between 20 to 69 years with residence in cities presents TG values of 200mg/dl or more, this being greater than that described in other ethnic groups. [45]

There are precedents that mention that even in children high figures of cholesterol and triglycerides in blood have been detected, which has been attributed to the massive commercialization of processed foods, the changes in alimentary regimes and the abuse of foods rich in animal fats. In some cases it has been detected that a change of 100 mg of cholesterol in the diet for every 1000 kilocalories modifies in 12 mg/dl the concentration of cholesterol in blood. [47]

On the other side according to the data reported in the ENSANUT 2012, in Mexico there is a prevalence of overweight or obesity of 73% for women and 69.4% for men, factor which correlates with the serum levels of lipids. In this year 49.9% of the population included referred that tests had been done to determine the levels of total cholesterol in serum, where 37% had a normal cholesterol result and 13% a result of Total Cholesterol equal to or greater than 200mg/dl. [48]

Demographic studies and studies of intervention with different hypolipemia therapies have shown a direct, gradual and continuous relation between plasmatic cholesterol and cardiovascular morbidity and mortality. In the MRFIT study, for example, it was observed that values of cholesterolemia greater than 200 mg/dl increased the risk of coronary accidents in an exponential manner. [49] In turn, in a study published in the year 2006 by the magazine Circulation, the risk of morbidity-mortality by cardiovascular disease secondary to serum levels of total cholesterol, was estimated at 38.7% for men 50 years or older if their levels in blood were greater than 180mg/dl and elevates to 64.6%, with figures equal to or greater than 240mg/dl. In women, the associated risk is less, with figures of 19.4% with serum levels of TC greater than 180mg/dl and 48% with figures equal to or greater than 240mg/dl. [50]

The consensus of experts of the National Association of Lipids in the United States of America in its Chapter III for detection, evaluation and treatment of Cholesterol in Adults, estimated the limit levels in concentrations of serum lipids. These estimations are found contained in the following chart: [L1]

Chart 1. Lipid levels recommended by the Adult Treatment Panel III

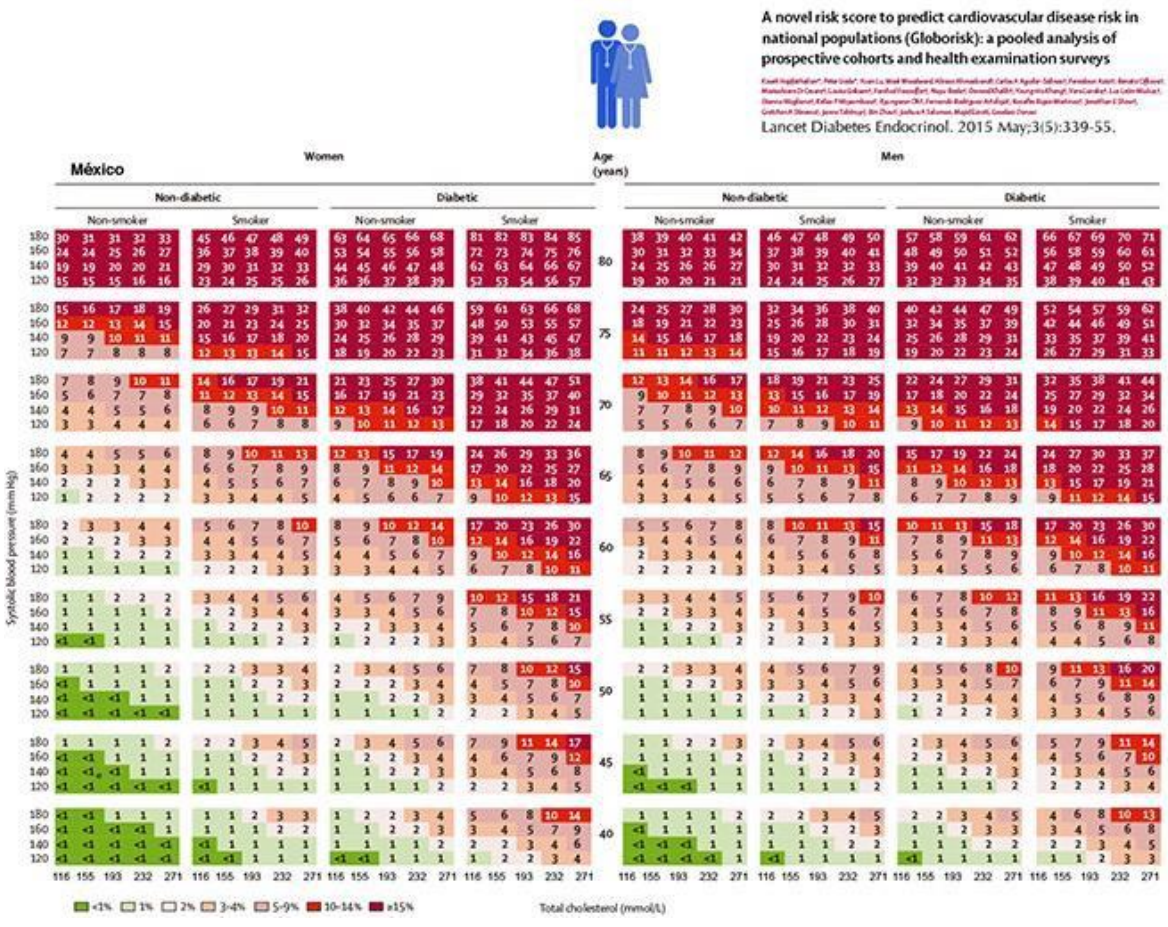
LIPIDS	Levels (mg//dl)	Category
TOTAL CHOLESTEROL	< 200	Desirable
	200-239	High limit
	≥ 240	High
CHOLESTEROL LDL	< 100	Optimal
	100 - 129	Desirable
	130-159	High level
	160-189	High
	≥ 190	Very high
CHOLESTEROL HDL	< 40	Los
	≥ 60	High

TRIGLYCERIDES	< 150	Desirable
	150 – 199	High limit
	200 – 499	High
	≥ 500	Very high
CHOLESTEROL NO HDL	< 100 -190	Depending on cardiovascular risk

Nowadays, it is known that the lipoprotein C-LDL shows a greater correlation with the risk of developing a cardiovascular disease associated to dyslipidemias; thus, it has replaced TC as the primary measure of risk for atherogenic lipoproteins and remains as the most used measurement as objective of treatment. [14, 15] So, it is known that the increase of 30mg/dl of C-LDL increases in 30% the risk of ischemic cardiopathy. In turn, if C-LDL levels are maintained between 77 and 116mg/dl, there is a decrease of 40 to 50% in the risk of presenting a heart attack, revascularization or a cerebral event of the ischemic type. [51] Besides, an alarming data which has been found in countries with high incomes is that the C-LDL with serum levels above 147mg/dl is responsible for more than half of cardiovascular diseases. [52] For its part, the Framingham study showed that subjects with serum levels of C-LDL greater than 160mg/dl, indistinctly between men or women, develop 1.5 times more cardiovascular diseases, in comparison with the subjects who have levels of C-LDL below 130mg/dl in serum. [15] For the relation between levels of C-LDL and atherosclerosis, it has been found that an increase of 39mg/dl of C-LDL increases in 40% the risk of presenting a cardiovascular event and conversely, reducing 39mg/dl the blood level of C-LDL decreases in 20% the risk of the presence of some cardiovascular event. [51]

Due to this relevance the monitoring of the levels of C-LDL and its optimal level, is objective to decrease the risk of cardiovascular diseases. The optimal levels in the patient have to be handled in a personal capacity according to the cardiovascular risk they present. For patients with a very high cardiovascular risk the goal is to maintain levels of C-LDL inferior to 70mg/dl, in patients with high cardiovascular risk, levels of C-LDL inferior to 100mg/dl are advised and in patients with moderate to low risk, the levels must be below 115mg/dl. [4] Then, there are 2 critical points; on one hand the estimation of the risk of suffering a cardiovascular disease, and on the other hand, the estimation of the levels of C-

LDL. The identification of both will lead to an adequate primary prevention; recommended even in subjects without clinical history of cardiovascular disease, the associated cardiovascular risk. For Mexico, there exists a validated multi-center prospective cohort known as “Globorisk”. Patients from 40 to 84 years of age were included, and the follow-up lasted 15 years. The results found a prevalence of associated cardiovascular risk of 16% for men and 11% for women. In reference to these data, a gauged equation was developed for Mexicans in the estimation of cardiovascular risk; besides adding other models of Framingham and SCORE. The result established a correlation of cardiovascular risk to 10 for Mexicans, where all those who have a probability over 10% of risk of occurrence of some cardiovascular event in 10 years, were graded as a very high risk: [53]



So then, it is necessary to estimate through the Globorisk scale modified for Mexicans the cardiovascular risk of our population. The second important point is the calculation of C-LDL, which if it isn't obtained from laboratory parameters, may use the Friedewald formula, as long as the reported values of triglycerides in blood are below 400mg/dl. The Friedewald formula is: C-LDL = CT – (C-HDL + TG/5). [53]

According to the cardiovascular risk, it is suggested to evaluate it in patients older than 40 years if they present one of the following: History of cardiovascular disease at a premature age, familial hyperlipidemia, smoking, systemic arterial hypertension, diabetes mellitus or elevated concentrations of lipids. Classified as a very high cardiovascular risk, someone who has an established cardiovascular disease, history of acute heart attack, any type of revascularization, history of cerebral event of the ischemic type, diagnose of type 2 diabetes mellitus or type 1 with damage to white organ (micro albuminuria) or, a calculated risk of Globorisk greater than 10% in 10 years. Individuals who classify as a high cardiovascular risk will be those who present a cardiovascular risk by the Globorisk scale of 5 to 10% in 10 years, moderately elevated risk such as arterial tension ≥ to 180/110mmHg, dyslipidemia with TC greater than 310mg/dl or primary familial dyslipidemia. [4] To classify subjects with moderate cardiovascular risk, they must have a Globorisk risk of 1-5% in 10 years, [4] for this being the classification level with the different established scales most susceptible to being sieved, it is recommended to complement it in an individualized manner with risk factors such as familial history of premature cardiovascular disease, abdominal obesity (men with abdominal perimeter ≥ 94cm and women ≥ 80cm), a sedentary lifestyle and the presence of inflammatory chronic disease. [36] In the low risk classification, those with a Globorisk value to 10 years below 1%. [4] Caution must be observe in the use of the adequate scale for the population to be analyzed; in the case of Mexico, the modified Globorisk for this population, with the aforementioned parameters.

On the issue of sieving in subjects to discard dyslipidemias; the consensus of experts of the National Lipid Association of the United States of America, recommends to do it in persons without associated cardiovascular risk factors starting form 20 years and to repeat it every 5 years in all those in which initial evaluation is normal and the condition of the patient remains stable. The lipids to be measured in this sieve must be obtained from peripheral blood and include Total Cholesterol, Cholesterol HDL, Cholesterol LDL and the Cholesterol No HDL must be calculated, for which the measurement of triglycerides is necessary. [54] The updated clinical practice guides of Mexico make the same recommendation.[2] The optimal serum levels of C-LDL will be according to the cardiovascular risk factor reported by the Globorisk scale for Mexicans, previously

mentioned. For the obtention of the blood levels of Cholesterol no HDL (C-No HDL) it's necessary to perform an estimation through the following equation: C-No HDL = CT – C-HDL. Since it has been observed that this type of proteins rich in TG and remnants of lipoproteins are atherogenic, this parameter is relevant in the evaluation of cardiovascular risk, although not as much as the levels of C-LDL; therefore, it is recommended to maintain as an objective value for C-No HDL levels below 100mg/dl in patients with very high cardiovascular risk, below 130 in patients with high cardiovascular risk and for those who present a moderate cardiovascular risk, levels below 145mg/dl. [4]

With the aforementioned data, the following chart which contains the optimal levels of lipids in blood was generated:

Chart 2. Recommended lipid levels. [4, 6]

LIPIDS	Levels (mg//dl)	Recommendation
CHOLESTEROL LDL	< 70	In very high cardiovascular risk
	< 100	In high cardiovascular risk
	< 115	In moderate to low Cardiovascular risk
CHOLESTEROL NO HDL	< 100	In very high cardiovascular risk
	< 130	In high cardiovascular risk
	< 145	In moderate cardiovascular risk

TOTAL CHOLESTEROL	< 200	Desirable
CHOLESTEROL HDL	> 40	Desirable
TRIGLYCERIDES	< 150	Desirable

Now, levels of C-LDL above 190mg/dl, carry the suspicion that the patient suffers from familial hypercholesterolemia; for which the previous exclusion of the secondary causes that contribute to the appearance of those figures will be necessary. Other aspects to consider in the suspicion of familial hypercholesterolemia are: the presence of premature coronary disease (in men, younger than 55 years and in women, younger than 65 years) in the case and/or in a first degree relative; xanthomas in the patient and/or first degree relative, familial history of high levels of serum cholesterol and; with an 80% probability of suffering this disease, having levels of C-LDL without treatment at 30 years or more than 250mg/dl, 220mg/dl from 20 to 29 years or, of 190mg/dl in persons under 20 years.[55] In case there is suspicion of the presence of familial hypercholesterolemia, a detailed physical exploration shall be performed; within the aspects to consider are: on inspection the presence of xanthomas in tendons at any age, being more frequent in the Achilles' tendon or in the extensor of the fingers and less frequently, in the patellar and triceps; presence of corneal arch in persons under 45, tuberous xanthomas in persons under 25 and xanthelasma (if it is present in persons over 25, it strengthens the suspicion). Despite having the knowledge that an intentioned search must be performed of these findings in those with suspicion of familial hypercholesterolemia, the majority of these subjects don't present the mentioned findings. [56]

If there is a course with figures of TC greater than 300mg/dl or C-No HDL greater than 220mg/dl, there are several conditions to discard, being the most common causal etiologies of familial hypercholesterolemia, hypothyroidism, cholestasis and nephrotic syndrome. It is unlikely that other primary hyperlipidemias which cause isolated hypercholesterolemia, cause concentrations of total cholesterol in such magnitudes. The concentrations of cholesterol between 200 to 300mg/dl are generally due to an excess in the consumption of saturated fats and/or cholesterol, use of drugs (referred in the section of secondary causes of dyslipidemias), obesity and other causes described as secondary. [19]

There are several studies which sustain the relation of consumption of Trans fats with the increase of TC and -LDL, besides the decrease of C-HDL. It is known that in the consumption of excessive fatty acids, the macrophages are the main ones, but not the only agents which respond to the change; for lipids are the

promoters of the production of inflammatory cytokines in macrophages and at hepatic level. On their part, the unsaturated fats and large amounts of saturated fats (particularly of long chain), have effects on the increase of TNF and MCP-1, IL-6, IL-1 and Protein C Reactive as a secondary hepatic response; joined to the contribution in the presentation of obesity diabetes and cardiac damage. Besides, it promotes atherosclerotic lesions through an induced cellular death cycle. [41]

The role of triglycerides in the promotion of atherosclerotic cardiovascular disease has had variable and inconsistent results in diverse epidemiologic researches. Solving this matter isn't free from problems, first because from a pathogenic point of view hypertriglyceridemia must be considered causal to cardiovascular diseases in the measure that an increase of atherogenic lipoproteins is reflected and that isn't always so; second because there is a narrow and inverse relation between it and the plasmatic levels of HDL with contributions relative to the cardiovascular risk of difficult dissection. In recent years and in a consistent manner, the measurement of triglyceridemia in postprandial state (2-4 hours following intake) has been recognized as a predictor of cardiovascular accidents, even after controlling other factors such as HDL. Recently, a post-hoc analysis of the assay PROVE IT-TIMI 22 demonstrated that patients that reached fasting levels of triglyceridemia lower than 150 mg/dl had a lesser cardiovascular morbidity-mortality even among those who had reached figures of LDL inferior to 70 mg/dl. [57]

Placing Mexico in the overall picture of the problem implied by dyslipidemias as the main modifiable cardiovascular risk factor, it is relevant to mention that according to the Global Burden Disease, cardiovascular mortality in the last 20 years has decreased globally in 21%. Although these data are in the context of developed countries, for in developing countries there remains an increase in mortality attributable to cardiovascular disease. This becomes relevant upon recognizing the strategies that developed countries used in comparison with undeveloped countries. In the last 60 years, strategies with 2 guidelines were implemented in countries with decrease of global risk by cardiovascular disease. The first guideline is in the population where public health policies were conducted with the objective of reducing the incidence and mortality by cardiovascular disease. The second strategic intervention was directly on the subjects, focusing on the decrease of probability of future cardiovascular events through the appropriate handling of the modifiable risk factors. [58] From this, it can be concluded that the primordial and critical step as strategy is the handling

of the cardiovascular risk in the clinical stage. With first-contact physicians, the evaluation of cardiovascular risk has shown to be useful, with the purpose of identifying patients who will benefit most from primary prevention therapies. [59]

Because most dyslipidemias are a silent disease, it is advisable for Mexicans that the scrutiny of the cardiovascular risk factors, including serum lipid profile, be done starting at age 20 and if result are normal without associated cardiovascular risk, which the evaluation of the lipid profile continue every 5 years. [2] This forms part of the primary prevention strategies, defined as the set of activities performed by the health personnel, community or government to prevent or delay the onset of a determined condition. [60] Besides the primary prevention strategies, there are secondary prevention strategies that for the particular condition are the interventions in patients with known cardiovascular disease and in those who gather the conditions that classify them as risky. The objective of this secondary prevention is to avoid the recurrence or exacerbations of a cardiovascular disease or the complication by use of a specific therapy. It is recognized that this offers a greater gain in health and in the cost / effectiveness relation. [32]

Starting from these observation, an integral treatment must be established, which consists in a non-pharmacological treatment and a pharmacological one, being combined or not. The non-pharmacological treatment must include the education for a healthy lifestyle, the promotion of physical activity of the patient, stress handling if present, avoid smoking and orient the subject in the diminishing of psychosocial risk factors. It is recommended that individuals with high cardiovascular risk be subject to a multi-disciplinary intervention (nutrition, nursing, psychology), with the aim of integrating the medical resources with the criteria to be included as part of the non-pharmacological treatment. [4]

A relation has been seen between loss of weight with a favorable impact in the decrease of serum lipids, so it is recommended to install a regime directed to combat this factor. Its known that with the weight loss of 3 kilograms of weight, triglycerides are reduces on an average value of 15mg/dl; if the patient manages to loose from 5 to 8 kg, the C-LDL will be reduced in average levels of 5mg/dl and the C-HDL will increase from 2 to 3 mg/dl in average. In patients that present a loss of 3 kg, the effect will be observed over TG, C-LDL and C-HDL. In adults who suffer from Diabetes mellitus 2 and overweight or obesity, if an 8% weight loss is achieved in 1 year or 5.3% in 4 years, the C-HDL will increase in 2mg/dl. [61]

Another primary prevention factor that contributes to the loss of weight is the diet of the patients who suffer dyslipidemias, and it is considered a cornerstone in the handling of this type of population. It is known that certain types of fat in the diet directly increase the figures of C-LDL, and these are denominated Trans fats and saturated fats. The Trans fats are found in foods such as margarine, vegetable lard, fast-foods, industrialized products, fried or baked bread, snacks, cakes, cookies and candy. The saturated fats are contained in food products like red meats, sausages, butter, coconut oil, cream, milk and cheese. [62] By contrast, it has been studied that a DASH diet (Diet Approach to Stop Hypertension) in subjects with stable weight and blood levels of TC of 260mg/dl and C-LDL over 160mg/dl reduces the C-LDL by 11mg/dl and the C-HDL by 4mg/dl. This diet is high in vegetables and fruits, potassium, magnesium and calcium; regular in whole grains, fish, nuts, protein and fiber and reduced in saturated fats, cholesterol, sugars and red meats. [62] It is known that a patient with dyslipidemias finds benefit in the correction of the lipid alterations if their meals count with the addition or substitution of unsaturated fatty acids; the linoleic acid, eicosapentaenoic (EPA) and docosahexaenoic (DHA) are unsaturated fats of Omega 3 and 6 that maintain the levels of cholesterol in serum. This type of fatty acids are found in soy, sunflower seed oil, dry fruits (nuts), fatty fish like salmon, herring, tuna, mackerel, sardine, etc. Therefore, it is recommended to substitute in the diet the saturated fats for this type of fats. [63]

The following scheme is advised as a healthy diet for a patient with dyslipidemia:

1. Have and intake of saturated fatty acids below 10% of the total intake of energy and replace these for polyunsaturated fatty acids. [4]
2. That the intake of Trans fats and unsaturated fatty acids are less than 1% of the total energy intake. [4]
3. Consume less than 5 grams of salt per day. [4]
4. Consume from 30 to 45 grams of fiber each day, preferably of integral products. [4]
5. Consume 200g or more of vegetables per day divided in 2 to 3 portions. [4]
6. Consume 200g or more of fruits per day divided in 2 to 3 portions. [4]
7. Consume fish once or twice a week. [4]
8. Consume 30g of unsalted nuts per day. [4]
9. Abstain from taking a maximum of 20 g of alcoholic beverages per day for men and 10 grams of alcoholic beverages in the case of women. [4]
10. Abstain from consuming beverages sweetened with sugar. [4]

Exercising has a direct impact on C-HDL; studies reveal that walking from 25 to 30 kilometers per week (which entails an average caloric burning of 1500 to 2000 kilocalories per week), raises the levels of CHDL in 3.1 to 6 mg/dl. [63] The European guides for the prevention of cardiovascular diseases in the clinical practice, stratify the physical activity in mild, moderate and intense; according to the values of elevation of maximum cardiac frequency (MCF). Mild activity is that in which cardiac frequency is maintained with values of 50 to 63% of the MCF and is achieved when performing activities such as walking at a speed of 4.7 km/hr. and domestic activities. The moderate physical activity maintains a cardiac frequency with values of 64 to 76% of the MCF; this objective is reached with activities such as walking at speeds of 4.8-6.5 km/hr., bicycling at a speed of 15 km/hr., practicing golf, cutting grass, dance, perform aquatic gymnastics, etc. Finally, intense physical activity consist of elevating the cardiac frequency from 77 to 93% of the MCF through the performance of activities such as running, bicycling at more than 15 km/hr., do continuous excavations of gardening, swimming, play tennis, etc. Healthy adults shall do at least 150 minutes of exercise of moderate intensity per week or 75 minutes of intense aerobic exercise in the same time lapse. For patients with cardiovascular risk factors who pretend to perform high intensity physical activities, it is recommendable to do it under previous clinical evaluation. [4]

In patients with dyslipidemia, as a preventive measure, it is recommended to advise the suspension of active and passive tobacco inhaling, as well as inhaling of herbal products. [4]

Groups of medicines that route their handling in the decrease of serum lipids are found in the pharmacological therapy of dyslipidemias. By their action mechanism, they are divided into inhibitors of the Hydroxymethylglutaryl Coenzyme A reductase, inhibitors of the absorption of cholesterol, sequestrants of biliary acids and inhibitors of the lipoprotein convertase subtilisin/kexin type 9 (PCSK-9). [4]

The inhibitors of HMG-CoA reductase which as a pharmacologic group are known as statins, are considered the first line of treatment. They have been available since 1987 and have been amply described and well tolerated. [3] This group reduces the synthesis of cholesterol at hepatic level, by competitive inhibition of the enzyme Hydroxymethylglutaryl coenzyme A reductase. This induces the expression of receptor LDL in the surface of the hepatocyte, which results in the decrease of circulating LDL, Apo B and triglyceride particles. [4]

They are usually classified according to their capacity of reduction in the C-LDL of statins of high intensity, moderate intensity and low intensity. The first reduce the levels of LDL with a proportion over 50% and these are Atorvastatin at doses of 40 to 80 mg/day and Rosuvastatin at doses of 40 mg/day. Moderate intensity statins have a percentage of reduction of C-LDL from 30 to 50%, and in this group are found Atorvastatin at doses of 10-20 mg/day, Lovastatin at doses of 40 mg/day, Pitavastatin at doses of 2-4 mg/day, Pravastatin at doses of 40-80 mg/day, Rosuvastatin at doses of 5-20 mg/day and Simvastatin at doses of 20-80 mg/day. The last group denominated as low intensity because of its reduction percentage, decreases the C-LDL in proportions below 30%; in this group are Fluvastatin at doses of 20-40 mg/day, Lovastatin at doses of 20 mg/day, pravastatin at doses of 10-20 mg/day and Simvastatin at doses of 10 mg/day. [6] The intensity of the treatment shall be guided according to the cardiovascular risk established by the Globorisk scale and its correlation with the C-LDL. [4]

In general, the therapy with statins shows a therapeutic effect which carries a reduction in the percentage of C-LDL from 20 to 60% with the secondary reduction of the morbidity-mortality of cardiovascular events and the decrease in the progression of coronary atherosclerosis; reason for which they are considered as part of the primary and secondary prevention. [3, 6] Associated to the reduction of C-LDL, it has also been observed that the statins maintain a relation with a reduction in serum levels of TC in 17 to 41% and a variable improvement in the levels of triglycerides and C-HDL. [65, 66] In isolated hypercholesterolemia, it is known that the reduction of C-LDL in 40 mg/dl shows an association with the reduction of 22% of cardiovascular morbidity-mortality and that in patients managed with statins, after a diminishing of C-LDL of 39 mg/dl (1mmol/l) the cardiovascular mortality and the non-fatal infarction are reduced from 20 to 25%. [51] In the wording of lipoproteins which are related to cardiovascular risk, properties have been added to the statins not only in the reduction of C-LDL, but also in the C-No HDL, associating its decrease with the reduction of cardiovascular risk. [67]

Among other benefic effects reported by the use of statins are: less endothelial dysfunction, increase in the bioavailability of nitric oxide with its ulterior effect on the relaxation of vascular musculature, antioxidant properties and inhibition in the vascular inflammatory process. [68]

For this reason, in primary prevention, the use of statins is adequate based on the calculation of risk established by the Globorisk cardiovascular risk scale for Mexicans correlated to the levels of C-LDL. [4] Among the patients who are benefited with the use of statins are those that have some cardiovascular disease, those who present serum levels of C-LDL equal to or above 190 mg/dl,

those who suffer from Diabetes Mellitus and are aged from 40 to 75 years, with elevated levels of C-LDL and a high or very high cardiovascular risk and, those aged from 40 to 75 years who don't suffer from Diabetes Mellitus but have a high or very high cardiovascular risk . [69]

In patients who course with familial hypercholesterolemia it is recommended to use as treatment nutritional therapy and statins of high intensity at the moment of diagnose with the subsequent evaluation of cardiovascular risk; for them, a very high risk will be denominated if they have a coronary disease or Diabetes Mellitus 2 and high with the presence of 1 cardiovascular risk factor. The goals in the treatment depend on this stratification; it is paramount for those of very high cardiovascular risk to reduce levels of C-LDL below 70mg/dl, below 100mg/dl of C-LDL for those classified as high cardiovascular risk and for those that don't have another cardiovascular risk, the therapeutic goals will be of C-LDL inferior to 130mg/dl. [70] In subjects older than 21 and younger than 0 with serum levels of C-LDL of 190mg/dl or more, it isn't necessary to estimate a scale to evaluate the cardiovascular risk to initiate therapy and the use of high-density statins is substantiated on the maximum dose tolerated as initial manner. Apart from studying the possibility of a genetic alteration (primary hypercholesterolemia) as originator of dyslipidemia, and the intent of approaching relatives of said patients will be sought to see the possibility, in case that they present the problem, of being favored with the therapy. [6]

For individuals from 40 to 75 years without Diabetes Mellitus, the treatment with statins must be initiated according to the level of C-LDL and the assessed cardiovascular risk. It is recommended to use high-density statins for those who have serum concentrations of C-LDL between 100 to 189 mg/dl with very high cardiovascular risk. In subjects who course with a moderate cardiovascular risk and a dyslipidemia of C-LDL greater than 190, a therapy of statins of moderate intensity must be started. [4, L3]

In the diabetic patient, special considerations must be taken in the handling of statins; hence patients younger than 40 with micro-vascular complications or multiple cardiovascular risk factors, will be benefited with the use of moderate to high intensity statins. For those who are between 40 to 75 years without cardiovascular risk, a treatment based on moderate to high density statins must be administered and, for those who present cardiovascular risk factors, the use of high intensity statins is suggested. [71, L3]

In clinical practice, the statin to utilize and the dose shall be adjusted based on the individual response of each patient. In patients with moderate cardiovascular risk, the goal of primary prevention must be of C-LDL under 115mg/dl and C-No HDL below 145mg/dl. In Diabetic patients the goals in primary prevention is of C-LDL below 100mg/dl and C-No HDL is an alternative goal that doesn't require fasting and is considered as a minor objective of 130mg/dl. [4] See Chart 2.

In patients with moderate risk who don't reach the goal with a change of lifestyle and/or present other factors of cardiovascular risk that can't be modified such as a history of premature cardiovascular disease in first degree relative and inflammatory chronic diseases, treatment with statins shall be individualized. [2]

In individuals who have serum levels of triglycerides greater than 200mg/dl, the C-No HDL is considered an objective of treatment. [72]

In secondary prevention the use of statins is justified in those with cardiovascular disease known as acute myocardial infarction, chest angina, coronary revascularization or high risk conditions such as cerebrovascular event, peripheral arterial disease, chronic renal disease and diabetes mellitus 2 with damage to target organ, which are considered patients of very high cardiovascular risk. [32] In turn, in those patients who have high cardiovascular risk and are older than 95 years, it is recommended to use as first line high density statins, remembering that the goal in patients with very high cardiovascular risk is C-LDL less than 70mg/dl and C-No-HDL less than 100mg/dl. [6]

Notwithstanding what's stated in the previous paragraph, in adults over 75 there isn't enough evidence for the generalized use of statins, since most clinical studies exclude adults older than that age. [69]

In persons over 80 who use statins, a higher index of associated falls and fractures have been seen in the first 2 years of treatment without a significant reduction in cardiovascular diseases, so the therapeutic handling of this age group with statins isn't recommended. [73]

The intolerance to the use of statins is defined by adverse signs or symptoms or laboratory abnormalities, in the majority perceived by the patient that interfere in their daily activities and lead to the decision of reducing or suspending the therapy with statins. [54] In patients who don't tolerate a low dose of statin, but where it is evaluated that the risk/benefit with the therapeutic incursion of some medicine of this pharmacologic group is favorable to the benefit of the subject,

some long half-life statin may be administered as is the case of atorvastatin or rosuvastatin with a frequency of once a week, or 2 to 3 times per week. [74]

There are individuals who are found with a predisposed risk to present adverse events related with the use of statins; in these groups are found those who course with multiple or serious comorbidities, including renal damage and hepatic failure, history of previous intolerance to statins by muscular comorbidities, elevation of ALT in blood to 3 times the upper limit considered as normal in an unexplainable manner (reported in international units), age above 75, have Asian descent, history of having suffered a cerebrovascular event of the hemorrhagic type and, characteristics proper of the patient or of the concomitant treatment that affect the metabolism of statins. [6]

The adverse event that maintains the most relevance in the patients treated with statins is myopathy. This includes several entities, but lacks evidence in that it initiates with myalgias and progresses to more severe clinical or laboratory manifestations associated to myopathy. In these cases, the patient may course with myalgia, myopathy, myositis, myonecrosis and myoglobinuria or acute renal damage. [5] The reported prevalence of myopathy in those who take statins is of 5 to 10%, but the risk of rhabdomyolysis is extremely rare. Its presentation is greater in older adults of the feminine gender and in those who course with complex medical problems or have a history of using multiple medicines. [4] The greater presentation in older adults is justified by the sarcopenia (decrease of muscular mass) increasing the risk of developing myopathy secondary to the use of statins, combined with the fact that the enzymes that metabolize statins may be less functional increasing the interaction among drugs. [75] The physiopathology base of the onset of myopathy in users of statins resides in that the inhibition of HMG-CoA reductase furthermore decreases other intermediaries like the dolichols, prenylated proteins and electron carrier proteins, hemo A and ubiquinone; these form part of complex I and II in the chain of transport of electrons at mitochondrial level of the skeletal muscle. The observation of diminished levels of ubiquinone, not only in circulation in skeletal muscle of those who are treated with statins, suggests that these interfere in mitochondrial function causing a secondary damage in muscular morphology. Studies in humans have shown the there is more lactate/pyruvate in those who used statins in comparison with the controls. In muscular biopsies of some patients, abnormal elevations with deposits of lipids in red fibers were found, and also a diminishment in the activity of cytochrome c, biomarker of mitochondrial activity at muscular level. Among the different statins, atorvastatin and rosuvastatin were the ones found

With less diminishment in the levels of Coenzyme Q10, even in a meta-analysis to that effect, it was found only in one study at doses of 40 mg of Atorvastatin with significant reductions of ubiquinone; [76] and in another that used doses of 80 mg/day, an elevation in muscular sensitivity was seen. [77] Even so, it is concluded that these effects are found in patients susceptible to suffer myopathy by statins. [78]

In the subjects who course with myopathy, the measurement of Creatine phosphokinase (CPK) is recommended, besides being recommended in individuals with a risk of presenting muscular adverse events or a familial history of intolerance to statins or muscular disorder, it is important to always correlate with the clinical presentation and the concomitant therapy in and individualized manner. In patients who course with muscular symptoms additional to the measurement of CPK, it is recommended to measure the creatine and perform a urinalysis with intended search of myoglobin to rule out rhabdomyolysis. At the resolution of muscular symptoms, if no rhabdomyolysis existed, then one can return to treatment with statins at low doses. If after 2 months of withdrawal of the use of statins muscular symptoms or CPK levels don't improve, then these must be considered secondary to other muscular causes. [6] Studies have sustained that in the presence of myalgias in patients with treatment based on statins without CPK elevation or intolerance, strategies of assay-error may be performed starting with low-potency statins at low doses. Also the change of statin used may be an option or through the administration of different doses between the days of treatment with a gradual increase by tolerance each week. [5]

Since hepatic damage secondary to the use of statins shows an extremely low annual incidence, less than 2 cases per million patients, the increase of hepatic enzymes associated to the use of statins is an occasional finding in the majority of the cases, potentially reversible, for which the routine hepatic enzyme measurement isn't recommended in the patient who uses statins. [69] Nevertheless, it is recommended to perform biochemical tests that evaluate hepatic function in those who present symptoms suggestive of hepatotoxicity such as unusual fatigue or weakness, loss of appetite, abdominal pain, choluria and jaundice. In turn, it is recommended not to include in clinical studies subjects that present basal levels of ALT above 1.5 to 2 times the normal superior limit reported in international units. [6] Combined with the non-recommendation of the use of statins in patients with hepatic failure or established hepatic cirrhosis. [69]

In patients who suffer chronic renal disease, Atorvastatin and fluvastatin don't require adjustment since their renal excretion is minimal. For Rosuvastatin it is

recommended to start with 5 mg and use a maximum of 10 mg in those who present a glomerular filtration rate lower than 30ml/min, the use of Rosuvastatin isn't recommended for patients undergoing dialysis. [75]

In patients who have HIV, the use of statins must be considered risky, especially in those who are under anti-retroviral treatment with protease inhibitors and/or non-nucleoside inhibitors of reverse transcriptase. If the benefit is adequate their use is justified but the therapy shall be performed with special care and may only be used as treatment options Atorvastatin and Rosuvastatin from the group of statins. [75]

In the presence of alterations in the state of alertness in subjects who use statins, the possibility must the evaluated that these are the causal factor. [69]

It has been debated whether the treatment with statins may have a relation with new cases of Diabetes Mellitus; it is known that it is associated to an increase of risk to acquire this disease in 9% (Odds ratio of 1.09, Confidence Interval 1.92-1.17) with low heterogeneity of studies (I^2: 11%). It is known that for 1 case of diabetes mellitus to be produced in 4 years, the necessary number of patients to be treated with statins is 255 subjects; likewise, in this period statins will prevent the occurrence of 5.4 events of coronary disease, cardiovascular death or non-fatal acute infarction of the heart. Therefore, it is not recommended to abandon treatment with statins for this cause. [79]

As part of the monitoring in the therapy with statins, it is recommended to perform a basal lipemic profile that reports biochemical levels of TC, TG, C-LDL and C-HDL, followed by another measurement in the following 4 to 12 weeks of the starting pharmacologic treatment and continuing with the same studies every 3 to 12 months. [6]

Another alternate drug used in the treatment of dyslipidemias is ezetimibe; inhibitor of the absorption of cholesterol directed to the protein similar to Niemann-Pick C1 (NPC1L1), the polymorphisms which affect NPC1L1 are associated to decrease C-LDL and the risk of presenting cardiovascular events. [80] These drugs have shown results when combined with the therapy of statins in the reduction of the percentage of C-LDL with an additional 24%. In a clinical assay, it was demonstrated that this reduction offers an absolute reduction in the risk of fatal and non-fatal cardiovascular risk at 6 months of follow-up of 2%. [80] It's because of this that it is recommended to add this drug to the combined therapy with statins in those patients who haven't reached the goal of prevention

with the maximum tolerated dose of statins or who are in the maximum recommended dose. What isn't justified is the use of medicines different to statins as monotherapy in the handling of dyslipidemias, including ezetimibe; this reasoning is because its potency to reduce C-LDL is low, being the exception to the rule those patients who are intolerant to statins. [4] Furthermore, it is known that the treatment with addition of ezetimibe to a moderate-intensity statin has an additional cardiovascular benefit in comparison with monotherapy in patients with diabetes and recent acute coronary syndrome or for those patients who can't tolerate therapy with high-intensity statins. [81]

The sequestrants of biliary acids are another pharmacologic group that may be used in patients with dyslipidemia; such is the case of cholestyramine which at doses of 24 grams it is associated to a reduction in serum levels of C-LDL of 23.5 mg/dl, although a significant decrease in the risk of coronary cardiac disease, acute infarction of the heart or cardiovascular mortality has not been seen. [82] Their use as second-line, non-statin agents has been recommended only in patients who don't tolerate ezetimibe and with levels of triglycerides lower than 300mg/dl in blood; [74] lacking this drugs the recommendation of use as routine treatment for the non-reduction of cardiovascular risk. [4]

Fibrates have their action on the receptor of peroxysomal proliferators (PPAR), expressed in their majority in the liver and in a lesser proportion in the heart, kidney, skeletal muscle and intestine. In these tissues the PPAR is implied in the control of the expression of proteins and catabolic enzymes for fatty acids; this leads to the reduction of the synthesis of triglycerides and a lower production of lipoproteins of very low density (VLDL) in the liver. This effect is done through the increase of the hepatic lipoproteinlipase enzyme and the reduction in the expression of the apolipoprotein C. As an added beneficial effect, the time of permanence of the VLDLs in the circulation is reduced and the acceleration of their transformation into C -LDL, favoring the formation of C-HDL. [83] A reduction in TG has been observed following the use of these agents in 20 to 50% with a slight increase of C-HDL from 5 to 15%; by contrast it is known that the decrease of C-LDL isn't significant and it may even increase. In a review of 18 clinical assays, it was demonstrated that fibrates reduce in 10% the cardiovascular morbidity but they lack effect on the decrease of mortality associated with cardiovascular events. [84] The use of an agent of this family called Gemfibrosil in combination with any statin is contraindicated, since it has been seen that this produces an alteration in its metabolism and increases the risk of myopathy. [72]

Niacin or vitamin B3 is a water-soluble vitamin that acts in reactions that generate energy thanks to the biochemical oxidation of carbohydrates, fats and proteins. In lipids it acts on the metabolic route of endogenous production, diminishing the synthesis of VLDL through two mechanisms: 1) anti-lipolytic effect with decrease in the release of free fatty acids from adipose tissue, through the receptor GPR109A coupled to protein G and 2) inhibition of the hepatic diaglyceryl acylytransferase-2 (DGAT-2) that participates in the synthesis of triglycerides. [85] The use of these agents is recommended as monotherapy for secondary prevention and management of hypercholesterolemia. [4]

With respect to the inhibitors of PCSK9 it is known that they inhibit the degradation of the receptors of LDL in the hepatocyte; they have been studied in patients with heterozygote familial hypercholesterolemia, intolerance to treatment with statins and in patients with very high cardiovascular risk, proving that they are safe and effective in the reduction of C-LDL and lipoprotein a. [86]

Carnitine was discovered in 1905 as a component of muscular tissue, from which it derives its name (from Latin *carnis*), its chemical structure was established in 1927 by Tomita and Sendju. For its synthesis, it requires essential amino acids like lysine and methionine, apart from the cycle of ascorbic acid, niacin, pyridoxine and iron; its active form is levocarnitine. [87] L-carnitine (levocarnitine) plays an essential role in the metabolism of energy production. It acts as fatty acid transporter from cytosol to the mitochondrial matrix, being the Beta-oxidation of intramitochondrial fatty acids the largest and most efficient energy source when producing Acetyl- CoA and ATP through the Krebs cycle. [88] It is indicated in the treatment of primary deficiencies of carnitine, problems in the biosynthesis starting from substrates of the diet or for the secondary treatment by alterations in its metabolism. [89, 90] It is approved by the FDA for the primary treatment of carnitine deficiency and for the acute and chronic treatment of patients with errors in the metabolism that is secondary to the deficiency of carnitine, amongst which Diabetes Mellitus type 2, methylmalonic aciduria, propionic academia, glutaric aciduria and deficiency in the middle chain of the enzyme Acetyl-CoA dehydrogenase, among others, and in patients with dialysis and chronic renal failure in terminal stage due to the deficiency of carnitine with which they course. [90] In nephropathy patients with hemodialysis it assists in the management of fatty acids that accumulate secondary to the blocking of the potassium channels, diminishing the resistance to insulin, arrhythmias and the patient's own weakness. Besides, it is used in the prevention and treatment by secondary deficiency due to the administration of valproic acid. [89]

The efficacy of L-carnitine has been proven in the decrease of C-LDL and TC,[91, 92] besides, there are also reports in which the consumption of this product offers a decrease in the serum levels of TG and an increase in the levels of C-HDL. [7, 92, 93] This generates a significant impact to execute the therapeutic management using L-carnitine in patients with dyslipidemias, decreasing the cardiovascular risk associated to these diseases of the lipids, favored by studies that have shown the clinical efficacy in patients that were medicated with L-carnitine after presenting a cardiovascular disease.[7, 90, 94, 95]

In the follow-up of patients with dyslipidemia, it is advisable to measure the lipids profile at 4 to 12 weeks from start-up of treatment or when the dose is adjusted to determine the adherence of the subject to the therapy employed; following this measurement it is recommended to measure the serum levels of TC, C-LDL. C-HDL and TG every 6 to 12 months. In turn, it is recommended to lower the dose of statins when two consecutive values of C-LDL less than 40mg/dl are obtained. [6]

In patients who don't reach the therapeutic objective in the reduction of C- LDL, the management with statins must be started with a greater intensity dosage. If the patient reaches the therapeutic objective then the statin must be continued with the currently used dose. [74]

It is recommended to refer to the second level of attention those patients who course with familial hypercholesterolemia and who don't reach the therapeutic goals of C-LDL despite being treated with the maximum doses and verifying the additional compliance by the patient in adherence to treatment and to the established non-pharmacologic measures. It is also recommended to send to the second level of attention to the users of statins with reactions such as myopathy or elevation of ALT in 3 times its normal value in international units. [2]

Patients with dyslipidemia must be counter-referred once they reach the therapeutic goals according to the cardiovascular risk stratified by the Globorisk scale for the Mexican population and/or to the resolution of the complications or secondary events that maintain relation with the pharmacotherapy employed in the patient; when counter-referring, the patient shall be made aware about the importance of the treatment and the first-level physician will be advised to keep a strict control on the associated cardiovascular risks and the non-pharmacologic measures employed in the therapeutic approach of the disease. [2]

Since statins are the primary management in dyslipidemias, it is adequate to study the formulation of products that add to them a greater therapeutic efficacy than what is reported and a better safety profile.

5. BACKGROUND

Dyslipidemias, especially the one related to the elevation of C-LDL, are a factor for cardiovascular disease. [2, 6, 54, L1]

Statins are the first-line drug; its effect on the decrease of fatty acids is due to the reduction of their synthesis through the inhibition of the HMG-CoA reductase. Several studies have proven the significant reduction of cardiovascular diseases in morbidity and mortality following the use of statins, thus having a favorable benefit/risk relation for the use of these pharmacologic agents. [2, 6, 54, L1] Despite these benefits, the risks of managing a therapy with statins are known.

The most common adverse events following treatment with statins are gastrointestinal ones, with a greater prevalence of mild diarrhea, although other manifestations such as mild abdominal pain and flatulence may exist; the occurrence in clinical studies is from 2 to 5%. Other gastrointestinal symptoms like nausea, vomit, constipation, dyspepsia, and heartburn occur in 1 to 4% of the patients who receive statins in clinical studies. Anorexia has also been reported as a gastrointestinal event associated to the use of statins. [96]

The Factors related with the hepatic abnormalities secondary to statins consist in the elevation of hepatic enzymes such as AST and ALT 3 times above their normal value and depend on pharmacokinetic and physiochemical factors accompanied by the selective transport mediated at hepatic level. [97] Besides, they show a predisposition to present adverse reactions in those patients who course with chronic infections by the hepatitis virus. [98] This effect keeps an occurrence of 0.1 to 3% with at least 2 times of presentation per individual (which aren't necessarily consecutive) in a period of treatment with statins of at least 11 months. It is very rare when this serum elevation is accompanied by jaundice or cholestasis; although in several clinical studies at least 1 patient has developed jaundice. Another important fact is that the serum elevation reported in the values of ALT and AST is usually transitory, decreasing when the treatment with statins is withdrawn. [96]

In the dermatologic area, the most common adverse reaction by the use of statins is the cutaneous rash, reported in 1 to 4% of the patients included in the clinical studies who received this pharmacologic group. Other less common effects may be the presence of alopecia, pruritus and changes in the skin (nodules, hypochromia, dry skin, changes in the parts attached to the skin). [99]

Within the adverse events of the nervous system, headache is the most commonly reported in clinical studies that used treatment with statins. The incidence is 3 to 17% of the patients. Other events such as asthenia, fatigue and dizziness have an occurrence of 1 to 4%. [99]

The cardiovascular effects reported in patients included in clinical studies following the administration of statins are very rare; these include precordial pain, hypertension, chest angina, palpitation, vasodilation, syncope, postural hypotension, peripheral edema and mild arrhythmias. [100]

In the genitourinary system, events have been reported as attributable to the use of inhibitors of the HMG-CoA reductase, and these are: loss of libido, erectile dysfunction, impotence, epididymitis, abnormal ejaculation, vaginal hemorrhages, uterine hemorrhages, metrorrhagia, fibrocystic mastopathy, cystitis, hematuria, dysuria, kidney stones, nocturia, albuminuria, nephritis, urinary incontinence, urinary retention and urinary urgency. [100] Other extremely rare events include gynecomastia, hyperglycemia, hypoglycemia, gout, weight gain, ecchymosis, anemia, lymphadenopathy, petechial exanthema, tinnitus, parosmia, agnosia and alterations in the sense of taste. [100]

The event of greatest relevance with clinical significance related to the use of statins is myopathy. All the statins have been associated with this condition and the secondary rhabdomyolysis it may entail, although these are generally reversible and mild and very rarely cause rhabdomyolysis. [101, 102] Although it was commented about the possibility of the mechanism associated to the myotoxicity of statins, this isn't clear, but is attributed to the mitochondrial dysfunction and to the defects in the regeneration of myocytes. [102] This adverse event shows predisposition for diverse factors with special demographic characteristics; for example, in persons over 75 they are related with the sarcopenia, proper of the age, women, polymorphisms of the gene SLCO1B1 (common in Asian populations), abnormalities in the polypeptide transporter, isoenzymes of the Cytochrome, depletion of ubiquinone, alcoholism, drug-addiction and hereditary myopathies. [101] The incidence of myopathy in subjects who take statins without any other concomitant drug that may by itself put the patient at risk of presenting myopathy is less than 0.1%. On the other hand, alcoholism in patients that use statins also increases the risk of myopathy due to

the synergic effect due to the alcoholic myopathy proper. [103]

Myalgia secondary to myopathy by statins is characterized by an intense muscular pain which starts in the arms, thighs and then extends to the whole body in a manner similar to that presented in the flu-like syndrome; the symptoms progress according to the continuation of use of the medicine or causal medicines. The levels of CPK reported as abnormal must be found 10 times above the normal superior limit and a urinalysis must be performed in search of myoglobin to rule out rhabdomyolysis. Among the motives to discontinue treatment with statins are: those patients who course with rhabdomyolysis and patients with high CPK levels attributed to the use of statins. Besides, it must also be considered to withdraw treatment with statins from those who aren't able to obtain serum levels of CPK and continue with the presence of myalgias; this once other causals are ruled out as responsible for the symptomatology. It is known that the use of statins at a dose not greater than 25% of the maximum dose of the drug, reduces the risk of presenting myopathy. [104]

Once it's been referenced about the adverse events found by statins, one in particular will be discussed for being part of the drug under study and for having a good profile of therapeutic efficacy and safety; atorvastatin.

Atorvastatin is a lipophilic statin that was authorized for sale for the first time in 1997. [105] In a few years it became stellar in the group of statins; this is postulated due to 2 important factors; the first one is that it has been proven that Atorvastatin and Rosuvastatin are the drugs that have the greatest potency in the diminishing of C-LDL and the second one is that Atorvastatin presents a better safety profile in patients with renal conditions. [105, 106] More than 500 randomized clinical studies that deal about the safety and efficacy of the use of Atorvastatin have been conducted. [107]

In terms of clinical benefits, it has been seen that atorvastatin provides an important reduction in the morbidity-mortality by cardiovascular diseases, including patients with Systemic Arterial Hypertension classified as high risk without established coronary disease, [108] patients with an associated comorbidity as is Diabetes Mellitus 2 and who don't course with an established coronary disease, [109] patients who suffer some type of acute coronary syndrome [110, 111] and those who course with a coronary disease in stable conditions [112] Besides, there are precedents that atorvastatin at doses of 80 mg/day compared with the use of placebo diminishes the incidence of cerebrovascular event in patients with previous cerebrovascular event but without

established coronary disease. [51]

Thus, Atorvastatin counting with more than 500 randomized clinical studies is the drug that counts with the greatest evaluated presence than any other drug that's effective in the treatment of dyslipidemia and prevention cardiovascular diseases. It is used extensively in a variety of circumstances, including primary and secondary prevention of cardiovascular events; for some years, it has also been used in patients with chronic renal disease and in diabetics; this is why it has been a bastion of safety and tolerability of the drug. [113]

A study in patients with chronic renal disease stage 5 showed the efficacy of administrating atorvastatin on the lipid levels in blood, reaching therapeutic goals in TC in 65% of the patients, of C-LDL in 50% of C-No-HDL in 40% and of TG in 45%. The dose used was on average 60.4 mg per day and its administration didn't cause significant adverse events. [114]

With respect to adverse events attributable to the use of atorvastatin, there are those that are pre-clinic and others that are clinic. Pre-clinic ones conclude that the use of atorvastatin has a lesser incidence of adverse events than those of other types of statins. While the inhibitors of HMG-CoA reductase such as fluvastatin, lovastatin, pravastatin and simvastatin don't show evidences of mutagenicity (bacterial assay of genetic mutation, clastogenicity assay and assay of genetic mutation in bacterial cells as well as in mammals), at long-term the studies of carcinogenicity in rodents resulted in a greater incidence in the development of tumors when high doses are used. [115] In oral doses of Atorvastatin in rats with concentrations of 10, 30 and 100 mg/kg per day for 2 years, there was an increase in the incidence of rhabdomyosarcoma and fibrosarcoma in 2 females treated with high doses. This represents an area under the curve of concentration-time (AUC) of an approximate value of 16 times the average of plasma concentrations of the AUC in humans at doses of atorvastatin of 80 mg. In mice that received oral doses of atorvastatin of 100, 200 or 400 mg/kg per day during 2 years there was an increase in the incidence of hepatic adenomas in males and hepatic carcinomas in females treated with high doses. This represents a value of plasma AUC of approximately 6 times the average of plasmatic concentrations of AUC in humans at a dose of atorvastatin of 80 mg. [116] In the rats that received oral doses of atorvastatin of 20, 100 or 225 mg/kg per day starting on day 7 of gestation until day 21 of lactation (weaning), there was a decrease of survival of the progeny when born. Corporal weight decreased on days 4 and 21 in the progeny of mothers that received 100 mg/kg on the day of birth.

The weight was reduced on days 4, 21 and 91 with 225 mg/kg daily. The development of the progeny was delayed, which was evaluated by performance (mothers that received 100 mg/kg daily). It was also observed that there was a delay in development, basically at the moment of detachment of the ear and ocular aperture (mothers that received doses of 225 mg/kg). These doses correspond to an exposition equivalent to 6 times (100 mg/kg) and 22 times (225 mg/kg) the AUC in humans at 80 mg per day. [116]

The most extensive clinical studied in which there's experience in the use of atorvastatin is "The Treating of New Targets". In this study were included 10,001 patients with coronary disease and they were randomized to receive doses of 10 or 80 mg per day of atorvastatin during 5 years. [112] No significant clinical differences were found associated with the use of atorvastatin among the subjects who reached levels of C-LDL from 66 to 106mg/dl; which coursed with myalgia in 5% and didn't present persistent elevated levels of CPK (superior to 10 times the normal upper limit through international units or that presented rhabdomyolysis). No persistent elevation level was found neither in the hepatic transaminase levels(less than 3 times above the normal upper level according to international units) with an incidence of 0.2% for the group that received atorvastatin in doses of 10 mg and 1.2% in the group of 80 mg. Serious adverse events such as suicides, cancer and cerebrovascular events of the hemorrhagic type, didn't present statistically significant differences among percentiles. [112]

An analysis that includes clinical studies in patients with coronary alteration, stable cardiovascular disease and cerebrovascular event without cardiovascular disease, comprising between 25,000 and 69,000 patient-years with the use of atorvastatin of 10 mg and 80 mg atorvastatin respectively, found an increase of ALT and AST greater than 3 times the normal international units from 1 to 3.3%, a persistent increase of 0.1 to 0.4% in CPK levels (greater than 10 times the normal upper limit in classified international units), and no case of rhabdomyolysis associated to atorvastatin. [117]

In a meta-analysis of 44 studies performed in 1,495 dyslipidemic patients treated with atorvastatin (9416 patients), other statins (5290 patients) and placebo (1789 patients), the safety of atorvastatin was evaluated in doses of 10-80 mg per day; it was found that the evidence of adverse events was only 3% for the subjects who used atorvastatin, 1% for those who used placebo and 4% for those who used other statins. [118] Reporting gastrointestinal events as the most frequent adverse event. The largest elevation to 3 times in normal values according to international units for hepatic enzymes ALT/AST had an incidence of 0.5% in those treated with atorvastatin. With respect to the CPK values, only

1 patient treated with atorvastatin showed a persistent elevation in values of CPK (elevation greater than 10 times the range established as normal in international units) and in this one, no association with myopathy was proven, for lacking muscle pain. The incidence associated to myalgia without elevations of CPK was low (1.9%) in those who received atorvastatin and no relation was shown with the used dose; the placebo group had 0.8% and the group treated with other statins had 2%. No case of rhabdomyolysis was reported in any group (myalgia with CPK greater than 10,000 international units that conditions acute renal damage). [118] In another meta-analysis it was reported equally the non-dependence of presentation of adverse events related to the dose used of atorvastatin. This analysis included 48 studies with more than 14,000 patients in treatment groups that received atorvastatin (doses of 10 to 80 mg per day) or placebo. [119] Besides, it was observed that the incidence of related events was 2.4% in the group of 10 mg of atorvastatin, 1.8% for the group of 80 mg of atorvastatin and 1.2% in the control group that received placebo. The serious adverse events related to the product were very rare and didn't present relation with the dose of atorvastatin used. Besides, no cases of rhabdomyolysis were observed and there was little impact of cases reported with myalgia; this was of 1.4% in patients who received atorvastatin 10 mg, 1.5% in the group of 80 mg and 0.7% for the placebo group. The persistent elevations of ALT/AST (in ranges greater than 3 times the normal upper limit according to international units) were of 0.1, 0.6 and 0.2% for the groups of patients with treatment of 10 mg of atorvastatin per day, 80 mg per day and the placebo group, respectively. [119] These studies support a positive safety profile for the use of atorvastatin, inclusively at doses considered as of high intensity.

In patients with treatment for DM2 and cardiovascular disease (through the use of atorvastatin at doses of 24 mg per day in comparison with the usual treatment) or without established cardiovascular disease (using atorvastatin 10 mg/day vs. placebo), a profile of tolerability similar with respect to the usual treatment or placebo was found. [109, 120]

For patients with chronic renal failure, atorvastatin doesn't require dose adjustment. [107, 121] Likewise, the good tolerability of atorvastatin was found in the groups of patients with diabetic nephropathy. [120] Atorvastatin reduced the levels of C-LDL in 42% compared with the basal values during the first month of treatment, without presenting any significant event such as death by cardiac causes, non-fatal acute cardiac infarction and cerebrovascular event. Besides, the reported safety was similar to that obtained with the use of placebo. [122]

Interactions have been proven with certain pharmacologic groups and atorvastatin. Within these it is known that atorvastatin shows interaction with gemfibrozil, clofibrate, phenofibrate and niacin, agents which are related among themselves for causing myopathies as secondary reactions; this is probably due to the inhibition of the synthesis of esters in the skeletal muscle. There is another type of drugs that increase the incidence of adverse events secondary to statins by affecting the metabolism of inhibitors of HMG- CoA reductase; causing the subsequent increase in its plasmatic levels and active metabolisms. Such is the case of macrolides (Erythromycin, Telitromycin and Clarithromycin), Azole anti-fungi: Ketoconazole, Itraconazole, Fluconazole, Cyclosporine, antidepressants of Phenylpiperacine, Nefazodone and protease inhibitors. [104]

In patients who use cholestyramine or colestipol along with inhibitor of HMG-CoA reductase, it is advisable that this latter drug be administered 2 to 4 hours previously to the use of the mentioned ones, due to the fact that these may reduce their viability. Besides, it is recommended that if the patient uses antacids, not to administer these along the statins, since it has been documented that antacids reduce the plasmatic concentration of atorvastatin in approximately 35%. [123]

One treatment group of the study will receive additionally to atorvastatin, L-carnitine. L-carnitine is a compound derived from essential amino acids that play an important physiological role in the transport of fatty acids of long chain towards the interior of mitochondrias for their β-oxidation and the production of ATP by oxidative phosphorylation. It may also translocate acetyl - CoA of the mitochondria to the cytoplasm of the cell. [124] In adipocytes it produces and antilipid activity and increases β-oxidation. [125] Besides, plasmatic levels of insulin above 90 µU/ml favor, in the presence of adequate amounts of L-carnitine, the accumulation of it in the striated muscle in healthy, non-obese volunteers. [126] Levocarnitine is used in states that course with deficiency of its basal concentration, caused by diverse pathologies whose primary characteristic is excessive corporal abrasion and hyper catabolism (sepsis, ischemia, myocardiopathy, etc.), or in diseased persons with frequent hemodialysis. Also, a decrease of its concentration has been reported in patients with type 2 diabetes mellitus and above all in women with diabetic complications. [127] It's not clear whether the deficiency of carnitine in diabetic patients is the result of the diabetic state or a factor that may contribute to the development of diabetes; [128] its administration is cataloged as dietary supplement and as medicinal therapeutic principle, which seeks to increase the energetic contribution. It favors the β-oxidation of fatty acids in mitochondrias and thus improves the energetic

performance of the fatty acids as well as the accumulation of triglycerides in tissues; there is evidence that upholds the hypothesis that se supplementation of carnitine improves the muscular lipid content, reduces oxidative stress and increases sensibility to insulin. [129] Instead, its deficiency leads to a progressive intracellular toxic state with accumulation of free fatty acids and triglycerides in tissues [130]

The evidence of the favorable effect following the use of L-carnitine on fatty acids in pre-clinical studies has been proven. It is known that it inhibits the increments of triglycerides by atherogenic diets, reduces circulating leptins and with that abdominal fat and, modulates the balance of insulin-like growth factors (ILGFs). This has been shown by the increase secondary to its administration of protein 3 of union to the growth factor similar to insulin (IGFBP-3) in diabetic rats, in which it is usually reduced. [125] There are reports of normalization in the concentrations of carnitine, plasmatic cholesterol and triglycerides in animal models with the use of Levocarnitine. [131] In more recent studies in hypercholesterolemic rabbits, it was demonstrated that Levocarnitine could prevent the progression of atherosclerotic lesions, thanks to its antioxidant and hypolipidemic effects. [132]

A multi-centric study, double-blind, controlled with placebo demonstrated, upon administering L-carnitine in patients who had suffered a first acute myocardial infarction, which they benefitted with a secondary reduction of cardiac failure and a decrease in mortality figures. [94] In another clinical study where a sample of 574 subjects was included, the effects were compared of administering L-carnitine in comparison with a placebo in patients with cardiac failure, where a significant difference was found in the results of resistance time in maximum duration during the exercise for the group of L-carnitine compared with the placebo group. [90] Combined to these results, a multi-centric study with 472 patients that received levocarnitine following an acute myocardial infarction, demonstrated an improvement in the parameters of ventricular remodeling and a lesser dilation of the left ventricle. [95]

Many experimental studies have observed that levocarnitine reduces myocardial damage after it was subject to ischemia and reperfusion, effect attributed to the action of L-carnitine to counter toxic effects of the free fatty acids secondary to ischemia. Additionally, it was found that the supplementation with L-carnitine increases the content of carnitine in the myocardium, functioning as prevention in the loss of storage deposits of phosphates, ischemic damage and the recuperation of cardiac reperfusion. Clinically, it has been proven that L-carnitine has anti-ischemic properties which favor the non-appearance of cardiovascular events. [95]

From January of 2013 to February of 2014 a randomized single blind study was performed, controlled with L-carnitine vs. Placebo, in patients diagnosed with arterial coronary disease (by catheters with stenosis of at least 50% in one of major coronaries or angioplasty with percutaneous transamination), some of which presented dyslipidemia and treatment with moderate density statins. It was concluded that with one dose of 1g a day of L-carnitine there was a significant increase in C-HDL and Apo-A1 lipoproteins, with a slight diminishing in TG. [7]

In patients with hemodialysis, a significant effect on the decrease of lipids has been demonstrated following the administration of L-carnitine. [94, 133]

Naini and collaborators found that after treating patients with a dose of 750 mg per day of L-carnitine, there were significant decreases in the serum levels of TC, TG and C-LDL; also that if the dose used is of 1g of L-carnitine, a significant increase in the level of C-HDL is added. [94] This effect is suggested since L-carnitine increases the mitochondrial transport of fatty acids and reduces the viability of fatty acids for the synthesis of lipids. [134]

In a meta-analysis about the impact of L-carnitine in the treatment of plasmatic lipoproteins, it was concluded that L-carnitine produces a significant reduction of TC and a reduction on the limit, after all significant, of C-LDL, without effects on the C-HDL and triglycerides. [91]

In turn, the supplementation with L-carnitine has been suggested in some forms of hepatic damage. This is due to the fact that in the final stages of hepatopathy, the deficiency in the synthesis of L-carnitine causes low levels of metabolically active carnitine in the myocardium and in skeletal muscle. [135]

In patients with resistance to insulin (entity with an important role in the development of Diabetes Mellitus type 2), its known that there exists a defect in the oxidation of muscular fatty acids; investigations suggest that the supplementation with L-carnitine may aid in the sensitivity to insulin in diabetics through the decrease of fatty acids in muscle and may diminish the levels of blood glucose through cellular oxidation. [94]

There are preceding studies, for the therapeutic intervention and the findings in the use of L-carnitine + atorvastatin or other statins, in pre-clinical as well as

in clinical phases.

The hepatoprotector effect of these drugs in rat livers was evaluated in a pre-clinical study, arguing that with a previous induction of hepatic toxicity by infusion of statins, there were going to be alterations of cellular markers and inclusively, on the cells proper. It was proven that the treatment with the addition of L-carnitine decreased cellular death, the instability of the mitochondrial membrane and the expression of free radicals and molecules that suggested damage to hepatocytes by the statins. [136]

A review made by experts with the premise of verifying that L-carnitine aids in the management of the symptoms of myalgia secondary to statins, mentions that owing to the fact that patients who course with myalgias secondary to atorvastatin present abnormalities in carnitine levels, it is recommended that studies be performed in which L-carnitine is proposed as an option to reduce the presentation of this adverse effect secondary to the administration of inhibitors of HMG-CoA reductase. [137]

In a study done on patients who suffered Diabetes Mellitus 2, the therapeutic efficacy on lipoproteins and apoproteins was compared in treatment groups composed by those who used statins + L-carnitine in comparison with only statins. It was identified that the group that used the combination of inhibitor of HMG-CoA reductase and L-carnitine in comparison with the group that was medicated only with statins, presented significant differences for the decrease of glucose, TC, C-LDL, TG, ApoB, Apo A and a significant increase in C-HDL. [138]

In 2009, Malguarnera and collaborators performed a study on the effects in the size of low-density lipoproteins when adding L-carnitine to patients with diabetes mellitus 2 on treatment with simvastatin. For this they included 80 randomized diabetic patients in a group with oral route simvastatin at doses of 20mg per day and another with simvastatin at 20mg/day + levocarnitine 2g per day. The duration of treatment was 3 months. The variables to study were total cholesterol, C-LDL, C-LDL subclasses, size of LDL, C-HDL, plasmatic glucose, glycosylated hemoglobin, index of corporal mass, triglycerides, apolipoprotein A-1 and apolipoprotein B-100. Upon completion of treatment a significant reduction was found in the group that received L-carnitine + simvastatin in the proportion of small size molecules of LDL, C-LDL, triglycerides, total cholesterol, glucose on fasting and Apo B-100 in comparison with the group of monotherapy with simvastatin. Besides, the group that received carnitine + simvastatin had a significant increase in comparison with the monotherapy group of simvastatin for C-HDL and large particles of LDL. [139]

To verify the efficacy and tolerability of a treatment of L-carnitine and simvastatin, a study was developed in which the intention was to verify the serum decrease of lipoproteins in patients with diabetes mellitus 2. The study was open, randomized with 52 patients that had diabetes mellitus 2, triglycerides levels below 400mg/dl and Lp (a) greater than 20mg/dl. They were randomized in 2 groups; the participants of the first group received simvastatin in monotherapy at doses of 20 mg per day and those of the other group received simvastatin + levocarnitine at doses of 20 mg/2 g once a day. Both treatments were through oral route. There was no treatment abandonment or adverse events. No significant differences were observed between the groups for the reduction of C-LDL, C-No-HDL and apoB; but significant differences were found in therapeutic benefit for those who received L-carnitine + simvastatin in the diminishment of the Lp(a). [140]

In a controlled randomized study with placebo on patients who were receiving hemodialysis, 52 patients were included, 27 men and 25 women who were being treated with atorvastatin or lovastatin to measure the therapeutic efficacy of a supplementary therapy. They were divided into 4 groups that received 1 g of intravenous carnitine 3 times a week, coenzyme Q10 in oral doses of 100 mg per day, both or placebo. After 3 months of treatment levels of lipoprotein (a), triglycerides, total cholesterol, C-LDL and C-HDL were measured. Significant differences were found in the reduction of lipoprotein (a), in the groups that received carnitine, coenzyme Q10 or both compared with the placebo groups. There were no changes that were significant in other lipoproteins. [141]

6. JUSTIFICATION

Cardiovascular diseases, including coronary arterial disease, cerebrovascular event and peripheral arterial disease, are causative at global level of a mortality rate that places them in the first place. It is estimated that in the year 2012 they were responsible for 17.5 million deaths; 7.4 million were secondary to acute myocardial infarction and 6.7 million were attributed to cerebrovascular disease. Apart from the mentioned figures, it is known that cardiovascular diseases or causal of almost half of the deaths by non-transmissible secondary diseases (46%) and of 37}5 of premature deaths in persons under 70. [1] The fact that the majority of these deaths are preventable is of a greater significance. It's projected that for the year 2030 mortality secondary to cardiovascular disease

has a figure of 22.2 million persons. [1]

These figures aren't apart from the reality that prevails in Mexico. According to the Organization for Cooperation and Economic Development (OCDE), cardiovascular diseases in Mexico 2015 were causative in the death of 292 persons for every 100,000 habitants, thus being considered a high-risk country for death associated to a cardiovascular disease. This death not only occurs prematurely, but causes the survivors to have a deficient quality of life, require long-term health care and have a reduced capacity in their work life. Besides, the years of life potentially lost by cardiovascular disease in the Mexican population, were 728 for every 100,000 habitant, 25% above the average of OCED countries. [44]

Confronting this problem shall maintain relation with the strategic design of the National Plan for development for the cycle 2013-2018, where it is posed by presidential decree as one of its 3 transversal strategies "Democratize Productivity"; its mentioned in this plan that democratizing productivity "means generating the correct stimuli to integrate all Mexicans in the formal economy …" [L4], elements to consider on knowing the secondary effects of dyslipidemias and the subsequent cardiovascular diseases in the reduction of the work life capacity and the potentially lost life years, combined to a premature death; leading to impingement in its management consistent with the aforementioned argument.

On the other hand, for the year 2006, costs generated by cardiovascular disease, diabetes and obesity were 40 billion pesos; figure that corresponds to 7% of the total expenditure for the health sector, were 55% is destined to that which is related with cardiovascular disease. It is estimated that for the year 2030, costs around 557 million dollars will be generated for cardiovascular and cerebrovascular disease, and for the year 2050, 797 million dollars generated for these conditions. [142] Once again, it's convenient to reference the National Development Plan 2013- 2018; for, since one of the 5 national goals is the proposal to be an Inclusive Mexico, which promotes the access to health to all Mexicans and avoids the unexpected health problems or economic movements, be a determining factor in its development. [L4] In this context, the expenses generated by cardiovascular diseases may be mitigated by a correct approach to prevent them and thus promote health in the Mexican Population.

There exist data on the global decrease of mortality secondary to cardiovascular diseases that may justify that these are secondary to a problem of social inequality. This argument rises from what was reported in the Global Burden Disease, where it was discovered that cardiovascular disease has diminished in 21% globally in the last 20 years, these being figures that have been observed only in developed countries and that remain with an increase in mortality rates for developing countries. [58]

This success in developed countries has been attributed to preventive strategies with inclusion in the last 60 years on two determinant items. The first one consists on implementing public health policies with the objective of decreasing the morbidity-mortality of cardiovascular diseases. The second one considers the strategy of focusing on decreasing the probability of presentation in individuals of future cardiovascular events, through the knowledge and appropriate management of the modifiable risk factors. [58] The definition of cardiovascular risk is defined as the risk of suffering death secondary to cardiovascular disease in a period of 10 years. [2, 143]

Having these considerations offers certain advantages such as: having an objective evaluation of cardiovascular risk favoring a common language among the different health professionals, acknowledging that cardiovascular disease has a multifactorial nature and, approaching the problem of young patients with low absolute risk but multiple risk factors through their stratification. [4]

An effective implementation of these considerations is recommended to detect these patients in a clinical scenario through the use of an adequate and validated tool for each geographic region through the recalibration of an already elaborated scale. [4]

Mexico participated in a validated multi-centric prospective cohort known as Globorisk with the inclusion of patients of 40 to 84 years with follow-up for 15 years. A high-risk prevalence was found for 16% of men and 11% of women. A recalibrated cardiovascular risk equation was developed starting from these data, with other models such as Framingham and SCORE that allowed the establishment of a risk correlation at 10 years for the Mexican population, identifying as high probability risk to present a cardiovascular event those where a risk over 10% was present. [53]

Starting from this, having an adequate control in the prevention of disease will lead to decreasing the incidence of new cases of these nosologic entities. The risk factors that are determinant for the presentation of cardiovascular disease have been identified. These are called cardiovascular risk factors, which estimate the probability of a subject being in risk of suffering a death associated to cardiovascular events within 10 years. The control of risk factors to present a cardiovascular disease is the main strategy to diminish morbidity-mortality caused by this disease. There are modifiable factors such as smoking, hypertension, diabetes mellitus, dyslipidemia and obesity and non-modifiable such as age (men over 45 and women over 55) sex, race, first-degree premature ischemic cardiopathy (men under 55 or women under 65). [2] Dyslipidemias are the most frequent modifiable cardiovascular risk factor. [2, L1]

That is why the control of dyslipidemia, especially the elevation of cholesterol-LDL, takes such relevance for diminishing the presentation of cardiovascular diseases. [4]

The argument quoted maintains a relation with the evidence that upon decreasing C- LDL 39mg/dl a diminishing 20% is achieved in the incidence of cardiovascular events without difference in gender; men and women are benefitted. [51]

The figures of C-LDL have shown elevation attributable to the development of the country. In the existing Mexican population the figure of serum levels of C-LDL between 100 and 160 mg/dl is considered normal, but when compared to healthy primate adults, who have C-LDL levels of 40 to 80 mg/dl, the slow increase in the last decades is reflected. [15] The Framingham study proved that men and women with C-LDL over 160 mg/dl develop 1.5 times more cardiovascular disease compared with a population with C-LDL below 130 mg/dl. In the same manner, in the study of communities in risk of atherosclerosis (ARIC) for every increase of 39 mg/dl, the risk of a cardiovascular event increases 40%. [15]

In the National Survey of Chronic Disease from 1993 to 1994, it was known that the prevalence of elevation of TC was of 27.1%, hypertriglyceridemia had a presentation in 42.3% of Mexicans and hypoalphalipoproteinemia prevailed in 61%. [17] Data from the ENSANUT survey 2006 reported a prevalence of cholesterol greater than 200mg/dl of 43.6% in people over 20.[20] On the other hand, in a recent, a prevalence of 50.5% with a greater predisposition for men and showing an increment according to age, with the exception of the group of

55 to 64 years, where it was greater in women. [18] These data suggest that the problem of dyslipidemia in the Mexican adult has increased.
The most frequent dyslipidemias in Mexicans are the diminishing of C-HDL and hypertriglyceridemia; [19] being the former the most frequent with a reported prevalence of 58.9%. [20]

It's important to highlight that the association of dyslipidemia with other cardiovascular risk factors like diabetes, hypertension, obesity and smoking increase the risk of ischemic cardiopathy. [2]

With respect to the pharmacologic therapy for hypercholesterolemia, statins, available since 1987m widely prescribed, well tolerated and with a proven reduction of cardiovascular events in primary as well as in secondary prevention. The levels of C-LDL decrease depending on the dose in 20 to 60%. [3]

Atorvastatin is a type of statin drug that began its commercialization in 1997 and since then it plays a stellar role in the group of statins, being atorvastatin the most studied drug of the group of those used for the management of dyslipidemias. [147] This is considered so since it is 1 of the 2 drugs that provide a greater diminishment in the levels of C-LDL. [106, 147] This association is sustained based on the levels of concentrations of the drug in blood with a half-life of 20 to 30 hours [104] and because it has a very good safety profile in comparison with other statins and its uses are documented in special populations [76, 106, 109, 114] and in patients who suffer some type of acute coronary syndrome. [107, 109, 110, 111, 112, 113, 117, 118, 119, 120, 121, 122]

Nevertheless, around half of the patients discontinue the therapy with statins during the first year, because of the cost or related adverse effects and up to 25% of patients in primary prevention abandon it after 2 years for not being convinced of requiring treatment. [14] It is also important to know that despite high dose of statins, up to 13%of the patients don't reach concentrations of C-LDL lower than 100 mg/dl and more that 40% don't reach levels below 70 mg/dl. [144]

The importance of initiating an adequate control of lipids entails the maintenance of optimum levels of fatty acids in blood which are implicit in the increase of the risk of acquiring some cardiovascular disease. For this reason, with the formulation of a medicine that is effective and has an adequate safety profile, the indexes of abandonment of treatment may be decreased.

It is with this objective that the necessity of creating a pharmaceutical composition that integrates 2 elements to potentiate the efficacy in the reduction of C-LDL and at the same time offer a lesser incidence of adverse events is proposed. These effects would be achieved with the use of L-carnitine and atorvastatin in a unique pharmaceutical form. The L-carnitine counts with studies that corroborate its efficacy in the reduction of blood fatty acids and it is known that it has a very good safety profile. [7, 90, 91, 92, 95, 124, 125, 129, 130, 133, 134, 135] So it is thought that this could attribute a benefic therapeutic factor in the combined administration of L-carnitine and atorvastatin for the percentage of reduction of C-LDL and C-No-HDL in blood. In the improvement of the safety profile of the treatment in the dyslipidemic patient, is assumed that the therapy with L-carnitine + atorvastatin may assist in the decrease of the incidence of adverse events attributable to the administration of statins, including those of greater clinical significance like hepatic alterations and at skeletal muscle level.

Another point in favor is that the use of L-carnitine with statins has been studied. [7, 91, 133, 136, 137, 138, 139, 140, 141] But there are still questions that may be proven or ruled out in the following study.

In the end one may have a novel, effective and adequate safety profile in this combination for the pharmacologic management in the primary and secondary prevention of dyslipidemias; once again highlighting the fact that dyslipidemias are the most frequently modifiable cardiovascular risk factor. With this, an ulterior benefit is postulated for the adult population that suffers from dyslipidemias, estimated in Mexico as half of its habitants.

The problem of some studies that have been performed for dyslipidemias is the process of the results of randomization, for they are assigned in groups of patients that differ one from the other with respect to the risk because of the clinical profile, the non-existence in the balance between the known risk factors and the unknown risk factors, and additionally the use of placebo minimizes the adverse events among the treatments of the study in the randomized groups, so the differences may be due to the differences of conformation of the groups once they are randomized. [146] For this reason in this study there is special care in the selection of subjects to be included so they present similitude in the associated factors. Finally, the idea is to control the assigned treatment and administer in both active groups, with the difference of the addition of L-carnitine in one of them and performing as a method of statistical analysis a test of superiority. So there is no predilection on assigning or pre-judging the experimental or the alternate treatment, one blind to the observer will be done.

7. HYPOTHESIS

7.1. Main hypothesis:

H_0: The combination of L-carnitine + atorvastatin doesn't show therapeutic superiority with respect to the use of atorvastatin as treatment to decrease the percentage of C-LDL in patients with dyslipidemia.

H_Δ: The combined use of L-carnitine + atorvastatin offers a therapeutic superiority with respect to the use of atorvastatin as treatment to decrease the percentage of C-LDL in patients with dyslipidemia.

7.2. Secondary hypothesis:

H_0: The combination of L-carnitine + atorvastatin doesn't show a lower incidence in the presence of adverse events attributable to the medicine in comparison with the use of atorvastatin as monotherapy, in the treatment of dyslipidemic patients.

H_Δ: The combination of L-carnitine + atorvastatin shows a lower incidence in the presence of adverse events attributable to the medicine in comparison with the use of atorvastatin as monotherapy, in the treatment of dyslipidemic patients.

8. OBJECTIVES

8.1. General Objectives:

8.1.1. Evaluate the therapeutic efficacy in Mexican adults with dyslipidemia through the oral route use of L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment.

8.1.2. Evaluate the safety of the medicines in the study.

8.2. Specific Objectives:

8.2.1. Evaluate the diminishing of Cholesterol LDL in Mexican adults with dyslipidemia through the use of oral route L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment.

8.2.2. Evaluate the diminishing of Cholesterol no-HDL in Mexican adults with dyslipidemia through the use of oral route L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment.

8.2.3. Evaluate the variability of serum levels of Total Cholesterol in Mexican adults with dyslipidemia through the use of oral route L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment.

8.2.4. Evaluate the variability of serum levels of Triglycerides in Mexican adults with dyslipidemia through the use of oral route L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment.

8.2.5. Evaluate the variability of serum levels of Cholesterol HDL in Mexican adults with dyslipidemia through the use of oral route L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment.

8.2.6. Evaluate the incidence, prevalence and progression of serious and non-serious adverse events related through the oral route administration of L-carnitine + atorvastatin in comparison with the use of Atorvastatin, after six months of treatment in the subjects participating in the study.

8.3. Premises of the study:

1. Evaluate the effect of the use of L-carnitine + atorvastatin in comparison with the use of Atorvastatin, in the basal levels of glycosylated hemoglobin after six month of treatment.

2. Evaluate the effect of the use of L-carnitine + atorvastatin in comparison with the use of Atorvastatin, in the figures of arterial tension of the subjects in the study, during their participation in the study.

3. Evaluate the effect of the use of L-carnitine + atorvastatin in comparison with the use of Atorvastatin, in the levels of corporal mass index after six months of treatment.

The cited premises will be demonstrated for effects of procurement, temporality and at the convenience of Valeant Pharmaceuticals International and may be included or not in their analysis in the report of the study. From these, significant findings may rise in benefit of the population and may allow for the generation of new investigations focused on new knowledge about the dynamics of cardiovascular risk factors associated in an overall manner and at first to the Mexican population.

9. DESIGN OF THE STUDY

The following study is a Phase III clinical assay, experimental, randomized with two treatment groups, multi-centric, longitudinal, to evaluate the therapeutic efficacy in the dyslipidemias in Mexican adults.

It is known that the main characteristic of experimental studies is the random assignation to the exposition of voluntary human beings that is used to evaluate the safety and efficacy of a treatment against diseases or health problems, including the adverse reactions. [146] For this case, it shall have the possibility of being included in one of the 2 treatment groups (group in which the investigational drug is administered or group with control of active). With respect to temporality, these are of a prospective character and is cataloged as longitudinal for having successive observations. This type of study will include homogeneous populations that may be comparable by their disease condition, biological and socio-demographic characteristics. Under controlled conditions of study, with a group that shall receive the investigational product and the other as control. The size of the sample used will be fixed; since it will be carried out in more than 1 location the study is multi-centric. Although the actives are separately commercialized and there's even existence of studies where they are used in combination, for Mexico there is no formulation that is commercialized in combination, for which it doesn't fit as being a Phase III study due to the pretension of generating additional information about the safety and effectiveness

of using L-carnitine + atorvastatin in the same presentation for the management of dyslipidemias.

This assay is a study of superiority, where the intention is to demonstrate that the intervention with L-carnitine + atorvastatin is better or equal to the control intervention, added to having a better safety profile.

9.1. Selection of the study population

The participants to be included in the study must comply with all the inclusion criteria that are required and no exclusion criteria previously to the process of Informed Consent. In turn, there are criteria that may lead to a patient terminating its participation in de study in a premature manner.

Hereunder, the requirements for the study are mentioned:

9.1.1. Inclusion Criteria.

- Mexicans between 35 and 75 years of age.
- Gender indistinct.
- Patient with abnormal lipid profile considered as serum levels of C-LDL of 100mg/dl or greater, obtained by laboratory parameters.
- Not being under pharmacologic treatment to manage its dyslipidemia or accept to suspend current treatment and be evaluated for inclusion in the next 3 weeks starting on the day of initial evaluation.

  Women in fertile stage with a safe, hormonal-free family planning method. A safe planning method includes surgical methods in women, intrauterine device that doesn't release progestines and use of preservative in all their sexual relations.

  Women in fertile stage who don't wish to become pregnant during their participation in the study.
- Post-menopause women or with hysterectomy history.
- Have a fixed and/or mobile telephone and accept to receive calls from the site for study processes.
- Grant their duly informed consent.

9.1.2. Exclusion Criteria.

- Subject lacking the mental capacity to understand the processes which imply their participation in the study and thus, not capable of granting their participation in a voluntary manner
- History of hypersensitivity to the medicines being studied.
- Daily intake of at least 240ml of grape juice or sporadic ingestion of 1 liter.
- Potentially fertile women without a safe family planning method, who wish to become pregnant during the study, are already pregnant or in lactation period.
- Having on Globorisk scale for Mexicans, or as an associated risk factor, a high stratification for cardiovascular risk.

  Basal laboratory values with elevation of ALT 1.5 times larger than the upper limit considered normal according to international units.

  Basal laboratory values with elevation of CPK not attributable to physical activity.
- Subjects who are under anti-coagulant treatment, suffer from coagulation disorders, or any circumstance which contraindicates the taking of a blood.
- History of acute myocardial infarction, unstable angina, some confirmed coronopathy, arrhythmias, congestive cardiac failure or cerebrovascular disease.
- History of muscular conditions of the genetic type or of rhabdomyolysis in the patient or first degree relative.
- History or diagnose of congenital hepatic disorders, chronic infection by hepatitis virus, hepatitis with fatty liver, alcoholic hepatitis, primary biliary cirrhosis, primary sclerosis, cholangitis or hepatic failure.
- History or diagnose of congenital renal disorders, chronic renal failure, acute renal damage or nephritic syndrome.
- History of infection by Human Immunodeficiency Virus.
- History of Acute or Chronic Pancreatitis.

  History of the following endocrine diseases: non-controlled Diabetes Mellitus, lipodystrophy, thyroid disorders, Cushing Syndrome and/or Polycystic Ovary Syndrome.
- Diseases which compromise immunity such as Systemic Lupus Erythematous, Rheumatoid Arthritis, Antiphospholipid Antibodies Syndrome or Psoriasis.

- Diseases by deposit such as Gaucher Disease, disease by glycogen deposit, Tay-Sachs juvenile disease or Niemann Pick Disease.
- Diagnose of Kawasaki Disease, Werner Syndrome, intermittent acute Porphyria, Idiopathic Hyperkalemia or Klinefelter Syndrome

  Suffer from Idiopathic Hyperkalemia, Klinefelter Syndrome, Werner Syndrome, Kawasaki Disease or Porphyria.
- History of epilepsy.
- History or diagnose of alcoholism.
- Intake of more than 20g of alcohol per day.
- User of marihuana.
- User of illegal drugs.
- Intake of medicines with pharmacologic interaction which increase or decrease the efficacy of L-Carnitine and/or atorvastatin or alter the lipids in blood such as:

  Macrolide antibiotics: Erythromycin, Telithromycin and Clarithromycin. Azole anti-fungi: Ketoconazole, Itraconazole, Fluconazole and Nefazodone. Quercetin, Amiodarone, Aprepitant, Cimetidine, Ciprofloxacin, Cyclosporine, Diltiazem, Imatinib, Echinacea, Enoxacin, Ergotamine, Metronidazole, Mifepristone, Tofisopam, Gestodene, Verapamil, Mibefradil, Fluoxetine, Phenobarbital, Carbamazepine, Phenytoin, Rifampin, Modafinil, Glucocorticoids, Felbamate, Rosiglitazone, Griseofulvin, Pioglitazone, Gemfibrozil, Clofibrate, Fenofibrate, Niacin, Nefazodone, Cholestyramine, Colchicine, Colestipol, Primidone, Topiramate, Troglitazone, Rifabutin, Digoxin, Thiazides, anabolic Steroids, Progestogens, Estrogens, Danazol, Amiodarone, fibric Acid, docosahexaenoic acid, Isotretinoine, Immunosuppressives, protease inhibitors of HIV or of the Hepatitis C Virus, Inhibitors of the co-transport of sodium-glucose, Tamoxifen, Raloxifene, non-selective Beta blockers, biliary acid sequestrants, asparginase, Sirolimus and Interferon.
- Patients who have been diagnosed with terminal conditions.
- Patients with recent Cancer diagnose or undergoing any type of therapy for same. Patients who have suffered skin cancer not of the melanoma type and have been cured and haven't been on treatment for at least 1 year before the start of their participation in the study may enter.

Patients under lipid lowering treatment and who, because of their clinical condition aren't candidates to the period of lavage or detoxification; or well reject it.

- Being participating in another clinical trial or having concluded their participation in the 30 days previous to beginning their participation in this study.
- Any other which, at the Investigator's criteria, puts at risk the safety of the participant and/or interferes with the results of the study.

9.1.3. Criteria for early termination.

- Subject's decision not to continue participating in study.
- Non-serious adverse event related to the medicine of the study.
- Serious adverse event related or not with the investigational drug.
- Lack of adherence to treatment evidenced by medicine count during the study. The lack of adherence is defined as the non-administration of the medicine, or incomplete or overdosed administration in 2 consecutive days or 3 alternate days in a period of 30 days.
- In fertile women, positive immunologic test for pregnancy in urine.
- Not attend to programmed visit after 2 times of being re-scheduled. For these criteria to be valid, the patient will not have shown-up for the third rescheduling of the appointment.
- Use of therapy or treatments not allowed in the study (See section 10.1.3 Banned medicines).
- Elevation of ALT 3 times above the superior limit considered as normal according to international units.
- Elevation of CPK above 10 times the normal superior limit according to international units.
- Diagnose during the treatment of some disease mentioned as part of the non-inclusion criteria.
- Any other circumstance not resolved in this protocol and that requires special evaluation by the department of clinical research of the sponsor.

9.2. Calculation of the sample size.

In clinical studies there is a challenge of determining the adequate sample size; on some occasions this is formulated based on studies performed previously with similar characteristics that give an idea of the sample based on the intervention's efficacy, persons that have the condition, etc. In randomization studies, the estimation of the adequate sample size is of vital importance, being these types of clinical studies the best method to compare the effects of the treatments. [148]

Based on the treatments posed in the present study, the type of design corresponds to a study of superiority, where the intention is to demonstrate the superiority of a new therapy (L-carnitine + atorvastatin) in comparison with the established therapy (atorvastatin). This under the premise that the new experimental therapy has a superior therapeutic efficacy and a lesser presence of incidence of adverse events related to the medicine. The declaration CONSORT (Consolidated Standards of Reporting Trials), that includes a list of flow diagram, is a guide developed to help authors to improve the divulgation of the results of the random controlled assays, in which it is suggested that, to estimate an initial sample size in superiority studies it is necessary to know by how much must the new therapy be better than the reference and influence of random effects. [149] The magnitude of the variation would be determined by the variance S^2 which is obtained from pilot studies or similar studies previously published.

It is known that the therapy with Atorvastatin at doses of 20 mg per day (considered as medium intensity) reduces the C-LDL in 30 to 50%, [6] for which it will be taken as reference; to estimate the variance, the maximum therapeutic efficacy over C-LDL will be taken at this dose (50%), being this value of p_1. To obtain p_2 the estimated percentage of superiority will be placed, being of 51% that expected for the treatment group of L-carnitine + atorvastatin (1g/20mg) per day. Since the secondary hypothesis held has to demonstrate the non-superiority of adverse events in the experimental therapy, the statistical analysis will be performed with the sample size estimated for the primary hypothesis.

In these type of studies, the true difference between the effect of the treatments has to be demonstrated; but due to the random variation the final result may deviate from the real difference with incorrect results. If the null hypothesis (H_0) of no difference were true, it could give some difference in the analysis. This type of error is called type 1 error (false positive) and would have as consequence the introduction of an ineffective therapy. If, on the contrary the alternative hypothesis (H_Δ) were true, the analysis could not show a significant difference in some cases; this is called error type 2 (false negative), resulting in the rejection of the effective therapy. [149] Thus, the confidence of the test and its potency must be analyzed. Representing α as the risk of committing the type 1 error; for being a test in which the investigational product is compared against another active treatment, a two-tailed hypothesis test is generated with the possibility of having different magnitude. For this study, a confidence interval (CI) of 95%. Thus, the risk of type 2 error in 2α is of 5%.

The type 2 error is the β risk, and in clinical studies it gyrates between 10 and 20%. Since a given value of Δ will always be above or below 0, the type 2 error will always be on one side only. In this study, a superiority of the therapeutic efficacy is expected in the experimental treatment group compared with the active control group, combined with a lesser incidence of adverse events by the combination of L-carnitine + atorvastatin; thus, the estimated potency of the test is of 75%.

The formula to be applied to estimate the size of the sample in the randomized clinical assay, based in the Hypothesis to prove the superiority of the new treatment is:

$$N = (Z_{2\alpha} + Z_{\beta})(\frac{S^2}{\Delta^2})$$

N = Sample size by treatment group.

$Z_{2\alpha}$ = Confidence interval at 95% with two-tailed hypothesis.

Z_{β} = Potency of the test at 75%

S = variance of the difference which is equal to a $p_1 (1 - p_1) + p_2 (1 - p_2)$

Δ = Relative difference or clinical meaning

With these values, the adequate sample size by treatment group is of: **54 subjects.**

Due to the nature of this clinical study, the possibility exists of losing participants during its course and this would compromise the number of data of the subjects necessary so that, if there are differences, these would result significant. To prevent this success, it was decided to increase the size of the sample as a way of compensating the losses with the implementation of a loss proportion, where R is the percentage of losses for the adjusted sample size. [150] Based on the experience of clinical studies, it is known that it is convenient to estimate a proportion of losses of 10% of participants, R being this value.

The formula for the estimation of the adjusted sample size will be the following:

$$n_{ajustado} = n\left(\frac{1}{1-R}\right)$$

n = Calculated sample size previous to adjustment which is of **108 participants** (**54 participants per treatment group)**

R = 10%

With these data the adjusted sample size will be of **120 participants, 60 subjects per treatment group.**

9.3. Assignation of treatment and treatment groups

To ensure a randomization a mechanism governed by chance is required with which treatments will be assigned to the subjects of the investigation in such a way that it may be proven that the randomization was kept free from sieve.[143] Since there are only two probabilities of treatment, the experimental treatment with be assigned in a random manner to each participant with the investigational drug or the control treatment with active.

To execute the randomization a simple random assignation technique will be used, using the program Research Randomizer. The previously randomized medicine will be provided to the site; the personnel delegated for the medicine provision will be in charge of dispensing treatment to the site in the order that the sponsor provides. To corroborate this, a treatment dispensation sheet with the treatment number code will be employed. The code of the treatment number is composed by the letter L or the letter C, followed by a 3-digit number for

assignation of a consecutive order. For example: L-001 or C-001.

The site will be provided with a 10% extra of treatments for the group that receives L-carnitine + atorvastatin and a 10% extra for the group of atorvastatin as monotherapy. These will be reassigned to the participants in case they lose the originally assigned treatment. Caution must be observed so the anterior doesn't happen; but in case the situation arises, the personnel of the site that reassigns treatment must notify to the sponsor the motives for which the treatment was reassigned and this notification shall be registered in a medical note and be added in the corresponding report format.

9.3.1. Experimental Group:

The population that comprises this treatment group will receive a dose of L-Carnitine + Atorvastatin in concentrations of 1g/20mg through oral route every 24 hours.

9.3.2. Control Group with Active:

The population that comprises this treatment group will receive a dose of atorvastatin in concentrations of 20 mg through oral route every 24 hours.

Assignation of treatment groups

CONTROL	ACTIVE	NUMBER OF SUBJECTS
EXPERIMENTAL GROUP	L-Carnitine + atorvastatin	60
CONTROL GROUP WITH ACTIVE	Atorvastatin	60

***The number of subjects in each treatment group may vary according to the randomization**.

9.4. Processes to perform during study

9.4.1. Recruitment of patients

From the moment the site is notified that it may begin recruitment of patients it will count with 45 natural days to carry out the search and recruiting of prospect participants to be included in the study. The strategies of recruitment and diffusion given to the study, as well as the material provided to the probable participant, must be subjected and approved by the Ethics Institutional Review Board.

Once the investigator and the personnel designated to carry out the recruiting identify the potential participants, these shall obtain the informed consent on part of the probable participants so they may commence with the processes of the study.

9.4.2. Process of Informed Consent

The Process of Informed Consent is a dynamic process, in which the main investigator shall inform through understandable words to the legally autonomous patient or a relative or legal representative, in presence of two witnesses, the possibility of being an investigation subject and that an experimental maneuver be applied; for which the subject shall receive from the Main Investigator or the delegate Sub-investigator sufficient, opportune, clear and truthful information about the risks and benefits expected by participating in the clinical trial.

The investigator must formulate said letter and shall submit the document for its approval before the Ethics Institutional Review Board; the approved document must contain the seal of the Ethics Institutional Review Board, autograph signature and date in which said document was authorized. In the event of having amendments on the document, the Informed Consent will be submitted again to the Ethics Institutional Review Board for its approval and, the Principal Investigator shall make sure that this is obtained once again by the participants in the study.

The letter of Informed Consent shall have numbering on each one of its pages, and must contain a precise and clear language addressed to the probable participant, in which the following are made known:

name of the sponsor who is implementing the study, name of the main investigator and contact info, name of the ethics committee and contact info, justification and object of the study, type of intervention done with the project, criteria for forming part of the research, clearly establish that the participation is plainly voluntary, procedures and protocols that will be carried out, possible risks and benefits associated to the participation, the guarantee of receiving answers to any question and explanation of any doubt about the procedures, confidentiality guidelines and divulgation of results, the commitment of providing updated information obtained during the study though it could affect the will to continue participating, treatments that may be administered during its participation such as investigational products, alternatives of treatment, its possibility of withdrawing its consent to participate in the study at any moment, who shall be responsible if the participant results hurt by the procedures of the study and who will be in charge of providing medical attention, urgency attention and compensations in case of disability; who to contact on part of the site in case of doubts and/or presentation of a suspicion of adverse event and who to contact on part of the Ethics Institutional Review Board in case of doubts. [151, 152, 153, L5, L6, L7] These documents shall be read in the time necessary to ensure that the subject understands what entails participating in the clinical trial and all doubts must be solved in the clearest manner. If the probable participant so desires, he/she may take the document to analyze it and is in full right of asking for the opinion of some medical professional in respect thereof. All the procedure must be done before two impartial witnesses who shall bear witness to the participation on a voluntary basis by the subject.

If the potential participant decides to participate, he shall place to bear witness of the fact with blue ink and print; according to the data contained in its official identification, complete name without abbreviations, autograph signature and date in which he/she agrees to participate in the clinical trial. In the event that the probable participant is illiterate, or presents some physical disability that prevents the fulfilling of this act, a person designated by the participant shall place the name of the participant and the date, attesting that the participant by its own will decides to participate; the participant shall place the fingerprint of the right thumb, with blue ink in the section designated for the signature of the participant. Afterwards, the two impartial witnesses who were present during the process of Informed Consent shall place in the designated section complete name, kinship with the participant, address and date. The kinship only considers blood relations; in case of not having kinship with the participant, the witness shall place in the section designated for kinship the legend “none”. Finally, the personnel that executes the process of Informed Consent shall place their full

name, signature and date according to the good practices of documentation. Once this section is duly filled, a faithful copy of the original shall be granted to the participant; the person who conducted the process shall place in the inferior part of the final sheet of the document “this document is a faithful copy of the original document”; through good practices of documentation and in blue ink. Said document shall be provided to the participant. If at the moment of signing the Informed Consent there is an error in the data, the person responsible of conducting the Informed Consent shall procure that these are corrected according to good practices of documentation and, shall clarify it in the note where the process of obtainment of Informed Consent is documented.

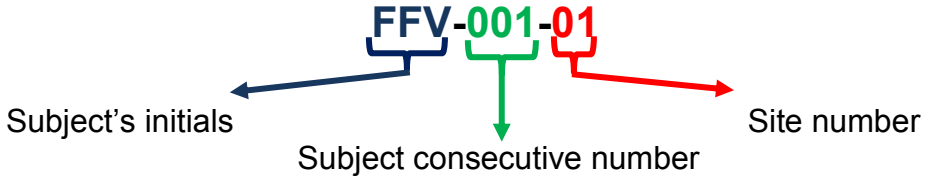
9.4.3. Assignation of the code of identification of the subject

With the objective of safekeeping of the confidentiality of the participants of the study and lead and adequate control of the procedures performed with each subject, a code shall be assigned to each one. The method to generate said code shall be in the following:

- **Subject’s initials:** These will be constituted by the first letter of the first name, first letter of the first surname and first letter of the second surname. No matter if they have more than one name or more that 2 surnames; in the event that the participant has only one surname, then only the first letter of the first name and the first letter of the surname will be placed. All the letters shall be in upper case.
- **Number of subject:** The number shall be assigned in consecutive to those who are included in the study once its proven that they fulfill all the inclusion criteria and none of the exclusion criteria. The number shall consist of 3 digits beginning with zeroes on the left. For example, the first number will be 001.
- **Number of the investigation site:** This number shall be obtained starting from the number that the sponsor assigns to each site.

Between each data an intermediate hyphen shall be placed in the registries where it isn’t pre-assigned.

With these requirements, the subject code will be conformed in the following manner:



9.4.4. Basal visit, day 0. Review of inclusion and exclusion criteria, formulation of clinical history, physical exploration, take of laboratory sampling and participant inclusion

Due to the temporality nature of the processes this basal visit will consist at least of 2 visits to the investigation site by the subject under investigation.

Prior to reviewing that the patient fulfills all the inclusion criteria and none of the exclusion criteria, the information of the subject shall be identified only by the initials, exactly as it is indicated in point 9.4.3 section "Subject's initials."

Review of inclusion and exclusion criteria

Once the process of informed consent is completed and with the participant's authorization, the physician in charge will review that the patient complies with all the inclusion criteria and none of the exclusion criteria. The laboratory values that will be necessary for the patient inclusion are not be considered at this moment.

The participants that comply with the analyzed criteria up to this moment to be part of the study shall proceed with the process of the basal visit.

The subjects that don't comply with the analyzed criteria up to this moment to be part of the study shall be notified about this and they will be thanked for their time.

Formulation of the clinical history

A complete clinical history of the participants that comply with the criteria to be included in the study (excepting until now the laboratory parameters) will have to be obtained. This clinical history shall be elaborated in accordance with the existing legislation in Mexico. [L8] It shall contain at least:

- Identification sheet.

- Hereditary-familial medical history, emphasizing those that could lead the participant to a cardiovascular risk according to the information contained in this protocol or that have bearing in the election for participation in the study.

- Non-pathologic personal background, emphasizing those that could lead the participant to a cardiovascular risk according to the information contained in this protocol or that have bearing in the election for participation in the study.

- Pathologic personal background, emphasizing those that could lead the participant to a cardiovascular risk according to the information contained in this protocol or that have bearing in the election for participation in the study.

- Current condition.

- Interrogation by organs and systems, emphasizing those that could lead the participant to a cardiovascular risk according to the information contained in this protocol or that have bearing in the election for participation in the study.

- Complete physical examination with exterior habitus, vital signs, weight in kilograms, height in centimeters, estimation of corporal mass index, data of head, neck, thorax, abdomen, extremities and genitals. Emphasis will be placed on those that could lead the participant to a cardiovascular risk according to the information contained in this protocol or that have bearing in the election for participation in the study.

- The taking of vital signs will always be performed with the patient in seating position and with the following particular considerations:

- Pulse: This shall be evaluated in the radial artery of the right or left arm, as convenient to the treating physician and disposition of the subject in the distal third of the chosen forearm and in the place clinically known as the anatomical snuff-box. The registries shall be expressed in number of pulsations per minute.

- Arterial tension: It shall be evaluated with a sphygmomanometer or manometer for which the standard process mentioned in NOM-030-SSA2-2009 will be used as reference. The registries shall be in millimeters of mercury.

- Temperature: Shall be evaluated in the axillar region through the use of a mercury or digital thermometer and will be expressed in degrees Celsius.

- Respiratory frequency: It shall be evaluated with the assessment of the number of times that a patient inspires per minute, expressing in this manner the results obtained.

- Previous results of laboratory and cabinet studies, with special emphasis of those that could lead the participant to a cardiovascular risk according to the information contained in this protocol or that impinge in the election for participation in the study.

- Therapeutic used and results obtained, placing emphasis in those that could lead the participant to a cardiovascular risk, interaction with the medicines of the study, that impinge with the election for participation in the study or that have current management for the problem to be studied.

- Diagnoses or clinical problems, performing an initial evaluation with the Globorisk scale for Mexicans contained in this protocol to estimate the cardiovascular risk, one that could compromise the subject's participation in the study or that could alter the results of same.

- Management plan, in which the consideration pertinent to the study shall be annotated.

In patient that have current management for dyslipidemias and that accept a period of lavage of 3 weeks, the risk of withdrawing this treatment shall be evaluated to find if it's not significant for the patient according to the results obtained in the scale of cardiovascular risk and the levels that have been achieved in the reduction of lipids with the current treatment. A patient with very high cardiovascular risk shall not abandon the therapy used and therefore must not be included in the study. If a favorable benefit that outweighs these risks is expected from participation in the study, the patient shall proceed to the taking of blood samples and electrocardiogram, described hereinafter. Besides, a visit will be scheduled to continue with the processes of sample taking for the laboratory and cabinet studies in at least 3 subsequent weeks.

If the participant, by clinical evaluation doesn't comply with the criteria to participate in the study, the motive will be indicated and he/she will be thanked for participating.

For those that do comply with the clinical parameters to join the study, they will be invited to proceed with the personnel in the place indicated for the obtaining of laboratory and cabinet studies.

Since for their inclusion the laboratory parameters are needed, the personnel designated for the gathering of samples shall be indicated to perform, in the following order:

1. Taking urine sample in case the subject is a woman in fertile period to perform an immunologic pregnancy test in urine. For the taking of the urine sample, the delegated personnel of the site will give the participants a sterile container for them to go to the bathroom and place the urine in it, after which the delegated personnel shall place enough urine in the dispensed device or reactive strip for this analysis and will wait and corroborate the result. The women who result with a positive result will no longer continue in the processes for their inclusion and they will be notified of the reason given counseling about their condition.

2. Taking of Electrocardiogram (EKG) of 12 derivations. If some abnormality is detected which compromises the participation of the subject upon consideration of the established criteria in this protocol or of the investigator or its designated personnel, the subject will be notified and will be given counseling about the condition if it applies; in turn, the participant will not continue with the processes of the study. In the process of taking of EKG the participant shall be provided with a new disposable gown so that the superior region may be uncovered; if there is an excess of corporal hair in the precordial region or in the distal extremes of the thoracic and/or pelvic limbs, it shall be procured that this doesn't interfere with the placing of the electrodes. The surface where these shall be placed must be clean and free of additives that interfere with the registry. In turn, a conductor gel shall be used at the site of placement of the electrodes. The patient must not have on him/her metallic objects that interfere with the study or any other that causes pressure such as sustainers, tight shoelaces, belts, etc.

3. Taking of blood sample: the patient shall have fasted for 9 to 12 hours for this; if this period is not observed, then the visit shall have to be rescheduled for the participant to comply with it. The process for the gathering of samples is contained in section 10.2 of this protocol. In subjects who have at least 12 hours of fasting, 2 tubes of 10 ml each will be obtained from each participant; in this sample, the following will be evaluated:

3.1. Blood Biometry without differential and Glycosylated Hemoglobin.

3.2. Blood Chemistry to evaluate: TC, C-LDL, C-HDL, TG, C-no HDL, Glucose, Urea, Creatinine, Uric Acid, ALT, AST and CPK.

Once these laboratory and cabinet studies have been obtained, the participant will be indicated the following date to continue with its inclusion with the previous analysis of the results or, its inclusion in the study will be ruled-out and the participant will be notified of the reason for not being able to participate.

9.4.5. Basal visit day 0, treatment assignment

Only the participants who comply with all the inclusion criteria and none of the exclusion criteria may be assigned to treatment.

At this point they will be assigned an identification code with the necessary requirements quoted before.

The personnel delegated with the responsibilities to assign treatment on part of the main investigator's team shall do it in accordance to what is described in point "9.3 Assignation of treatment and treatment groups"- The treatment number will be registered, lot number, expiration date and number of tablets dispensed. All this will be contained in the report format of corresponding cases.

Moreover, the delegated personnel shall corroborate in combination with the participant that he/she was given treatment for 33 days, for the matter of window period for the next visit. The designated personnel of the investigation site will indicate the patient the method of administration according to the reference point in this protocol, "Administration of the investigational product". Emphasis shall be placed in that the designated treatment is unique and non-transferable, so the only person who shall undergo this treatment is the participant. Besides, a card contained in Annex 2 will be provided, which has the title: "Treatment Control Card of the Participant Basal Visit"; explaining how to fill it and referring that the participant must bring it in the next visit.

In the event of adverse events, the patient shall be informed of any new clinical or laboratory condition, it shall be reported to the investigation site, reminding

contact numbers of the site and work hours to do it and the telephone number of the designated personnel to receive notifications in working hours.

Finally, the date of the next visit shall be assigned and be reminded that he/she will be contacted by telephone by site personnel 7 days after the basal visit.

9.4.6. Telephone call posterior to basal visit, day 7 +/- 2 days

A telephone call will be made to the participant at 7 days +/- 2 days posterior to the initiation of the treatment (complete basal visit). The finality of this call is to corroborate that the investigational product is being adequately administered and find out about the incidence of adverse events related to the product and/or new concomitant medicines. In turn, the participant will be asked about the filling of the treatment control card and if there are any doubts these will be solved. This information must be registered. Besides, the next appointment day will be corroborated and the participant will be reminded to attend with a 9 to 12 hour period of fasting, and to bring the package of the investigation drug and all the elements it included, even if the pharmaceutical forms had been concluded. In the telephone call it will also be verified that the subject has the necessary medicines to be administered at least until the following visit.

If there is any relevant finding that deviates what's accented in this protocol, it shall be notified in the corresponding instances.

9.4.7. Visit 1, day 30 +/- 3 days with respect to complete basal visit

The patient will be asked and referred that he/she attended with 9 to 12 hours of fasting.

A clinical evaluation will be performed with the aim of updating the clinical history in accordance to what is contained in the Mexican Official Norm of the Clinical Expedient. [L8] Besides, the CMI will be evaluated.

The patient will be asked about the incidence of adverse events and/or about new concomitant medicines that have been administered.

It will be verified that the patient has administered the medicine with the adequate posology; if there is any non-compliance a note shall be made and the continuation of the subject will be evaluated. The site staff shall collect the package of the anterior medicine, even if it has remnants of the investigational product. The treatment number shall be registered, along with lot number, expiration date, number of tablets used and number of remaining tablets. Also, the basal treatment card will be received, clarifying the pertinent discrepancies in the filling of the form. Everything will be contained in the format of corresponding case report.

It will be corroborated that the participant doesn't fulfill criteria for early termination of the study.

In the case of fertile women, they will be questioned and registration will be made about the family planning method used, seeing that these are permitted in the study; besides, a urine sample will be obtained to perform an immunologic pregnancy analysis according to the characteristics referred in the basal visit.

In this visit a blood sample will be taken to evaluate through blood chemistry the following laboratory parameters: Glucose, urea creatinine, ALT, AST, TC, C -LDL, C-HDL, C-No-HDL, TG and CPK. Upon reception of the results, it will be seen if there was any change in comparison with the previous results; all new parameters must be registered; if the laboratory analysis doesn't include the measurement of C-No-HDL, the investigator or delegated staff shall calculate it through the use of the equation contained in this protocol. Besides, if there is any suspicion of adverse event by the laboratory parameters, this shall be reported according to the classification and notified to the investigation subject and to the pertinent authorities in the temporality contained in the section of adverse events of this protocol.

The designated staff will ask the sponsor to grant the treatment code and will give the investigation subject enough medicine to complete 66 days of treatment. The patient will be reminded about the administration method of the medicine. The number of treatment, lot number, expiration date and number of tablets dispensed. Everything will be contained in the corresponding case report formats. Besides, the patient will be provided with the card contained in Annex 3 that has the title "Control Card of Treatment of Participant Visit 1", explaining its filling and referring that it must be brought on the next visit.

A date for the next visit will be assigned and the contact numbers of the site will be reminded, in work-hours and non-work-hours. Also, the participant will be reminded that at 37 and 60 days posterior to basal visit he/she shall be contacted on the telephone by staff from the site.

9.4.8. Telephone calls posterior to visit 1, days 37 (+/- 3) and 60 (+/- 3)

A telephone call will be made to the participant after 37 days of completing the basal visit with a window period of +/- 3 days and at 60 days with a window period of +/- 3 days, both concerning the completion of the basal visit.

The finality of these calls is to corroborate that the investigational product of investigation is being administered adequately and to find about the incidence of adverse events related with the product and/or new concomitant medicines. In the telephone calls it will also be verified that the subject has the necessary medicine to be administered at least until the next visit. In turn, the subject will be asked about the filling of the treatment control card and if there are any doubts these will be clarified. This information must be registered.

If there is any relevant finding that deviates what's accented in this protocol, it shall be notified in the corresponding instances.

In the call of day 60 the date of the next appointment will be corroborated and the subject reminded to bring the package of the drug in investigation with all the elements it included, even if its pharmaceutical forms have been concluded.

All the information gathered in these calls must be registered.

9.4.9. Visit 2, day 90 +/- 5 days to compete basal visit

It must be verified that the patient attended with 9 to 12 hours of fasting.

It will be verified that the patient has administered the medicine with the adequate posology; if there is any non-compliance a note shall be made and the continuation of the subject will be evaluated. The site staff shall collect the package of the anterior medicine, even if it has remnants of the drug in investigation. The treatment number shall be registered, along with lot number, expiration date, number of tablets used and number of remaining tablets. Also,

the basal treatment card will be received, clarifying the pertinent discrepancies in the filling of the form. Everything will be contained in the format of corresponding case report.

A clinical evaluation will be performed with the aim of updating the clinical history in accordance to what is contained in the Mexican Official Norm of the Clinical Expedient. [L8] Besides, the CMI will be evaluated.

The patient will be asked about the incidence of adverse events and/or about new concomitant medicines that have been administered.

It will be corroborated that the participant doesn't fulfill criteria for early termination of the study.

In the case of fertile women, they will be questioned and registration will be made about the family planning method used, seeing that these are permitted in the study; besides, a urine sample will be obtained to perform an immunologic pregnancy analysis according to the characteristics referred in the basal visit.

In this visit a blood sample will be taken to evaluate through blood chemistry the following laboratory parameters: Glucose, urea creatinine, ALT, AST, TC, C -LDL, C-HDL, C-No-HDL, TG and CPK. Upon reception of the results, it will be seen if there was any change in comparison with the previous results; all new parameters must be registered; if the laboratory analysis doesn't include the measurement of C-No-HDL, the investigator or delegated staff shall calculate it through the use of the equation contained in this protocol. Besides, if there is any suspicion of adverse event by the laboratory parameters, this shall be reported according to the classification and notified to the investigation subject and to the pertinent authorities in the temporality contained in the section of adverse events of this protocol.

The designated staff will ask the sponsor to grant the treatment code and will give the investigation subject enough medicine to complete 99 days of treatment. The patient will be reminded about the administration method of the medicine. The number of treatment, lot number, expiration date and number of tablets dispensed. Everything will be contained in the corresponding case report formats. Besides, the patient will be provided with the card contained in Annex 4 that has the title "Control Card of Treatment of Participant Visit 2", explaining its filling and referring that it must be brought on the next visit.

A date for the next visit will be assigned and the contact numbers of the site will be reminded, in work-hours and non-work-hours. Also, the participant will be reminded that at 97 120 and 150 days posterior to basal visit he/she shall be contacted on the telephone by staff from the site.

9.4.10. Telephone calls posterior to Visit 2, days 97 (+/- 3), 120 (+/- 5) and 150 (+/- 5)

A telephone call will be made to the participant after 97 days of completing the basal visit with a window period of +/- 3 days, at 120 days with a window period of +/- 3 days and at 150 days with a window period of +/- 3 days. All dates and periods of estimated windows shall be used as reference the complete basal visit of each subject. The finality of these calls is to corroborate that the medication is being administered adequately and to find about the incidence of adverse events related with the product and/or new concomitant medicines. In the telephone calls it will also be verified that the subject has the necessary medicine to be administered at least until the next visit. In turn, the subject will be asked about the filling of the treatment control card and if there are any doubts these will be clarified. This information must be registered.

If there is any relevant finding that deviates what's accented in this protocol, it shall be notified in the corresponding instances.

In the call of day 150 the date of the next appointment will be corroborated and the subject reminded to bring the package of the investigational drug with all the elements it included, even if its pharmaceutical forms have been concluded.

All the information gathered in these calls must be registered.

9.4.11. Visit 3, day 180 +/- 7 days with respect to complete basal visit (Final Visit)

It must be verified that the patient attended with 9 to 12 hours of fasting.

It will be verified that the patient has administered the medicine with the adequate posology; if there is any non-compliance a note shall be made and the continuation of the subject will be evaluated. The site staff shall collect the package of the anterior medicine, even if it has remnants of the treatment. The treatment number shall be registered, along with lot number, expiration date, number of tablets used and number of remaining tablets. Also, the basal treatment card will be received, clarifying the pertinent discrepancies in the filling of the form. Everything will be contained in the format of corresponding case report.

A clinical evaluation will be performed with the aim of updating the clinical history

in accordance to what is contained in the Mexican Official Norm of the Clinical Expedient. [L8] Besides, the CMI will be evaluated.

The patient will be asked about the incidence of adverse events and/or about new concomitant medicines that have been administered.

It will be corroborated that the participant doesn't fulfill criteria for early termination of the study.

In the case of fertile women, they will be questioned and registration will be made about the family planning method used, seeing that these are permitted in the study; besides, a urine sample will be obtained to perform an immunologic pregnancy analysis according to the characteristics referred in the basal visit.

In this visit a blood sample will be taken to evaluate through the following laboratory parameters:

1.1. Blood Biometry without differential and Glycosylated Hemoglobin.

1.2. Blood Chemistry to evaluate: TC, C-LDL, C-HDL, TG, C-no HDL, Glucose, Urea, Creatinine, Uric Acid, ALT, AST and CPK.

Upon reception of the results, it will be seen if there was any change in comparison with the previous results; all new parameters must be registered; if the laboratory analysis doesn't include the measurement of C-No-HDL, the investigator or delegated staff shall calculate it through the use of the equation contained in this protocol. Besides, if there is any suspicion of adverse event by the laboratory parameters, this shall be reported according to the classification and notified to the investigation subject and to the pertinent authorities in the temporality contained in the section of adverse events of this protocol.

9.4.12. Summary of the processes to be performed by the subjects during their participation in the study.

Process to perform during the visits

VISIT	PROCEDURES

PATIENT SELECTION	- Acquiring letter of Informed Consent.
BASAL VISIT, DAY 0 (FIRST PART)	- Review of inclusion and exclusion criteria that don't require laboratory parameters. - Lavage period of 3 week for those who apply. - Formulation of clinical history that counts with: identification sheet, hereditary-familial background, non-pathologic personal background, pathologic personal background, current condition, interrogatory by organs and systems, physical exploration with exterior habitus, taking of vital signs, weight, height, estimation of CMI, data of head, neck, thorax, abdomen, limbs and genitals; previous laboratory and cabinet results, therapeutic used, diagnose and plan. - Taking of urine sample in case of women in fertile period to perform immunologic pregnancy test. - Taking of Electrocardiogram of 12 derivations. - Taking of blood sample with 9 to 12 hours of fasting; two 10 ml tubes will be obtained to perform the following studies: Blood Biometry without differential and Glycosylated Hemoglobin. Blood Chemistry to

	evaluate: TC, C-LDL, C-HDL, TG, C- no HDL, Glucose, Urea, Creatinine, Uric Acid, ALT, AST and CPK.
BASAL VISIT, DAY 0 (SECOND PART)	- It will be verified that the participant counts with all the inclusion criteria and none of the exclusion criteria, including those of laboratory. - Assignation of identification code of the subject. - Assignation of treatment. - Assignation of next date of appointment for visit 1.
TELEPHONE CALL POSTERIOR TO BASAL VISIT, DAY 7 +/- 2 DAYS	- Corroborate adequate administration of investigational product and filling of treatment control card. - Obtain information about the occurrence of adverse events. - Corroborate date of next appointment for visit 2, reminding that participant must attend with a fasting period of 9 to 12 hours and with the packages and remnants of the investigational drug.
VISIT 1, DAY 30 +/- 3 DAYS	- Verify fasting of participant of 9 to 12 hours. - Make medical note and update of clinical history. - Ask about and record the occurrence or non-occurrence of adverse events. - Review the administration of the medicine of study and collecting of packages and packages if there are any. - In women in fertile phase, urine sample to perform immunologic pregnancy test. - Verify criteria of early termination.

	- Taking of 10 ml of blood sample to evaluate: Glucose, urea, creatinine, ALT, AST, CT, C-LDL, C- HDL, C-No-HDL, TG and CPK. - Assignation of treatment. - Assignation of next appointment date for visit 2.
TELEPHONE CALL POSTERIOR TO VISIT 1, DAY 37 +/- 3 DAYS	- Corroborate adequate administration of the investigational drug and filling of treatment control card. - Obtain information about the occurrence of adverse events.
TELEPHONE CALL POSTERIOR TO VISIT 1, DAY 60 +/- 3 DAYS	- Corroborate adequate administration of the investigational drug and filling of treatment control card. - Obtain information about the occurrence of adverse events. - Corroborate date of next appointment for visit 2, reminding that participant must attend with a fasting period of 9 to 12 hours and with the packages and remnants of the investigational drug.
VISIT 2, DAY 90 +/- 5 DAYS	- Verify fasting of the participant of 9 to 12 hours. - Make medical note and update of clinical history. - Ask about and record occurrence on not of adverse events. - Review of administration of medicine of study and gathering of packages and, it there are any, the remaining pharmacologic forms. - In women in fertile phase, urine sample to perform immunologic pregnancy test.

	- Verify criteria of early termination. - Taking of 10 ml of blood sample to evaluate: Glucose, urea, creatinine, ALT, AST, CT, C-LDL, C- HDL, C-No-HDL, TG and CPK. - Assignation of treatment. - Assignment of date for nest appointment for visit 3.
TELEPHONE CALL POSTERIOR TO VISIS 2, DAY 97 +/- 3 DAYS	- Corroborate adequate administration of the investigational drug and filling of treatment control card. - Obtain information about the occurrence of adverse events.
TELEPHONE CALL POSTERIOR TO VISIT 2, DAY 120 +/- 5 DAYS	- Corroborate adequate administration of the product of the investigational drug and filling of treatment control card. - Obtain information about the occurrence of adverse events.
TELEPHONE CALL POSTERIOR TO VISIT 2, DAY 150 +/- 5 DAYS	- Corroborate adequate administration of the investigational drug and filling of treatment control card. - Obtain information about the occurrence of adverse events. - Corroborate date of next appointment for visit 2, reminding that participant must attend with a fasting period of 9 to 12 hours and with the packages and remnants of the investigational drug.
VISIT 3, DAY 180 +/- 7 DAYS (FINAL VISIT)	- Verify fasting of the participant from 9 to 12 hours. - Make medical note and update of clinical history.

	- Ask about and register the occurrence or not of adverse events. - Review of administration of medicine of study and gathering of packages and, it there are any, the remaining pharmacologic forms. - In women in fertile phase, urine sample to perform immunologic pregnancy test. - Verify criteria of early termination - Taking of blood sample with 9 to 12 hours of fasting; two 10 ml tubes will be obtained to perform the following studies: Blood Biometry without differential and Glycosylated Hemoglobin. Blood Chemistry to evaluate: TC, C-LDL, C-HDL, TG, C- no HDL, Glucose, Urea, Creatinine, Uric Acid, ALT, AST and CPK.

***Window periods: Will be taken starting on the date of complete basal visit. Being the visit date considered as 0 and the window periods in less or more days with respect to this day. For example, a patient who has visit 2 in December 31 of 2017, December 31 will be considered as day 0 and having a window of +/- 5 days, it will be counted starting from this day in more or less, the visit being had form December 26 of 2017 to January 5 of 2018.**

9.4.13.Patients to Sieve to comply with the Sample Size

It is estimated that around 400 subjects will have to be sieved to comply with the desired sample size, this based on the calculation of excluded patients. For this, it is calculated that of the total of evaluated subjects for selection 75% will accept to participate in the study; of the 350 remaining subjects it is estimated that 75% will comply with clinical, electrocardiographic, and/or non-pregnancy criteria for their inclusion; finally, it is estimated that an aggregate of 46% will comply with the laboratory parameters to be included (for example, it is known that the prevalence of hypercholesterolemia in Mexican adults is 50.5% [18]). Truncating the result to whole numbers 120 investigation subjects remain.

Evaluated for selection: 400.

Subjects who wish to participate: 75% of the 400 = 350.

Of the subjects who wish to participate, subjects who comply with clinical, electrocardiographic and non-pregnancy criteria for their inclusion:

75% of 350 = 262.5

Of the remainder, the estimate of subjects who'll comply with laboratory criteria in blood for their inclusion is of:

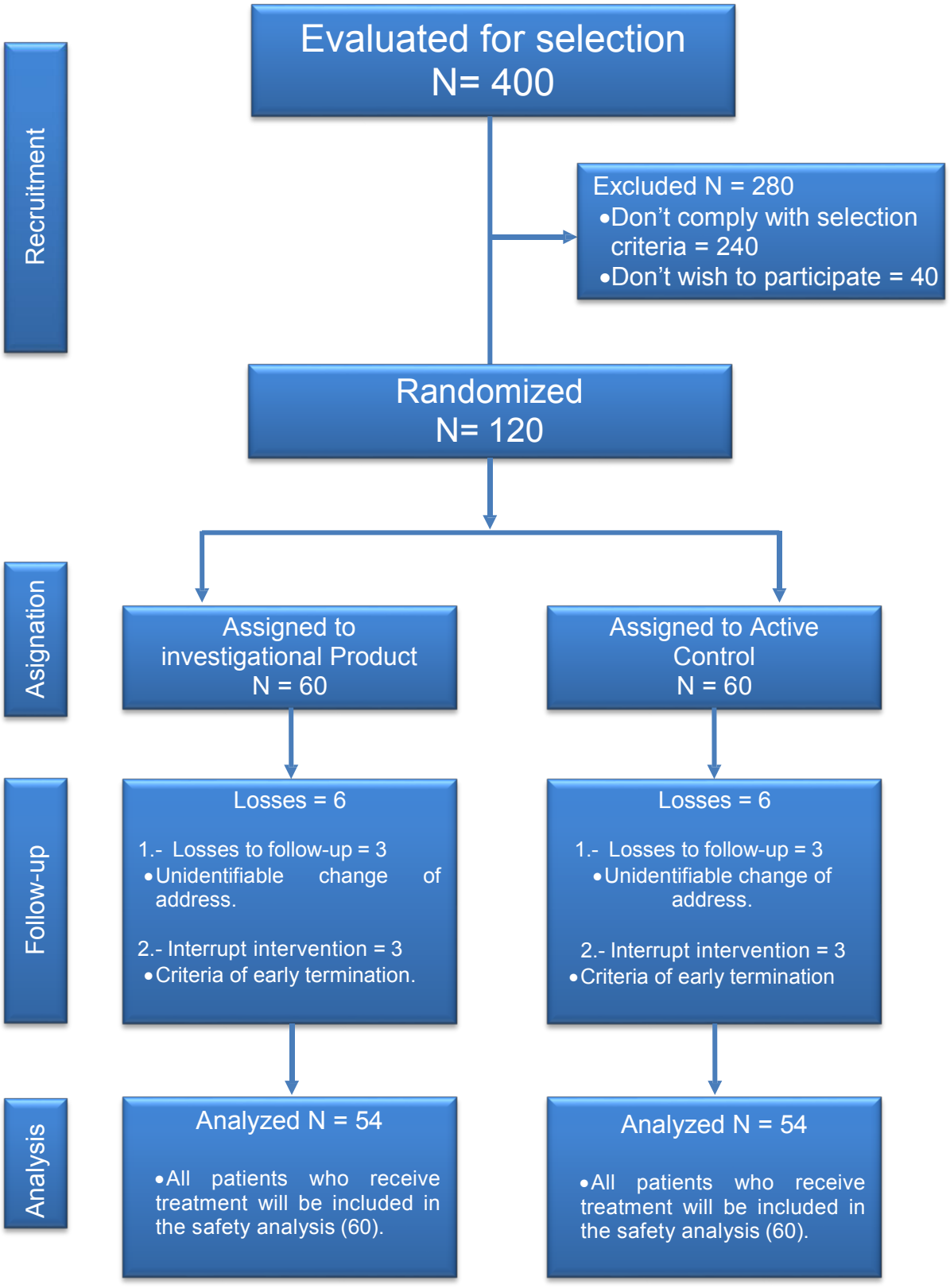
46% of 262.5 = 120.75, **120 subjects.**

The 120 patients will be randomized with the "Research Randomizer" program to receive treatment with the investigational product (atorvastatin + l- carnitine) or with the active control (atorvastatin); being able to have 60 patients per group.

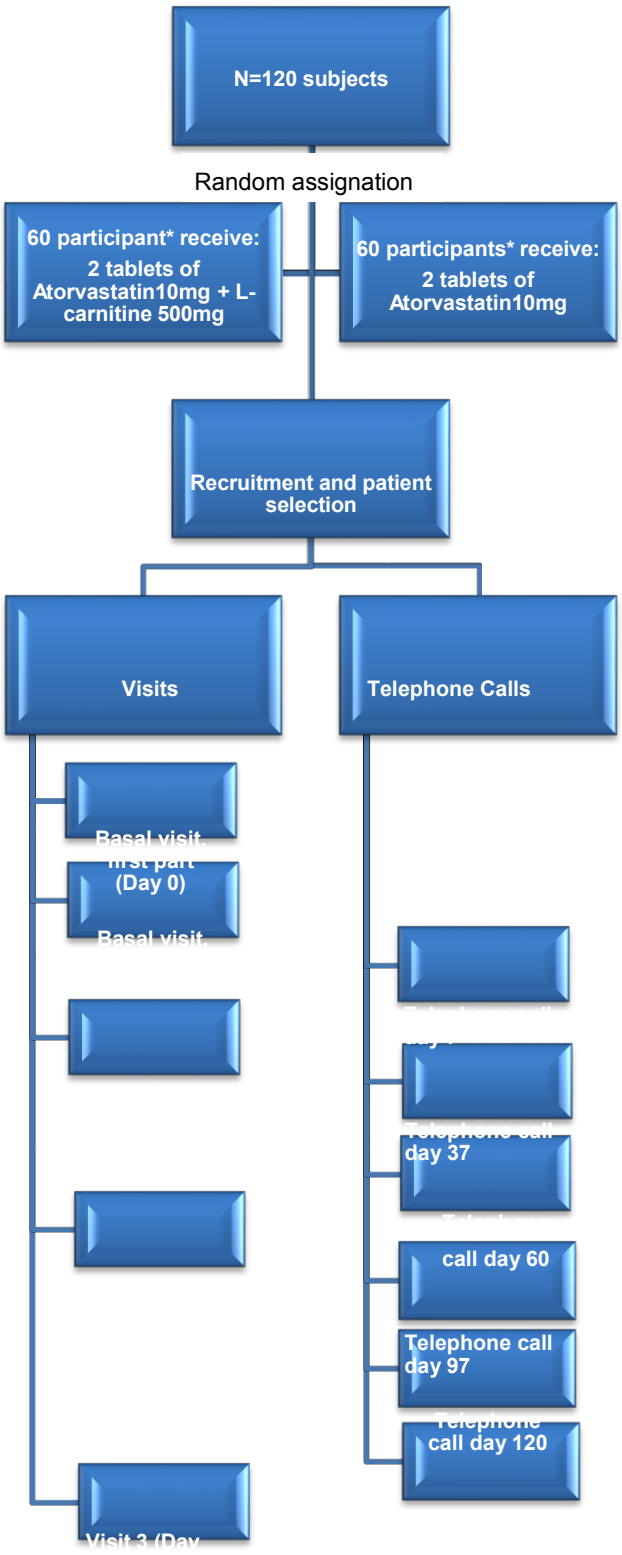
This number of patients was the one calculated in the size of sample per group based on an estimate of losses which are expected:

Patients per group = 60, of which a 10% loss is estimated = 6 losses per group; completing analysis of efficacy **54 patients per group.**

As is mentioned in the protocol, the intention is to analyze the efficacy data in those that finish the intervention, but for the safety analysis of the medicines of the study, the data of all the participants who receive treatment will be included, whether they concluded or not all the processes of the study.


Recruitment
Evaluated for selection
N= 400
Excluded N = 280
•Don't comply with selection criteria = 240
•Don't wish to participate = 40
Randomized
N= 120
Asignation
Assigned to investigational Product
N = 60
Assigned to Active Control
N = 60
Follow-up
Losses = 6
1.- Losses to follow-up = 3
•Unidentifiable change of address.
2.- Interrupt intervention = 3
•Criteria of early termination.
Losses = 6
1.- Losses to follow-up = 3
•Unidentifiable change of address.
2.- Interrupt intervention = 3
•Criteria of early termination
Analysis
Analyzed N = 54
•All patients who receive treatment will be included in the safety analysis (60).
Analyzed N = 54
•All patients who receive treatment will be included in the safety analysis (60).

9.4.14.Procedures based on the study groups



***The sample size per group of treatment may change according to the result of simple randomization.**

VISIT PROCEDURE	Patient Selection	Basal Visit, Day 0 (First Part	Basal Visit, Day 0 (Second Part)	Telephone Call Day 7 + 2	Visit 1 Day 30 ± 3 days	Telephone Call Day 37 ± 3 days	Telephone Call Day 60 ± 3 days	Visit 2 Day 90 ±5 days	Telephone Call Day 97 ± 3	Telephone Call Day 120 ± 5	Telephone Call Day 150 ± 5	Visit 3 Day 180 ± 7 days (final visit)
Obtention of Informed Consent Form	X											
Review of Inclusion /Exclusion Criteria		X	X									
Period of lavage of 3 weeks (for those who have previous treatment for dyslipidemias)		X										
Revision of Early Termination Criteria					X			X				X
Clinical history		X	X		X			X				X
Verify 9 to 12 hour fasting		X			X			X				X
Taking of urine sample for IPT*		X			X			X				X
Taking of EKG		X										
Taking of samples for laboratory exams (BH, HbA1c, Glucose, Urea, Cr, uric acid, TC, C-LDL, C-HDL, TG, C-no HDL, ALT, AST and CPK)		X										X
Taking of samples for laboratory exams (Glucose, Urea, Cr, uric acid, TC, C-LDL, C-HDL, TG, C-no HDL, ALT, AST and CPK)					X			X				
Assignation of identification code of subject			X									
Assignation of treatment			X		X			X				
Delivery of 33 days of treatment			X									
Delivery of 66 days of treatment					X							
Delivery of 99 days of treatment								X				
Corroborate administration of the medicine				X	X	X	X	X	X	X	X	X
Information about adverse events				X	X	X	X	X	X	X	X	X
Date of next visit			X	X	X		X	X			X	X
End of the study												X

***IPT: Immunologic pregnancy test for female patients in fertile stage**

9.4.15. Visits not stipulated by protocol

Visits not stipulated by protocol may be secondary to events detected through the telephone on part of the investigation site, from the participant and even upon request from the investigator during visits established in the protocol. Also, the participant may go to the investigation site for medical evaluations.

These, shall be registered in a medical note and be referred in the corresponding CRF for visits not stipulated in protocol.

9.4.16.Capture and processing of data

The data obtained during the study will be registered in the case report formats (CRF) that the sponsor indicates, filled by hand, with blue ink and in script. No registry of any data shall be omitted in these. The personnel delegated for CRF registry shall do it with the use of good documentation practices. This doesn't omit the fact that the source documents are found at the investigation site with the information of who originally gathered the data and the follow-up of good practices of documentation. Once this information is obtained the personnel of the investigation site shall capture them in an electronic database created by the sponsor and provided by the main investigator. The sponsor will have faculties of edition of the registries captured by the site personnel, generate questions about unclear data in the registries and modify the format and the operation of the database if deemed pertinent; for their part, the personnel delegated on the site will only have faculties for inclusion and reading of new data. Once the data are saved, it may only be modified with the authorization of the sponsor based on doubts generated for their clarification.

The data obtained will be used for their processing by the competent person to do this on the sponsor's behalf.

9.4.17.Statistical analysis and interpretation of the information

A first analysis which is performed in the controlled clinical assays is to compare the groups of treatment in their basal conditions and that generally are demographic characteristics (for example: age, gender), anthropometric measures (for example, corporal mass), inherent conditions to its clinical state (for example, severity of the disease, metabolic control) and other prognosticate variables related with the primary result variable. Usually presented as summary measures (means, medians) and dispersion (standard deviations and ranges) in continuous variables and in percentages for the categorical variables. This comparison is also useful to describe the sample of subjects who entered the study. Significance tests are used (t or Ji squared) with values of p. When a difference occurs between groups, they aren't necessarily due to a failure in randomization, but by accident. Altman recommends that the descriptors are basally compared using a combination of clinical knowledge and common sense. If the groups aren't balanced a non-adjusted analysis must be made and another one adjusted by the variable that unbalanced both groups. [146, 154] The statistical method used to compare 2 averages in different groups of treatment is the t test of student, compares the media of 2 groups of continuous variables and expresses the probability that any difference is due to the role of chance (rejects the null hypothesis). The assumptions that follow the t of student is that the data in both groups follow a normal distribution and that for non-paired samples the variance for each group is equal. [146]

Base on the above, for the descriptive statistic the media and median will be used as measures of central tendency. As measures of dispersion, variance, standard and minimum and maximum values will be used.

For the inferential statistic the analysis of variance (one-way ANOVA) will be used to compare the variations in the levels of TC, C-LDL, C-No-HDL, C-HDL and TG, from the basal values to the end of the study. In turn, the laboratory values that give correlation with incidence of adverse effects may be analyzed by laboratory parameters and, if convenient, the ones required to obtain the premises of the study. This test will also be used to search for significant association within the two groups of treatment.

The non-paired, two-tailed test of Student will be used to evaluate these comparisons between the two groups of treatment and its reduction in the

percentage of C-LDL and C-No-HDL.

The intergroup stratification will be done based on the concentration of plasmatic C-LDL, taking as the cutting point the upper limit for the cardiovascular risk of the patients and the χ^2 test for comparison of proportions between the groups of the study.

Values of $P < 0.05$ (2 tails) will be considered statistically significant.

For the statistical treatment of the data thrown by the study one of the professional programs of statistics may be used (SPSS, SigmaPlot, Origins, GraphPad Prism, etc.).

10. OBSERVATIONS OF THE STUDY.

10.1. Medicine

10.1.1. Doses

The patient will self-administer the medicine through oral route, at least 30 minutes before the intake of food in a nocturnal intake schedule between 20:00 to 21:00 hours and with a temporality of 1 time per day.

The patient must not administer the medicine of the study in combination with any other medicine.

So much the experimental group as the active control will have to administer 2 caplets or tablets.

The aforementioned process is the same for the subjects who participate in any group, the difference is in the active of each group.

The differences between the medicines of the study consist in that the experimental medicine is in caplets in which L-carnitine is added to the atorvastatin; in the active control group the medicine only contains atorvastatin (in the same concentrations as the experimental group). The formulations are exemplified hereunder:

Active content according to treatment group

TREATMENT GROUPS	Active by pharmaceutical form	Product to be administered per day and content of final active
EXPERIMENTAL GROUP	L-Carnitine 500mg + atorvastatin 10mg	2 caplets that contain in total L- Carnitine 1g + atorvastatin 20mg
ACTIVE CONTROL GROUP	Atorvastatin 10mg	2 tablets that in total contain atorvastatin 20mg

10.1.2.Labeling of the medicine.

The label will indicate the following: the patient's code, the study code, the month of treatment, the bottle corresponding to the month of treatment, the consecutive code of treatment, the number of the treatment, the lot number, the expiration date, the administration instructions and the legend "Exclusive use for investigation; its sale is forbidden".

The treatment code shall be formed by 1 upper-case letter and 3 consecutive digits. In the case of the experimental treatment the letter will be "L" and for the active control the letter will be "C". For example: L-001.

In the extra treatment the month of treatment will not be placed and its code will be formed by the upper-case letters "EXT", followed by an L or C as is the case previously explained and 3 consecutive digits. The rest of the label will be the same.

EXAMPLE:

Patient:_____.
Code of study GMX-001-2017
Month 1: Bottle 1
Treatment code: L-001.

Exclusive use for investigation, its sale is forbidden.

Bottle with 66 caplets.
Lot No. 14DY4837. Expiration date: JAN/2018

Dosage: Take 2 tablet at night through oral route 30 min before dinner.

Patient:_____.
Code of the study GMX-001-2017
Month 1: Bottle 1
Treatment code: C-001.

Exclusive use for investigation, its sale is forbidden.

Bottle with 66 tablets.
Lot No. 14DY4837. Expiration date: JAN/2018

Dosage: Take 2 tablets at night through oral route 30 min before dinner.

10.1.3.Banned medicines.

The following are the medicines that may cause some interaction with the experimental or active control treatment; besides the ones that may modify the serum levels of lipids relevant for this study; for which this shall be considered as not-authorized use during the present study; if its administration is necessary, it shall be a criteria for early termination of the participant:

- Macrolide antibiotics: Erythromycin, Telithromycin and Clarithromycin.
- Azole anti-fungi: Ketoconazole, Itraconazole, Fluconazole and Nefazodone
- Protease inhibitors: Saquinavir, Indinavir y Ritonavir

- Quercetin
- Amiodarone
- Aprepitant
- Cimetidine
- Ciprofloxacin
- Cyclosporine
- Diltiazem
- Imatinib
- Echinacea
- Enoxacin
- Ergotamine
- Metronidazole
- Mifepristone
- Tofisopam
- Gestodene
- Verapamil
- Mibefradil
- Fluoxetine
- Phenobarbital
- Carbamazepine
- Phenytoin
- Rifampin
- Modafinil
- Glucocorticoids
- Felbamate
- Rosiglitazone
- Griseofulvin

- Pioglitazone
- Gemfibrozil
- Clofibrate
- Fenofibrate
- Niacin
- Cholestyramine
- Colchicine
- Colestipol
- Primidone
- Topiramate
- Troglitazone
- Rifabutin
- Digoxin
- Thiazides
- anabolic Steroids
- Progestogens
- Estrogens
- Danazol
- Amiodarone
- fibric Acid
- D ocosahexaenoic acid
- Isotretinoine
- Immunosuppressives
- protease inhibitors of HIV or of the Hepatitis C Virus
- Inhibitors of the co-transport of sodium-glucose
- Tamoxifen
- Raloxifene
- non-selective Beta blockers

- biliary acid sequestrants
- asparginase
- Sirolimus
- Interferon

Antacids, alone or in combined use with the administration of the investigational product.

10.1.4. Inventory of the medicine

The medicines of the study will be received in the investigation center by the principal investigator or the delegate personnel. Once identified the medicines, they will remain under safeguard by the investigation site until its dispensation to the patients; the corresponding sponsor format will be filled for assignation of medicines and its capture in electronic will be done subsequently.

The patient must return all the bottles and/or boxes, either empty or containing medicines from the study. The amount of medicine dispensed will be quantified for its registry and control.

The medicine of the study that is returned by the patients shall be quantified, stored and safeguarded in wait of instructions by the sponsor.

The main investigator or delegate personnel shall keep and store all the original containers returned by the patients, until this containers are inventoried by the sponsor, unless the sponsor indicates otherwise.

At the end of the study, the main investigator or the delegate personnel will return all the original containers, either empty or with the surplus medicine of the study, as instructed through the monitor.

The main investigator or the delegate personnel shall not store or manage the medicine in study in any other place other than the ones agreed on previously with the sponsor.

The sponsor will guarantee an adequate disposition of the original containers, either empty or full of returned or unused medicine. The adequate documentation will be kept.

10.1.5. Storage of the medicine

The main investigator or the person designated by her/him will ensure that the medicine of study will be stored in a safe manner, in a dry place, in a cabinet under lock and key, at a temperature not greater than 30°C, with restricted access.

All the supplying of the medicines will be registered in the accountability inventory forms of the medicines, according to the procedure indicated by the sponsor.

The medicine in the study may not be re-labeled or reassigned for use in other patients except under special circumstances approved by Valeant Pharmaceuticals International.

The main investigator must make sure that the medicines supplied for the study be kept under lock and key in a place of access limited to those assigned by her/him.

The main investigator shall keep a record of the medicine stored in accordance with the format generated by Valeant Pharmaceuticals International. This format will include spaces for registering the reception date, amount of treatment, treatment code, lot number, expiration date and amount received. When the medicine is received at the site, a reception note must be filled by the main investigator or the delegate personnel.

The administration registry must be kept updated indicating the amount of medicine provided to each patient, which patient received the medicine and the amount that was left over after the treatment period. All the surplus medicine and the one that hasn't been used must be returned to Valeant Pharmaceuticals International at the end of the study. The processes for medicine return will be specified by the sponsor, with the proper filling of the format provided by the sponsor.

10.2. Taking and processing of laboratory samples

To avoid biases in the quality of the information, the taking of laboratory samples and its processing is important, for the efficacy and safety profile of the study will depend on the laboratory results.

The taking of blood samples and its processing will be identical for each occasion these are obtained in the different visits, differing in the parameters to analyze, it will be performed by trained personnel that proves to have the capacity to obtain it. The main investigator will delegate to the ideal personnel. New material shall be used, which will be labeled with the identification code of the subject. Once the sample is contained, it will be transported to the laboratory of the site, where its processing may begin according to the required particulars.

For the taking of the blood sample, the personnel shall use sterile gloves, new and sterile equipment, and label the tubes with the data previously to extraction with the data of the code of the subject of investigation. Afterward, the personnel shall locate the vein to puncture and perform antisepsis of the region; the puncture may be done with a needle of 21 to 23 G, mounted on a hub or by means of a device with "butterfly" needle. Once the site is punctured, the blood must be extracted in the adequate type of tube (see in the next section). If 2 different tubes are required, the effort shall be made not to puncture more than once the vein of the patient and extract the blood through 1 sole puncture. The ideal site is that where the trained and delegate personnel may obtain with the least number of tries venous blood. It is suggested, but isn't exclusive, that the puncture be done in the "venous M" of the ante-cubital fold; formed by the basilic cephalic, median basilic and median cephalic veins. If it isn't possible to obtain a blood sample in this region, or another is preferred to procure causing the least harm to the patient, it can be done.

The preservation and processing of each blood sample will depend on the studies to be performed. Hereunder are mentioned the peculiarities to consider for the laboratory analysis according to protocol.

- **Blood biometry and glycosylated hemoglobin:** Non-coagulated blood is required, that is, total or complete blood. The anticoagulant of choice in hematology must meet the following basic characteristics: not alter the size of erythrocytes, not produce hemolysis, and avoid platelet aggregation and not to alter the morphology of the leukocytes. The most indicated in these type of studies is potassium salt of ethylendiaminotetraacetic acid (EDTA), dipotassium salt (EDTA-K2) at a concentration of 3.7 to 5.4 µM, or tripotassium salt (EDTA-K3) at a concentration of 3.3 to 4.0 µM. The use of heparin is totally contraindicated.
  The sample must be delicately homogenized, moving the tube with smooth oscillatory movements, to avoid hemolysis and impregnate well the blood with the anti-coagulant to avoid the appearance of small clots. Once the blood is homogenized, it shall be refrigerated with continuous monitoring of temperature at 4°C, with a possibility of deviation of +/- 2°C. The maximum admitted period of refrigeration shall be 24 hours. The sample must never be frozen or located in direct contact with the thermal accumulators uses for the delivery in refrigeration.

- **Biochemical studies:** For these, blood serum will be used. The processing of samples in the laboratory of the investigation site will require that the sample be laid to rest at ambient temperature during 15 to 20 minutes for the adequate formation of the clot. The serum shall never be processed until the clot has completely formed. The tubes to be used for an adequate separation of the clot shall be of treated polystyrene or glass. Once the clot is formed it shall be centrifuged at a speed of 1500 G for 15 minutes.
  Once the serum is obtained it shall be deposited in another tube with the previous labeling with the patient's data and caution that it isn't confused with another sample.
  The sample of final serum will be refrigerated with continuous monitoring of temperature of 2 to 6 °C. The maximum period of refrigeration will be 24 hours.

Once the samples are processed in the laboratory of the site, they will be prepared for their shipping to the laboratory that the sponsor designates. The delivery shall be made with monitoring of temperature at departure from the laboratory of the site and the arrival for processing of sample. No more than 24 hours must pass for their processing. The reminder of blood and/or serum of the samples will be disposed of by the designated and the laboratory analysis

contained in this protocol will only be performed in the samples of the participants of the study.

All the processes of the taking and processing of samples must be recorded in the report format of corresponding case.

10.3. Records of the study, case report forms and source document

The information gathered in the study shall be registered under the following principles:

Attributable: to person that obtains it.

Legible: for which caution has to be observed when recording information.

Contemporary: the hour must be indicated in the format of 24 hours and 60 minutes; also the date in format of 2 digits for the day, the first 3 letters of the month and the 4 digits of the year. This with the aim of preserving the moment of obtention.

Original: the obtained information shall not be modified for the compliance with this precept and it must be truthful. In the event that errors exist in the registry, the corrections must be made according to the good clinical practices of documentation.

Accuracy: it must contain pertinent information and of the subject of investigation to whom its executed.

Use of blue ink: it will be used for all registries of the study.

The site where the information was recorded originally is denominated the source document. Every place where the initial information is recorded or from where it is obtained must be annexed, even when the information were registered in the place where it originally should be placed; not omitting annexing the source document the registry in the corresponding place. This shall be clarified in the section of notes of the case report format. If nothing is annotated in this section it shall be cancelled according to good practices of documentation.

Also, the information reported in the case report formats will be recorded by the delegate personnel of the investigation site on an electronic database created

by the sponsor and provided to the main investigator. The sponsor will have faculties for the editing of the records already captured by the personnel of the site, generate questions about unclear data in the registries and modify the format and the operation of the database if pertinent; for their part, the delegate personnel of the site will only have faculties for inclusion of new data and reading of same. Once the data are saved, they may only be modified with the authorization of the sponsor based on the doubts generated for their clarification.

10.4. Efficacy criteria

10.4.1. Success

The efficacy of the treatment will be evaluated by the measurements of the biochemical parameters.

Final Comparator vs. basal: The lipid-lowering effect on the following variables: TC, C-LDL, C-No-HDL, and TG, will be identified.

Therapeutic efficacy: The percentage of decrease of C-LDL of both treatment groups will be compared after 6 months of treatment.

10.5. Safety criteria.

The safety shall be evaluated through the report of adverse events, physical exams and laboratory results between the 2 treatment groups.

The subjects shall report to the medical personnel responsible for the conduction of the study any symptom they present. In the same way, the investigator or delegate personnel will ask the subjects, at every period of the study, about the symptoms presented during the study period, and in case of manifestation will provide attention to the subject and annotations will be made in the corresponding Case Report Forms.

11. SAFETY

The opportune and adequate report of the adverse events, suspect of being associated to the medicine under study, helps the sponsor to identify reactions that are potentially related with the medicine. This permits a) to evaluate the safety of the medicine, b) possess a greater comprehension of the toxicity potential of the medicine, c) perform indispensable modifications in the study protocol, and d) adhere to the regulatory requirements designed for the protection of the patient, of the prescribing physician, of the sponsor and of the participating pharmaceutical companies.

During the study, the safety of the treatments will be monitored through laboratory tests, by collecting information from the patient, as well as by the search for signs and symptoms that may identify adverse events that lead to the causal suspicion of the administration of the medicines of the study. The subjects shall report to the medical personnel responsible for the conduction of the study any symptoms they present. In the same manner, the investigator or delegate personnel will ask the subjects about the symptoms presented during the period of the study, and in case of a manifestation, annotations will be made in the corresponding Case Report Formats, as well as in the internal format of adverse events

11.1. Adverse events

The adverse events in a clinical trial are diseases, signs and/or symptoms, or abnormal laboratory values that appear or worsen since the inclusion of a participant in the clinical trial, related or not with their participation in the study. [L9] The adverse event, whether thought to be related or not, must be recorded.

All the adverse events that occur in subjects who are participating in this study must be reported to Valeant Pharmaceuticals International regardless of the severity or causal relation. The format and the time of the report are determined by the classification of the event. The following definitions will be used to make the determination:

1. **Adverse Event (AE):** any alteration and/or physiological occurrence that may present during the treatment with a pharmaceutical product, but than

doesn't necessarily present a causal relation with the treatment. [L9]

2. **Adverse Drug Reaction (ADR) or Secondary Effect:** Response to a pharmaceutical product that is harmful, unintentional and that occurs at normal doses used in humans for prophylaxis, diagnose, therapy for a disease, or for the modification of a physiological function. [L9]

3. **Expected adverse event:** Harmful, unintentional and undesirable response to a pharmaceutical product which has been observed and recorded in the monograph for the investigator or in the information for prescription. The possibility that these reactions appear must be included in the informed consent. [L9]

11.1.1. Classification of adverse events, suspicion of adverse reaction and the adverse reactions of the medicines:

I. Intensity

The severity of the adverse event, suspicion of adverse reaction and the adverse reaction, regardless of the cause, must be graded by the investigator using the following terms:

A. Mild. These present easily tolerated signs and symptoms, don't require treatment or prolong hospitalization and don't necessarily require the suspension of the medicine. The patient is aware of the sign or symptom but easily tolerates it. [L9]

B. Moderate: Interferes with habitual activities (perhaps causing work or academic leave), without directly threatening the patient's life. Requires pharmacological treatment and doesn't necessarily require the suspension of the medicine that caused the event, reaction or suspicion of adverse reaction. Consider it as a discomfort sufficient to cause interference with normal activity. [L9]

C. Severe: Interferes with habitual activities (able to cause work or academic leaves). Requires pharmacological treatment and the suspension of the medicine causing the event, reaction or suspicion of reaction. These events are Disabling with impossibility

of working or performing normal activities. [L9]

II. Severity or seriousness

Based on the outcome, adverse events, the suspicions of adverse reaction and adverse reactions are classified according to the seriousness of the clinical manifestation in:

A. Serious Adverse Events (Severe). Any clinically significant manifestation that presents with the administration of any dose of a medicine, and that :

a. Cause the death of the patient. [L9]
b. Put the life of the patient at risk at the same moment they appear. [L9]
c. Makes hospitalization necessary or prolongs hospital stay. [L9]
d. Causes disability, or persistent or significant inability. [L9]
e. Causes alterations or malformations in the newborn. [L9]
f. For this study, Serious Adverse Event will be considered the elevation of 3 times the normal upper value of ALT with clinical correlation and confirmation of occurrence due to the investigational product.
g. For this study, Serious Adverse Event will be considered the elevation of CPK in 10 times its upper limit reported as normal in ranges of international units and its causality proven with the investigational product.

The investigation site shall have 24 hours starting from the moment the serious adverse event is known to inform the sponsor and fill the corresponding report format; this report may be completed afterwards with documents. In turn, the site of must report this occurrence to the Ethics Institutional Review Board.

The sponsor will be in charge of reporting the serious adverse events to the health ministry.

B. Non-serious adverse events (Not Severe). The events, suspicions and adverse reactions that don't comply with the criteria of severity specified in the anterior numerals of the section of Serious Adverse Events. [L9]

The investigation site must report them in the corresponding format to the sponsor and generate the subsequent report to the ethics committee. The occurrence may be informed to the sponsor, who'll ask for the information to be completed before the next programmed monitoring visit.

The sponsor will be in charge of reporting the non-serious adverse events to the health ministry.

11.1.2. Quality of the obtained information

The notification of adverse events, suspicions of adverse reaction and adverse reactions, according to the quality of the information, understanding by it the exhaustive quality and integrity of the data contained, are classified in:

Grade 0. When the notification only includes one identifiably patient, one suspicion of adverse reaction, adverse event or adverse reaction to a suspect medicine and the notifier's details. [L9]

Grade 1. When in addition to data from Grade 0, the dates of the start of the suspicion of adverse reaction, adverse event or adverse reaction and of start and end of treatment (day, month and year) are included. [L9]

Grade 2. When in addition to data from Grade 1, the generic and distinctive denomination, posology, route of administration, motive of prescription, consequence of the event and important data of the clinical history are included. [L9]

Grade 3. When in addition to the data from Grade 2, the reappearance of the clinical manifestation consequent to the re-administration of the medicine (positive re-administration) is included. [L9]

11.1.3. Causality

The adverse reactions are classified according to the evaluation of causality under the following probabilistic categories:

Certain. Consists in an event (clinical manifestation or abnormal result of a laboratory test) that occurs with plausible time relationship to drug intake and can't be explained by the natural evolution of the condition, a concomitant pathology or

to the administration of other medicines. The response to the suspension of the medicine must be clinically evident. [L9]

Probable. Consists in an event (clinical manifestation or abnormal result of a laboratory test) that follows a plausible time sequence posterior to the administration of the medicine and can hardly be attributed to the natural evolution of the condition, concomitant pathologies or to the administration of other medicines. On suspension of the administration of the suspect medicine(s), a reasonable clinical response is obtained. [L9]

Possible. Consists in an event (clinical manifestation or abnormal result of a laboratory test) that follows a plausible time sequence posterior to the administration of the medicine, which may also be attributed to the natural evolution of the condition, concomitant pathologies or the administration of other medicines. The information related with the suspension of the administration of the suspect medicine isn't available or isn't clear. [L9]

Doubtful. Consists in an event (clinical manifestation or abnormal result of a laboratory test) that follows a plausible time sequence posterior to the administration of the medicine that makes the causality relation improbable (but not impossible), which could be explained in an acceptable manner for being part of the natural evolution of the condition, or due to the presence of concomitant pathologies or to the administration of other medicines. [L9]

Conditional-Unclassified. Consists in an event (clinical manifestation or abnormal result of a laboratory test) that can't be adequately evaluated due to the fact that additional data is required or these are being analyzed. [L9]

Unassessable-Unclassifiable. Consists in a report suggesting an adverse reaction that can't be assessed because the gathered information is insufficient or contradictory. The report can't be completed or verified. [L9]

The causality of the adverse events shall be reported by the main investigator and/or the delegate personnel based on clinical findings, which may or may not be related to the investigational drug; this shall be recorded in the corresponding format. Nevertheless, the personnel in the Pharmacovigilance area of the sponsor will evaluate among other things the causality of the adverse event using the algorithm of Naranjo and collaborators (See ANNEX 5). [155]

11.1.4. Special conditions

There are special conditions that must be reported; their report is specified hereunder:

Pregnancy. [L9] If a woman resulted pregnant during the study, this event shall be reported to the sponsor and to the ethics committee. The participant may not continue in the study and a follow-up will be made until the pregnancy period ends, reporting the conditions that arise during the pregnancy and its resolution, in the mother as well as in the product.

Lactation. [L9] This condition doesn't apply for this protocol because of the non-inclusion of lactating women.

Event related to the quality of the product. [L9] This will be considered an adverse event and will be reported to the sponsor, until the sponsor confirms the causality or not with the quality of the product.

Overdose. [L9] Overdose shall be reported as an adverse event and be notified to the sponsor and the ethics committee.

Error in medication. [L9] This condition doesn't apply to the investigational drug, in case of taking a different product this must be reported and the criteria of early termination be evaluated to see the relation of the non-administration of the investigational drug.

Misuse. [L9] This shall be reported to the sponsor detailing on what consists the misuse.

The others such as lack of efficiency, degenerative chronic disease, transmission of infectious agent and abuse don't apply because of the methodology or detailed compilation of same in this protocol. [L9]

11.2. Report of the adverse events

It shall be performed in temporality according to its aforementioned severity classification; the filling of the report shall be in electronic format. Also, it must be registered in the CRF corresponding to the adverse event.

11.3. Follow-up of the adverse events

Any abnormal finding either clinic or in the laboratory values shall be kept under narrow watch until it is resolved.

According to the characteristics of the adverse event, the sponsor may require copies of the medical record of the patient, as well as the results of the laboratory tests performed. If the patient was hospitalized, an effort will be made to gather a copy of the summary of the hospital stay to be sent with all the source documents recovered to Valeant Pharmaceuticals International, indicating that they are faithful copies of the original with good practices of documentation and with blue ink as soon as they are available. In some cases a letter may be required from the investigator where the adverse events related with the case will be summarized. In all cases, the main Investigator must perform follow-up to the patients until the final result of the event is known.

If a patient is eliminated or excluded from the study due to the occurrence of abnormal laboratory values, these must be repeated at adequate intervals (determined by the investigator) until they return to normal or during the time the investigator considers convenient. If it is clinically indicated, the patient must be referred to his/her treating physician or to an external physician for a posterior evaluation. If the patient is withdrawn before termination of the study, the decision of this action shall have to be plainly justified and recorded in the case report forms and included in the analysis of this study.

11.4. Data for notification of serious adverse events

The serious adverse events shall be reported and investigated on part of the investigation site and its personnel, in turn; the sponsor of the study shall be notified within the first 24 hours following its presentation and/or detected.

The contact data are the following:

Clinical Research Coordinator: Dr. Francisco Javier Figueroa Vallejo.

Responsible of Pharmacovigilance: Dr. Paola Andrea Martínez Serrano.

Office telephones: 01-55-50624190 and 01-55-50624175

24-hour Emergency mobile telephones for SAE: 5523009656 and 5543731344.

Report of SAE by electronic mail: farmacovigilancia.mexico@valeant.com and francisco.figueroa@valeant.com

11.5. Expected adverse events for the medicine in study

11.5.1. Atorvastatin

There are individuals who find themselves with a predisposed risk to present adverse events related with the use of statins; conformed (not in a limited manner) by those who course with multiple or serious comorbidities, including renal damage and hepatic failure, history of previous intolerance to statins in muscular comorbidities, elevation of ALT in blood 3 times the upper limit considered as normal in an unexplainable manner (reported in international units), age above 75, have Asian descent, history of having suffered a cerebrovascular event of the hemorrhagic type and, characteristics proper to the patient or of the concomitant treatment that affect the metabolism of statins. [6]

Nevertheless, atorvastatin is usually well-tolerated; the adverse reactions are usually mild and transitory. In clinical studies less than 2% of the patients were discontinued due to adverse effects attributed to atorvastatin.

In a meta-analysis of 44 studies in which were included data of 16,495 patients with dyslipidemia treated with atorvastatin (9416 patients), other statins (5290 patients) and placebo (1789 patients), the safety of atorvastatin was evaluated in doses of 10 to 80 mg per day; it was found that the incidence of adverse events was of only 3% for the individuals who used atorvastatin, 1% for those that used placebo and 4% for those who used other statins. [118]

The most frequent adverse reactions that were found associated to the use of atorvastatin had an incidence a little over 1% and these are: constipation, flatulence, dyspepsia, abdominal pain, headache, nausea, myalgia, asthenia, diarrhea and insomnia.

Likewise, there are reported effects that haven't necessarily been associated to

the use of atorvastatin such as: muscular cramps, myositis, myopathy, paresthesias, peripheral neuropathy, pancreatitis, hepatitis, cholestatic jaundice, anorexia, vomit, pruritus, impotence, hyperglycemia and hypoglycemia.

Gastrointestinal disorders, not including hepato-biliary:

This type of effects are the most common related with the use atorvastatin reported in clinical studies, being the most frequent mild diarrhea. Other effects are intestinal constipation, flatulence, dyspepsia, abdominal pain, nausea and with a lesser frequency, vomit [113, 118]. Adverse effects that have been documented in patients that use atorvastatin but causality hasn't been proven in clinical studies are: cholestatic jaundice, hepatitis and pancreatitis.

Common: constipation, flatulence, dyspepsia, nausea, mild diarrhea.

Uncommon: vomit, superior and inferior abdominal pain, eructation, pancreatitis.

Disorders of the nervous system:

In a meta-analysis of 44 clinical studies an incidence of adverse events related to the nervous system was found in 3% of the patients who used statins compared with 2% for the placebo group. Among these, the most frequent is headache; although paresthesias and peripheral neuropathy have also been documented. [118]

Common: headache.

Uncommon: dizziness, paresthesia, hypoesthesia, dysgeusia, amnesia.

Rare: peripheral neuropathy.

Disorders of the skin and of subcutaneous tissue:

The incidence of adverse events by atorvastatin is of 2% compared with the placebo which is 1% in disorders of the skin and subcutaneous tissue. It has been found without verifying if the causal effect is the medicine; the most common effects found are pruritus and urticaria. [118]

Uncommon: urticarial, cutaneous eruption, pruritus, alopecia.

Rare: angio-neurotic edema, epidermolysis bullosa, including multiform erythema, Stevens-Johnson syndrome and toxic epidermal necrolysis.

Hepato-biliary disorders:

Initial post-commercialization studies were performed of the statins and data of elevation in ALT 3 times superior to the normal limit were found in 1%, finding relation dependent on the dose used. Law and collaborators in 2003 conducted a study with statins (among them Atorvastatin at 10 and 40mg) and placebo. Their reported results were from 1 to 3% in elevation of ALT in comparison to the 1.1% of the placebo group. There were no cases of hepatic damage. Due to the fact that hepatic damage secondary to the use of statins shows an extremely low annual incidence, less than 2 cases per million patients, the increase of hepatic enzymes associated to the use of statins is an occasional finding in most cased, potentially reversible, for which the routine measurement of hepatic enzymes isn't recommended in the patient who uses statins. [69] In spite of this, in those who present symptoms suggestive of hepatotoxicity such as unusual fatigue or weakness, loss of appetite, abdominal pain, choluria and jaundice, it is recommended to perform biochemical tests that evaluate the hepatic function. In turn, it is recommended not to include in clinical studies subjects that present basal levels of ALT above 1.5 to 2 times the normal superior limit reported in international units. [4] It is also recommended that they don't be used in patients who suffer from hepatic failure or established cirrhosis. [69] In the meta-analysis performed by Newman and collaborators, an incidence without dependency on the dose was found in 0.5% if elevation of ALT/AST 3 times greater than the superior limit on at least 2 consecutive takes in comparison with the 0.3% of the placebo population. Of these patients less than 1% had persistent elevations of transaminases. [118] In another analysis derived from 49 clinical studies with 14,236 patients who received atorvastatin at doses of 80mg through oral route, 10 mg or placebo; the findings were of persistent elevations in hepatic transaminases (in ranges greater than 3 times the normal upper limit according to international units) in 0.1% for atorvastatin 10 mg, 0.6% for atorvastatin 80 mg and 0.2 for the placebo group. [119] La Rosa and collaborators performed an analysis of 10,001 patients with evidence of cardiovascular disease and levels of C-LDL of 130 mg/dl or less. Once randomized, 5,006 patients were assigned atorvastatin in doses of 10 mg/day and 4,995 atorvastatin in doses of 80 mg/day. After a 4.9 follow-up they found an incidence of sustained elevation of

aminotransferases in at least more than 3 times the upper limit in 1.2% of those who received 80mg/day and in 0.2% of those who received 10mg/day. The report system of the FDA mentions that 1 event appears in 1 million study-years of persons. Even so, it is justified to measure ALT to keep a control with respect to this effect. [113]

Uncommon: Hepatitis

Rare: cholestasis.

Very rare: hepatic failure.

Musculoskeletal disorders, and disorders of connective tissue:

The muscular effects associated to the use of statins have an important clinical relevance; previously, the physiopathologic bases of this condition have been commented upon. [76, 77] Their presentation is greater in adults of the female gender and in those who course with complex medical problems or have a history of using multiple medicines. [6] The greater presentation in elder adults is justified by sarcopenia (diminishing of muscular mass), increasing the risk of developing myopathy secondary to the use of statins; combined with the fact that enzymes that metabolize the statins may be less functional increasing the interaction among drugs. [75]

Among the effects secondary to the use of statins, the patient may course with myalgia, myopathy, myositis, myonecrosis and myoglobinuria with a possible secondary acute renal damage. [6] The measurements of Creatin kinase are advised for individuals with an elevated risk of suffering muscular adverse events based on familial history of intolerance to statins, muscular disease, clinical presentation or concomitant therapy that increases the risk of suffering myopathy. It is reasonable to measure the levels of CPK in patients who present muscular symptoms, including pain, augmented sensitivity, cramps, tiredness or generalized fatigue. [6] In patients who course with muscular symptoms additional to the measurement of CPK, it is recommended to measure creatinine and perform a urinalysis with intentional search of myoglobin to rule out rhabdomyolysis. Upon resolution of the muscular symptoms, in the absence of rhabdomyolysis, the patient may return to treatment with statins at low doses. If after 2 months of withdrawal of the use of statins the muscular symptoms or the levels of CPK don't improve, these levels must be considered secondary to other muscular causes. [6] Studies have sustained that in the presence of myalgias in patients with statins treatment without elevation of CPK or intolerance,

strategies of error assay may be performed, starting with statins of low potency at low doses. Also, we may recur to the change of statin used or through the administration of different doses between the days of treatment, with a gradual increase by tolerance each week. [5] In the study of La Rosa and collaborators where 10,001 patient were included who used atorvastatin in doses of 10 mg or 80 mg, no persistent elevations of CPK were found in none of the groups (defined as elevations of 10 times the upper limit in consecutive measurements with differences of 4 to 10 days). 2 cases of rhabdomyolysis were reported for the group of atorvastatin in doses of 80 mg/day and 3 for the group of 10 mg. Of the 5 cases of rhabdomyolysis only 3 presented elevations greater than 10 times the limit for CPK. The presentation of the clinical condition per patient was posterior to: congestive cardiac failure with infarction of the myocardium and pneumothorax, accidental fall, pneumonia and sepsis, muscular cramps with concomitant ingestion of alcohol and cetirizine and post-operatory thromboembolic disease. [112] Newman and collaborators in a meta-analysis of 44 clinical assays with 9,416 patients found that with the use of atorvastatin and other statins 4% of the patients presented myalgia. In this analysis only 1 patient presented persistent elevations of CPK greater than 10 times the upper limit and they weren't accompanied by muscular symptoms. The patient was a man of 16 years with severe hypercholesterolemia and a history of xanthomas, systemic arterial hypertension, headache and who received atorvastatin through oral route at doses of 40 mg for 28 days followed by 80 mg per day of atorvastatin through oral route during 479 days. [118] In another meta-analysis which evaluated the safety of using atorvastatin at 10 mg per day or at 80 mg per day in comparison with placebo, found an incidence of myalgia in 1.4% of those who took 10 mg/day of atorvastatin, 1.5% in the group of 80 mg/day and 0.7% in the placebo group. Not one case of rhabdomyolysis was reported. The elevations in CPK of at least 10 times the upper limit considered as normal were of 0.21% for the group of 10 mg/day of atorvastatin and of 0.47% for the group of 80 mg/day of atorvastatin. With respect to the severity of the myalgia, it was reported as serious in 0.09% of the patients who received placebo, 0.08% of those who received doses of 80 mg and there were no serious adverse events related to myalgia in those who received atorvastatin in doses of 10 mg. [119]

Between 1987 and 2001 the FDA found 42 deaths by rhabdomyolysis associated to the use of statins. This range is maintained in 1 death per 1 million prescriptions.

In clinical studies, rhabdomyolysis occurs in 8 patients compared with 5 in the placebo population. Besides, of the patients who have active medication with

statins, 0.17% develops levels of CPK 10 times above the normal limit (limit used to define rhabdomyolysis secondary to statins), compared with the 0.13% presented in those who received placebo. In conclusion, the incidence of myopathy is of 0.01%, but the risk of myopathy and rhabdomyolysis increases according to a larger proportion of plasmatic concentrations of the statins. [104] The concomitant therapy with drugs that diminish the catabolism of the statins is found in 50 to 60% of the patients who coursed with myopathy and rhabdomyolysis. The most common interaction occurs with fibrates of gemfibrozil in the 38%, cyclosporine in 4%, digoxin in 5%, warfarin in 4%, macrolides in 3%, Mibefradil in 2% and Azole Antifungal in 1%. [104] Within the clinical presentation, it is characterized by intense myalgia similar to that of a cold, it starts in arms and thighs and then it disseminates to the whole body, accompanied by fatigue. The symptoms are progressive if the use of statins continues. Myoglobinuria, renal failure and secondary death have been reported. The serum levels of CPK are typically elevated in these patients. As soon as myopathy is suspected in patients that are users of statins, a laboratory measurement must be made of these parameters. As a common rule, statins that are administered in combination with the drugs that predispose these reactions must be administered at no more than 25% of their maximum dose to decrease the risk of these events, for atorvastatin at doses of 20 mg/day. [104]

Common: myalgia, arthralgia, pain in limbs, muscular spasms, swelling of joints, dorsal spinal pain.

Uncommon: pain in neck, muscular fatigue.

Rare: myopathy, myositis, rhabdomyolysis, tendinitis, sometimes complicated with rupture of the tendon.

Disorders of the blood and lymph system:

Rare: thrombocytopenia.

Disorders of the immunologic system:

Common: allergic reactions.

Very rare: anaphylaxia.

Metabolic and nutritional disorders:

Common: hyperglycemia.

Uncommon: hypoglycemia, increase of weight, anorexia.

Psychiatric disorders:

Uncommon: nightmares, insomnia.

Disorders of the ear and labyrinth:

Uncommon: tinnitus.

Very rare: loss of hearing.

Disorders of the genitals:

Very rare: gynecomasty.

General disorders:

Uncommon: general discomfort, asthenia, peripheral edema, fatigue, pyrexia.

Infections and infestations:

Common: nasopharyngitis.

Ocular disorders:

Uncommon: blurry vision.

Rare: visual disturbance.

Respiratory, thoracic and mediastinal disorders:

Common: pharyngeal-laryngeal pain.

Uncommon: epistaxis, thoracic pain.

Alterations in laboratory tests:

Common: tests of abnormal hepatic function, increase of blood creatin kinase.

Uncommon: leukocytes in urine positive.

11.5.2.L-Carnitine

The only documented contraindication is hypersensitivity to the drug.

Since L-carnitine is a product which is habitually found in the organism, it is safe even in doses of 15 g/day.

Body odor:

In some individuals, especially in men (less than 1.9% of the population), trimethylaminemia has been described with presence of discreet smell of fish, which is avoided when dose is lowered. Patients who receive levocarnitine expel a fish-like smell which is eliminated decreasing the dose. [156] In a clinical study this relation was seen after the oral administration of L-carnitine due to the formation of trimethylamine. [157]

Gastrointestinal disorders:

Diarrhea: In adults, using a dose of L-carnitine of at least 3 g/day has been related with softening of feces, and in some cases, presence of diarrhea without clinical significance. [156, 158, 159, 160, 161, 162] The adverse effect decreases with the

slow intravenous administration or with a greater dilution in the oral solution. [156, 158, 160] Ellaway and collaborators found in patients from 3 to 35 years of age with Rett syndrome that when they were administered with L-carnitine at doses of 100 mg/kg/day they experienced diarrhea. This effect disappeared when reducing the dose to 75 mg/kg/day. [159] In a study of mitochondrial myopathy 10% of the patients experienced gastrointestinal adverse effects, including diarrhea. [161]

Nausea: In a study of mitochondrial myopathy, 10% of the patients experienced gastrointestinal adverse effects, including nausea. [161] This adverse effect is reduced with the slow administration through intravenous route and a greater dilution of the oral solution with levocarnitine. [156, 158, 160]

Vomit: Vomit has been found with a greater prevalence in high doses of L-carnitine than in placebo (21% vs. 16%) or low doses (9-16%). This effect is reduced with the slow administration or with a greater dilution of the oral solution.[156, 158, 160]

Heartburn: Heartburn was reported in 1 patient with chronic stable angina who received L-carnitine at doses of 1 gram 2 times a day to increase tolerance to exercise. [162]

Disorders of the nervous system:

Dizziness: Dizziness was reported in 1 patient who received 6 grams of intravenous levocarnitine. [163]

Headache: Levocarnitine has been reported as related to headache. Harper and collaborators reported the presence of headache in 1 patient who received a dose of levocarnitine through intravenous route. [163] During an intravenous treatment subsequent to sessions of dialysis in patients with chronic renal failure, stage 5; the headache was more common in those who received levocarnitine (22%) in comparison with placebo(16%), with a larger prevalence in the group that received 20 mg/day (37%). Also, it was reported in one patient that received 6 g intravenously of levocarnitine. [164]

Convulsions: With the oral or intravascular route use of levocarnitine, an increase in the frequency and/or severities of the convulsions in patients with antecedents has been reported. Besides, they have also been reported in patients without pre-existing activity of convulsions. [164]

Transitory blurry vision: It was reported in 2 patients who received intravenous carnitine in 6 grams.

Disorders of the genitourinary system

Change in the color or urine: the association has been reported in those who use levocarnitine.

Adverse effects in chronic renal failure in end stage

Care must be observed in the administration of L-carnitine in nephropathy.

Hyperkalemia: During the intravenous treatment of levocarnitine in dialyzed patients with end stage of chronic renal failure, hyperkalemia was found in 15% of those treated with doses of 10 mg/kg, 6% at doses of 20 mg/kg and 8% at doses of 40 mg/kg compared with 3% of the patients who received placebo. [164]

Paresthesias: Levocarnitine in 40 mg/kg intravenously was associated to paresthesia in 12% of the patients, in contrast with 3% presented by the placebo group or at doses of 10 to 20 mg/kg. [164]

Parathyroid disorders: Disorders of the parathyroid gland were found after an administration of levocarnitine of 10 mg/kg intravenously in 4% of patients compared with 2% in placebo. [164]

Disorders of the sense of taste: dysgeusia was found in 9% of those who received levocarnitine at doses of 40 mg/kg by infusion. An additional 2% of patients who received this drug at doses of 20 mg/kg has disorders of the sense of taste. This wasn't found in those who received L-carnitine at doses of 10 mg/kg or placebo. [164]

Cardiovascular disorders: Auricular fibrillation was found by electrocardiogram with the intravenous use of L-carnitine at doses of 40 mg/kg in 6% compared with 3% or less in the patients that received lesser doses of levocarnitine. The patients who received placebo had no changes. With respect to arterial tension, it was common in those who received levocarnitine in doses of 10 mg/kg (18% presented the effect) at 40 mg/kg (21% presented the effect) compared with placebo (14%). Also tachyarrhythmia was observed with a greater incidence in those who received levocarnitine at doses of 40 mg/kg in comparison with those that received placebo or levocarnitine at doses of 10-20 mg/kg with percentages of 9% and 5-6%, respectively. [164]

Anemia: Anemia after administrating L-carnitine at 40 mg/kg was reported in 12% administrated posterior to dialysis, in contrast with 3% found in patients with doses of 10 to 20 mg/kg or placebo. [164]

There are no restrictions of use during pregnancy and lactation. L-carnitine is a

normal component of maternal milk.

12. ADMINISTRATIVE ASPECTS OF THE STUDY

12.1. Confidentiality

Upon acceptance of this protocol the investigator compromises to maintain (confidentiality) of the information provided, and that it shall only be divulged to the Ethics Institutional Review Board on the understanding of confidentiality of this group.

The names, identities of the subjects and any information of the participant which could place at risk the confidentiality of the participant in the study, shall be safeguarded in the site, consequently it will not appear in the case report forms or any other record granted or withheld by Valeant Pharmaceuticals International.

To safeguard the identity of the subjects, they will be assigned a code in the study; the method of obtention of the code may be seen in the section corresponding to protocol.

12.2. Retention of the data

All records and documents pertinent to the study, including those described in records of the study, not being limited to these shall be kept by the investigator for a period of:

Five years following the conclusion of the clinical trial.

Two years after the approval of the medicine for the indication in study.

Five years after the rejection of approval or the medicine or

Two years after the cancellation of the authorization under which the study was performed.

To avoid any possible error, the investigator will get in contact with Valeant Pharmaceuticals International previous to the destruction of any record of the study. The investigator shall notify immediately to Valeant Pharmaceuticals International in case of accidental loss or destruction of the records of the study.

12.3. Authorization of the protocol by the Institutional Review Board

The registry of the protocol and documentation such as: investigator's manual, informed consent and case report formats before the Ethics and Research Institutional Review Board, has the purpose of assessing that it complies with the necessary requirements according to the law for clinical studies and that in turn considerations be kept for an ethical treatment of the participants in the clinical trial. Also, it is a documental requisite to present and obtain registry before the Federal Commission for Protection against Health Risks (COFEPRIS) of the Health Ministry.

Before initiating the recruitment of patients in the study, the protocol and the form of informed consent, these shall be reviewed and approved by the Ethics and Research Institutional Review Board. On signing the "approval of the investigator", the investigator will guarantee that all the aspects of the review by the Ethics and Research Institutional Review Board will be performed in accordance with the applicable regulations.

The Ethics and Research Institutional Review Board shall issue a letter documenting the approval of the following documents:

1) Informed Consent.
2) Study Protocol.
3) Investigator´s Brochure.
4) Case Report Formats.

The amendments to the protocol and informed consent shall be subjected to the same requirements as the original protocol.

12.4. Authorization of the protocol by the Federal Commission for Protection against Health Risks (COFEPRIS)

An enabled unit of COFEPRIS may be used for it to perform a pre-verdict of the protocol study.

The following documents must be sent by the investigator to the sponsor for registry of the protocol in COFEPRIS:

1) Letter of approval of protocol by the Ethics and Research Institutional Review Board.
2) Letter of informed consent issued by the Ethics and Research Institutional Review Board.
3) Letter of approval of the investigator's brochure issued by the Ethics and Research Institutional Review Board.
4) Simple copy of the operating permit (Sanitary license or notification of operation as the case may be).
5) Letter of authorization to conduct the clinical trial, signed by the titleholder of the unit or institution where the clinical trial will be effected.
6) Document where the description of the available resources of the unit or institution where the clinical trial will take place is expressed, including areas, equipment, auxiliary services of laboratory and cabinets, number of personnel; all the previous solely and specifically for the development of the i clinical trial.
7) For the case of investigation centers that hold agreements for the attention of medical emergencies with other institutions, include simple copy of the existing agreement.
8) Simple copy of the Operating Permit of the Institution for attention of emergencies.
9) Letter of the description of available resources for the management of emergencies.
10) Letter of acceptance, confidentiality and commitment of report of suspicions of adverse events, dated and signed by the main investigator.
11) Summary of the professional history of the main investigator.
12) Simple copy of the documentation, legally issued and registered by the competent educative authorities in case of license numbers.
13) Summary of the academic preparation and experience of the medical personnel, infirmary and other experts who will participate in the activities of the clinical trial.

14) Descriptive letter of the delegating of responsibility of the investigator´s team.

12.5. Start of the study

The approval of the Federal Commission for the Protection against Health Risks (COFEPRIS) of the Health Ministry will be necessary for the commencement of the study.

Once the favorable verdict is issued, an initial visit to the site will be made, previous to the inclusion of patients. In this visit, the procedures of the protocol and case report forms, areas to be used and documents of the study will be reviewed.

13. DURATION OF THE STUDY

The time of participation of each patient in the clinical assay will not be greater than 6 months. 45 days will be considered for the inclusion of the patients and 6 months of treatment. Considering times in the processes of the study, the estimated duration is from 10 to 11 months until the delivery of the report and briefing of the results. The exception to the rule would be the presence of adverse events, in which case a follow-up will be made until the event is resolved; for example, pregnancies.

14. MONITORING OF THE STUDY

According to the Mexican normativity and the guidelines of clinical practice of the International Conference of Harmonization, [151, L5, L6, L7] Valeant Pharmaceuticals International will perform periodic monitoring of the study at the commencement, during and at the termination of the study on mutually agreed dates with the site of the research.

The monitoring visits will allow Valeant Pharmaceuticals International the opportunity to evaluate the progress of the study, verify the veracity and filling of the Case Report Forms, guarantee that all the requirements of the protocol are being met, including the characteristics of the design of the study; the compliance of the regulations and the obligations of the investigators will be reviewed, resolve

any inconsistency in the records of the study; this includes the inspection of all documents and records, which must be kept by the investigator and includes the clinical files of the subjects being studied.

The study shall be executed exactly as described in this approved protocol. The monitor designated by the sponsor will be in charge of verifying that all the actions described in the protocol are carried out neatly.

The regulations require that the investigator permit access to authorized representatives of the Health authorities to review and obtain information from the clinical files. The names and identities of the subjects may not be revealed to Valeant Pharmaceuticals International; however, all the documents where the personal information of the subject in the study is not included may be reviewed. The confidentiality of the patient may be kept with the number of identification of the study and initials. If these requirements come into conflict with local regulations or policies of the institution, the investigator shall report it to Valeant Pharmaceuticals International before commencing the study.

The 3 grand objectives of the monitoring will be kept:

1. Review and document that the rights and well-being of the human beings are protected.
2. Review and document that the reported data of the study are complete, precise and may be verified in the source documents.
3. Review and document that the conduct of the study is in conformity with the protocol and/or amendments if these are approved, with the Good Clinical Practices and with the applicable regulatory requirements.

14.1. Responsibilities during the monitoring

The sponsor's personnel that performs the monitoring shall make sure that the study is conducted and documented appropriately, carrying out the following activities when they are relevant and necessary for the study and the site where the study is being done:

1. Act as the main communication line between the sponsor and the investigator. [151]

2. Verify that the investigator is qualified and counts with the adequate resources

and that these are maintained during the study; that the facilities, including the laboratory, equipment and personnel are ideal to conduct the study in a safe and appropriate manner and remain as such for its duration. [152]

3. Verify with respect to the investigational product(s) that:
    a) the timing and conditions of storage are acceptable and that the supplies are sufficient during the study. [151]
    b) the investigational products are supplied only to the subjects who are eligible to receive it and at doses specified in the protocol. [151]
    c) the necessary instructions are provided to the subjects about the appropriate use, management, storage and return of the products of investigation. [151]
    d) the reception and use and return of the investigational products in the places where the study is carried out is adequately controlled and documented. [151]
    e) the disposition of the unused investigational products, in the sites where the study is conducted complies with the applicable regulatory requirements and is in conformity with the sponsor. [151]

4. Verify that the investigator follows the approved protocol and all the approved amendments, in case there are any. [151]

5. Verify that the written informed consent of each subject has been obtained before they participate in the study. [151]

6. Make sure that the investigator receives the prevailing Brochure of the Investigator, all the documents and supplies necessary to appropriately conduct the study and to comply with the applicable regulatory requirements. [151]

7. Make sure that the investigator and the personnel of the study of the investigator are adequately informed about the study. [151]

8. Verify that the personnel of the study of the investigator is performing the specific functions of the study in conformity with the protocol and any other

agreement in writing between the sponsor and the investigator/institution and that they haven't delegated these functions to unauthorized persons. [151]

9. Verify that the investigator is only including eligible subjects. [151]

10. Report the rate of recruiting of subjects. [151]

11. Verify that the source documents and other records of the study are precise, complete and are kept updated. [151]

12. Verify that the investigator provides all the reports, notifications, requests and submissions required and that these documents are precise, complete, opportune, legible, dated and identify the study. [151]

13. Revise the precision and that the data of the case report formats, source documents and other records related with the study are complete, maintaining correlation among themselves. [151]

14. Determine if all the adverse events are appropriately reported within the time periods required by the Good Clinical Practices, the protocol, the Ethics Institutional Review Board, the sponsor and the applicable regulatory requirements. [151]

15. Determine if the investigator preserves the documents essential for the conduction of the study. [151]

16. Communicate deviations of the protocol, standard operative procedures, good clinical practices and applicable regulatory requirements to the investigator and take the appropriate measures to prevent a recurrence of the detected deviations. [151]

17. All the processes shall be done according to the procedures of the sponsor. [151]

14.2. Reports on monitoring

The monitor shall present a report in writing to the sponsor after each visit to the

place where the study is carried out or a communication related with the study. This report shall include the date, place, name of the monitor and name of the investigator or other individuals who have been contacted.

In the reports will be included studies in summary of what the monitor reviewed as well as declarations regarding findings, significant deviations, conclusions, actions taken or to be taken and the actions recommended to guarantee compliance.

All of the above shall be documented.

15. AUDITS

The sponsor may perform audits as implementation of the assurance of quality. Besides, any regulatory authority may perform them, in which case the sponsor must be notified. [151]

For the audits on part of the sponsor, it must be understood that these are independent and separate from the routine monitoring and quality control. [151]

In these, the conduction of the study and the compliance with the protocol, standard operative procedures, good clinical practices and applicable regulatory requirements will be evaluated. [151]

The sponsor shall designate persons to perform audits that are independent of the clinical studies or systems. [151]

The sponsor must make sure that the auditors are qualified based on their training and experience to conduct audits appropriately. The aptitudes of the auditor must be documented. [151]

The following are procedures of auditing:

Conformity of the auditing: shall be with the written procedures of the sponsor about what to audit, how to audit, frequency of audits and the form and content of the reports of an auditing. [151]

Plan and procedures of auditing: shall be guided by the importance of the study for submitting to the regulatory authorities, the number of subjects in the study, the type and complexity of the study, the level of risk for the subjects of the

study and any issues identified. [151]

All the observations and findings of the auditing must be documented. [151]

Preservation of the independence of the audit: to comply with this, the regulatory authorities must not routinely request reports of same. They may do it in specific cases when there is evidence of a serious non-compliance of the Good Clinical Practices or in the course of legal procedures. [151]

Certificate of auditing: Shall be provided by the sponsor when required by the law or applicable regulation. [151]

In the case of auditing by regulatory authorities, the main investigator shall immediately notify Valeant Pharmaceuticals International any inspection programmed by the competent authorities and deliver without delay the copies of the inspection reports.

16. NON-COMPLIANCE

Non-compliance with the protocol, standard operative procedures, good clinical practices and/or applicable regulatory requirement(s) by an investigator/institution or by the member(s) of the sponsor's personnel, shall conduct an immediate action by the sponsor for assurance of compliance. [151]

If the monitoring, and/or auditing identifies a serious and persistent non-compliance on part of the investigator or institution, the sponsor shall terminate the participation of the investigator and/or institution in the study. In this case, the sponsor shall notify the regulatory authorities as soon as possible. [151]

17. SUSPENSION OF THE STUDY

Valeant Pharmaceuticals International reserves the right of suspending the study totally or partially at any moment for administrative or scientific reasons that so require.

This study may be suspended temporarily or definitively by duly justified decision of the Sponsor, Main Investigator, the CIEI or the Health Ministry.

The causes may be diverse, among others the frequency and/or type of adverse events, new information of the drug that directly affects the safety of the patients or the implementation of the study or by a substantiated decision of the Ethics Institutional Review Board and/or COFEPRIS.

In case of temporary suspension the patiens selected for the study shall be informed immediately and an appointment will be scheduled to make known the definitive decision of the course of the study. In case of definitive suspension, the Main Investigator will inform of this decision and will determine the application of the procedures of withdrawal of the study.

If the suspension of the study is by decision of the Sponsor and/or the Main Investigator, the decision shall be documented between both of them and informed in writing, giving a detailed explanation of the temporary or definitive suspension to the Ethics Institutional Review Board.

If for any reason the treatment is suspended before the completion of the active phase, the reason shall be reported in the case report form, with a detailed description of the event.

If the treatment is suspended because of intolerance, the patient must not be restored and it must be reported as an adverse event, and also be monitored until the outcome.

If the suspension of the treatment was due to an adverse event, the patient shall continue with follow-up by the investigator during the time he/she deems necessary.

18. DEVIATIONS FROM PROTOCOL

Every process which isn't contemplated in this protocol and results during the study shall be notified to the Institutional Review Board and to the Sponsor.

When it is necessary to implement a deviation or modification to the protocol to eliminate an immediate risk or risks, Valeant Pharmaceuticals International shall be notified as soon as possible.

It is necessary to count with the approval/favorable opinion of the Medical Direction of Valeant Pharmaceuticals International to establish said deviation or modification in an operative and sequential manner.

The main Investigator shall not implement any deviation or modification of the protocol without the previous review and approval of said amendment, which shall be duly documented, excepting those necessary to eliminate an immediate potential risk(s) to the subjects of the study.

Any significant deviation from the protocol shall be documented in the clinical record and Case Report Form.

19. AMENDMENTS

All the revisions to the protocol shall be discussed with the sponsor.
Any amendment to the protocol must be approved by the Institutional Review Board and by the Federal Commission for Protection from Health Risks (COFEPRIS).

Once authorized, the participants in the study must be informed about the modifications and apply the due informed consent for those that apply.

20. ETHICAL ASPECTS

This study shall be implemented in conformity with the ethical principles that originate in the Good Clinical Practices (GCP), [151] the ethical guidelines issued by the 64th World Medical Assembly, Fortaleza, Brazil, October 2013, of the Helsinki Declaration [153], the General Health Law, [L6] the Regulations of the General Health Law on Matters of Research for Health [L7] and the Mexican Official Norm NOM-012-SSA3-2012, which establishes the criteria of research projects in human beings. [L5] According to what is established in these laws, this research implies a risk above the minimum. All the personnel involved in this study and who deals with patients must have verifiable knowledge about ethics in research and the processes to implement for the research in humans. Thereby, they must have verifiable knowledge about the good clinical practices.

The sponsor may request this documentation on part of the main investigator and delegate personnel.

In light of every process the ethical principles for the medical reseaeches in human beings must be safeguarded. The sponsor shall verify that the personnel dealing with the human subject has verifiable knowledge of the general principles of ethics in researches in human beings, risks, costs and benefits of the protocol of research in human beings, groups and vulnerable persons, shall have knowledge about the scientific background of the study, the documents to apply for submitting or reporting to the committee of ethics in research, the privacy and confidentiality of the subject, that the personnel that applies the informed consent be competent and implements it in an adequate manner and has the knowledge that the publishing and diffusion of the results requires previous authorization of the sponsor.

The personnel that performs functions at the site or who may be under any circumstance that positions them as ethically vulnerable, may not be included in this study. [153]

21. MATERIAL RESOURCES AND FINANCING

Valeant Pharmaceuticals International will be responsible of providing the financing so the clinical trial is implemented under the postulates of this protocol. Every omission to be considered her that is detected on part of the sponsor and results in a secondary expense, shall be notified to Valeant Pharmaceuticals International and they will evaluate that it isn't cohesive for the investigator or the patient. Also, the economic rectification is determined or not.

The investigational product to use and the material that Valeant Pharmaceuticals International provides to the site shall be returned to the sponsor; unless there is another indication on part of the sponsor.

ANY SEVERE ADVERSE EVENT, INCLUDING DEATH DUE TO ANY CAUSE THAT OCCURS DURING THE RESEARCH, BE IT RELATED OR NOT WITH THE INVESTIGATIONAL MEDICATION, SHALL BE IMMEDIATELY REPORTED TO THE MEDICAL DIRECTOR, MANAGER OF PHARMACOVIGILANCE AND CLINICAL RESEARCH COORDINATOR FOR MEXICO AND LATIN AMERICA OF VALEANT PHARMACEUTICALS INTERNATIONAL.

MEDICAL DIRECTOR, MEXICO AND LATIN AMERICA

DR. VENTURA AGUIRRE ROJAS

MANAGER OF PHARMACOVIGILANCE, LATIN AMERICA

M.C. SAR ALIK PEDRAJO ZENTENO

RESPONSIBLE OF PHARMACOVIGILANCE, MEXICO

DR. PAOLA ANDREA MARTÍNEZ SERRANO

CLINICAL RESEARCH COORDINATOR, MEXICO AND LATIN AMERICA

DR. FRANCISCO JAVIER FIGUEROA VALLEJO

ADDRESS: CALZADA TLALPAN 2021
COL. PARQUE SAN ANDRES
C.P. 04040
CIUDAD DE MÉXICO
MÉXICO
TEL: (55) 5062 4190
TEL 24 HORAS: 044(55) 23009656, 044 (55) 43731344
FAX: (55) 5062 4172
E-MAIL:
farmacovigilancia.mexico@valeant.com
francisco.figueroa@valeant.com

BIBLIOGRAPHIC REFERENCES

1. World Health Organization: Global status report on non-communicable diseases 2014. (Acceso mayo 2017). Disponible en: http//www.who.int/healthinfo/global.

2. Diagnóstico y tratamiento de dislipidemias (hipercolesterolemia) en el adulto. México: Secretaría de Salud; 03 de noviembre de 2016.

3. Bou MS, Goldberg AC. Cardiovascular risk reduction: the future of cholesterol lowering drugs. Current Opinion in Pharmacology. 2016 Apr;27:62-9.

4. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FD, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WM; Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts): Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). European Heart Journal. 2016.

5. Rosenson RS, Baker SK, Jacobson TA, Kopecky SL, Parker BA. An assessment by the Statin Muscle Safety Task Force: 2014 update. The National Lipid Association's Muscle Safety Expert Panel. Journal of Clinical Lipidology. 2014 May-Jun;8(3 Suppl):S58-71.

6. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S1-45.

7. Lee BJ, Lin JS, Lin YC, Lin PT. Effects of L-carnitine supplementation on lipid profiles in patients with coronary artery disease. Lipids in Health and Disease. 2016;15(107): 1-8.

8. Chawla A, Repa JJ, Evans RM, Mangelsdorf DJ. Nuclear receptors and lipid physiology: opening the X-files. Science. 2001;294(5548): 1866-70.

9. Botham KM, Mayes PA. Síntesis, transporte y excreción del colesterol. En: Rodwell VW, Bender DA, Botham KM, Kenelly PJ, Weil PA. Harper Bioquímica Ilustrada. 28 ed. México: Mc Graw Hill; 2009. p: 224-243.

10. Botham KM, Mayes PA. Transporte y almacenamiento de lípidos. En: Rodwell VW, Bender DA, Botham KM, Kenelly PJ, Weil PA. Harper Bioquímica Ilustrada. 28 ed. México: Mc Graw Hill; 2009. p: 212-223.

11. Barter PJ, Rye KA. Relationship between the concentration and antiatherogenic activity of high-density lipoproteins. Current Opinion in Lipidology. 2006; 17(4): 399-403.

12. Cooney MT, Dudina A, De Bacquer D, Wilhelmsen L, Sans S, Menotti A, et al. HDL cholesterol protects against cardiovascular disease in both genders, at all ages and at all levels of risk. Atherosclerosis. 2009;206(2): 611-6.

13. Teoh YP. Advances in the diagnosis and management of dyslipidemia. Drug Review. 2015;26(4):21- 25.

14. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GB, McPherson R, et al. 2012 update of the Canadian Cardiovascular Society guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. Canadian Journal of Cardiology. 2013 Feb;29(2):151-67.

15. Wadhera RK, Steen DL, Khan I, Giugliano RP, Foody JM. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. Journal of Clinical Lipidology. 2016 May-Jun; 10(3):472-89.

16. Grundy SC, Becker D, Clark LT, Cooper RS, Denke MA, Howard WJ, et al. Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Circulation. 2002 Dec 17; 106(25):3143-421.

17. Aguilar CA, Canizales S, Rojas R, García E, Olaiz G, Gómez FJ, Tusié MT. Colaboraciones exitosas entre tres instituciones mexicanas en el estudio de las dislipidemias, la obesidad y la diabetes. Gaceta Médica de México. 2007;143(5):355-364.

18. Escobedo J, Pérez RJ, Schargrodsky H, Champagne B. Prevalencia de dislipidemias en la ciudad de México y su asociación con otros factores de riesgo cardiovascular. Resultados del estudio CARMELA. Gaceta Médica de México. México, 2014;(150):128-36.

19. Aguilar Salinas CA, Zamora M, Gómez Díaz RA, Mehta R, Gómez Pérez FJ, Rull JA. Familial combined hyperlipidemia: controversial aspects of its diagnosis and pathogenesis. Seminars in Vascular Medicine. 2004 May;4(2):203-9.

20. Olaiz Fernández G, Rivera-Dommarco J, Shamah-Levy T, Rojas R, Villalpando-Hernández S, Hernández-Avila M, Sepúlveda-Amor J. Encuesta Nacional de Salud y Nutrición 2006. Cuernavaca, México: Instituto Nacional de Salud Pública, 2006.

21. Arellano O, Barquera S, Barriguete J, Lara A, López A, Rosas M. Protocolo clínico para el diagnóstico y tratamiento de las Dislipidemias. CENAPRECE, Secretaria de Salud, D.F. México. 2da. Ed. 2011 (Acceso mayo 2017). Disponible en: www.cenaprece.salud.gob.mx/programas/interior/adulto/descargas/pdf/ProtocoloClinico_diagnóstico_tratamiento_dislipidemias.pdf.

22. Badzioch MD, Igo RP, Gagnon F, Brunzell JD, Krauss RM, Motulsky AG, et al. Low-density lipoprotein particle size loci in familial combined hyperlipidemia: evidence for multiple loci from a genome scan. Arteriosclerosis, Thrombosis, and Vascular Biology. 2004;24(10):1942-50.

23. Sniderman AD, Cabezas MC, Ribalta J, Carmena R, Bruin TWA, de Graaf J, et al. A proposal to redefine familial combined hyperlipidaemia -- third workshop on FCHL held in Barcelona from 3 to 5 May 2001, during the scientific sessions of the European Society for Clinical Investigation. European Journal of Clinical Investigation. 2002;32(2):71-3.

24. Veerkamp MJ, de Graaf J, Bredie SJH, Hendriks JCM, Demacker PNM y Stalenhoef AFH. Diagnosis of familial combined hyperlipidemia based on lipid phenotype expression in 32 families: results of a 5-year follow-up study. Arteriosclerosis, Thrombosis, and Vascular Biology. 2002;22(2):274-82.

25. Sullivan DR, Craig IH, van Bockxmeer F, Watts GF. INTERIM Guidelines for the Diagnosis and Management of Familial Hypercholesterolemia. Heart, Lung and Circulation. 2012; 21:159-162.

26. Alonso R, Castillo S, Civeira F, Puzo J, de la Cruz JJ, Pocoví M, et al. Heterozygous familial hypercholesterolemia in Spain. Description of 819 non related cases. Medicina Clínica (Barcelona). 2002;118(13):487-92.

27. Blom DJ, O´Neill FH, Marais AD. Dysbetalipoproteinaemia by Plasma Cholesterol and Apolipoprotein B Concentrations. Clinical Chemistry. 2005;51(5):904-7.

28. Cohen JC, Boerwinkle E, Mosley TH, Hobbs HH. Sequence variations in PCSK9, low LDL, and protection against coronary heart disease. New England Journal of Medicine. 2006;354(12):1264-72.

29. Abifadel M, Varret M, Rabes JP, Allard D, Ouguerram K, Devillers M, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nature Genetics. 2003;34(2):154-6.

30. Garcia CK, Wilund K, Arca M, Zuliani G, Fellin R, Maioli M, et al. Autosomal recessive hypercholesterolemia caused by mutations in a putative LDL receptor adaptor protein. Science. 2001; 292(5520): 1394-8.

31. Vodnala D, Rubenfire M, Brook RD. Secondary causes of dyslipidemia. The American Journal of Cardiology. 2012 Sep 15;110(6):823-5.

32. Rosenson RS. Treatment of lipids (including hypercholesterolemia) in secondary prevention. This topic last updated: Apr 04, 2016. [Acceso mayo 2017]. Disponible en URL:http//www.uptodate.com.

33. Vaziri ND. Disorders of lipid metabolism in nephrotic syndrome: mechanisms and consequences. International Society of Nephrology. Publicación electronica 26 Abr 2016.

34. de Jager DJ, Grootendorst DC, Jager KJ, van Dyk PC, Tomas LMJ, Ansell D, et al. Cardiovascular and noncardiovascular mortality among patients starting dialysis. American Medical Association. 2009; (302):1782–9.

35. Glass TR, Ungsedhapand C, Wolbers M, Weber R, Vernazza PL, Rickenbach M, et al. Prevalence of risk factors for cardiovascular disease in HIV-infected patients over time:

the Swiss HIV Cohort Study. HIV Medicine. 2006;(7):404–10.

36. Reiner Ž, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, et ak. Clinical Practice Guidelines Committee of the Spanish Society of Cardiology. ESC/EAS Guidelines for the management of dyslipidaemias. Revista Española de Cardiología. 2011 Dec;64(12):1168.e1-1168.e60.

37. Bays HE, Jones PH, Orringer CE, Brown WV, Jacobson TA. National Lipid Association Annual Summary of Clinical Lipidology 2016. Journal of Clinical Lipidology. 2016 Jan-Feb;10(1 Suppl):S1-S43.

38. Levenson JW, Skerrett PJ, Gaziano JM. Reducing the global burden of cardiovascular disease: the roles of risk factors. Preventive Cardiology. 2002;(5):188-99.

39. Goff DC Jr, Lloyd-Jones DM, Bennett G Coady S, D´Agostino RB Sr, Gibbons R, Greenland P, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk,: a report of the American College of Cardiology/American Heart Assocaition Task Force on Practice Guidelines. ACC/AHH Prevention Guidelines. Circulation. 2014;129(suppl 2): S49-S73.

40. Austin MA, McKnight B, Edwards KL, Bradley CM, McNeely MJ, Psaty BM, et al. Cardiovascular disease mortality in familial forms of hypertriglyceridemia: A 20-year prospective study. Circulation. 2000; 101(24): 2777-82.

41. Blair HC, Sepulveda J, Papachristo DJ. Nature and Nurture in Atherosclerosis: The Roles of Acylcarnitine and Cell Membrane- Fatty Acid Intermediates, Vascular Pharmacology. 2016 Mar; (78): 17-23. Publicación electronica 30 Jun 2015.

42. Detección y Estratificación de factores de riesgo cardiovascular. México: Secretaría de Salud, 2010.

43. Stamler J, Wentworth D, Neaton JD. The Multiple Risk Factor Intervention Trial (MRFIT)--importance then and now. American Medical Association. 2008;300(11):1343-5.

44. OECD. Organization for Economic Cooperation and Development. Cardiovascular disease and diabetes: Policies for better health and quality of care. In series: OECD Health Policies Studies. June 2015. (Acceso mayo 2017). Disponible en: http://www.oecd.org/health/cardiovascular-diseaseand- diabetes-policies-for-better-health-and-quality-of-care-9789264233010-en.htm.

45. Morán S, Rodríguez-Leal G, Ramos M, Duque MX, Guevara L, Uruibe M. Concentración de colesterol plasmático; prevalencia y factores asociados con hipercolesterolemia. Revista Médica Sur. 2007;7(1): p. 6-9.

46. Acosta B, Escobedo J. High burden of cardiovascular disease risk factors in Mexico: An epidemic of ischemic heart disease that may be on its way? American Heart Journal. 2010;160(2):230-6.

47. Shafer EJ, Levy RI, Pathogenesis and management of lipoprotein disorders. New England Journal of Medicine. 1985 May 16;312(20):1300-10.

48. Gutiérrez JP, Rivera-Dommarco J, Shamah-Levy T, Villalpando-Hernández S, Franco A, Cuevas-Nasu L, Romero-Martínez M, Hernández-Ávila M. Encuesta Nacional de Salud y Nutrición 2012. Resultados Nacionales. Cuernavaca, México: Instituto Nacional de Salud Pública (MX), 2012.

49. Stamler J, Wentworth D, Neaton JD. The Multiple Risk Factor Intervention Trial (MRFIT)-Importance Then and Now. American Medical Asociation. 2008; 300(11):1343-1345.

50. Lloyd-Jones DM, Leip EP, Larson MG, DÁgostino RB, Beiser A, Wilson PWF, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation.2006; 113(6):791-8.

51. Cholesterol Treatment Trialists (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.

52. Cooper A, Nherera L, Calvert N, O´Flynn N, Turnbull N, Robson J, et al. Clinical Guidelines and Evidence Review for Lipid prevention of cardiovascular disease. London: National Collaborating Centre for Priary Care and Royal College of General Practitioners; 2008. Última modificación: marzo de 2010.

53. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. Lancet Diabetes Endocrinology. 2015 May;3(5):339-55.

54. Bays HE. A lipidologist perspective of global lipid guidelines and recommendations, part 1: Lipid treatment targets and risk assessment. Journal of Clinical Lipidology. 2016 Mar-Apr;10(2):228-39.

55. Bouhairie VE, Goldberg AC. Familial Hypercholesterolemia. Endocrinology Metabolism Clinics of North America. 2016 Mar;45(1):1-16.

56. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ; Familial hypercholesterolemias: prevalence, genetics, diagnosis and screening recommendations from the National Lipid Association Expert Panel on Familial Hypercholesterolemia. National Lipid Association Expert Panel on Familial Hypercholesterolemia. Journal of Clinical Lipidology. 2011 Jun;5(3 Suppl):S9-17.

57. Miller M, Cannon CP, Murphy SA, Qin J, Ray KK, Braunwald E. Impact of triglyceride levels beyond low-density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial. Journal of the American College of Cardiology. 2008;51(7):724-30.

58. Zhao D, Liu J, Xie W, Qi Y. Cardiovascular risk assessment: a global perspective. Nature Reviews Cardiology. 2015 May;12(5):301-311.

59. Sheridan SL, Viera AJ, Krantz MJ, Ice CL, Steinman LE, Peters KE, et al. The effect of giving global coronary risk information to adults: a systematic review. Archives of Internal Medicine. 2010 Feb 8;170(3):230-9.

60. Rubinstein A, Terrasa S. Medicina Familiar y Práctica Ambulatoria. 2da Ed. Madrid España. Médica Panamericana. 2006.

61. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. 2014; 29(supll2):S102-S138.

62. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014 Jun 24;129(25 Suppl 2):S76-99.

63. Food and Agriculture Organization of United Nations. Fats and fatty acids in human nutrition: Report of an expert consultation. FAO Food and Nutrition Paper No. 91". Ginebra, Swiss, 2010.

64. Kraus WE, Houmard JA, Duscha BD, Knetzger KJ, Wharton MB, McCartney JS, et al. Effects of the amount and intensity of exercise on plasma lipoproteins. New England Journal of Medicine. 2002;347: 1483–92.

65. Haney EM, Huffman LH, Bougatsos C, Freeman M, Fu R, Steiner RD, et al. Screening and treatment for lipid disorders in children and adolescents: systematic evidence review for the US Preventive Services Task Force. Pediatrics. 2007;120(1):189-214.

66. Avis HJ, Vissers MN, Stein EA, Wijburg FA, Trip MD, Kastelein JJP, et al. A systematic review and meta-analysis of statin therapy in children with familial hypercholesterolemia. Arteriosclerosis, Thrombosis, and Vascular Biology. 2007;27(8):1803-10.

67. Robinson JG, Wang S, Jacobson TA. Meta-analysis of comparison of effectiveness of lowering apolipoprotein B versus low-density lipoprotein cholesterol and nonhigh-density lipoprotein cholesterol for cardiovascular risk reduction in randomized trials. American Journal of Cardiology. 2012;110(10):1468-76.

68. Zárate A, Apolinar M, Basurto L, De la Chesnaye E, Saldívar I. Colesterol y atherosclerosis. Consideraciones históricas y tratamiento. Archivos de Cardiología de México. 2016 Abr-Jun;86(2):163-9.

69. Bays HE, Cohen DE, Chalasani N, Harrison SA, The National Lipid Association's Statin Safety Task Force. An assessment by the Statin Liver Safety Task Force: 2014 update. Journal of Clinical Lipidology. 2014 May- Jun;8(3 Suppl):S47-57.

70. Mata P, Alonso R, Ruiz A, Gonzalez-Juanatey JR, Badimón L, Díaz-Díaz JL, et al. Diagnóstico y tratamiento de hipercolesterolemia familiar en España: Documento de Consenso. Atención Primaria. 2015 Jan- Feb;41(1):24-33.

71. ADA. American Diabetes Association. Cardiovascular Disease and Risk Management. Diabetes Care. 2016 Jan;39(Supplement 1):S1-S2.

72. Jacobson TA, Maki KC, Orringer CE, Jones PH, Kris-Etherton P, Sikand G, et al; NLA Expert Panel. National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia: Part 2. Journal of Clinical Lipidology. 2015 Nov-Dec; 9(6 Suppl):S1-122.e1.

73. Ble A, Hughes PM, Delgado J, Masoli JA, Bowman K, Zirk-Sadowski J, et al. Safety and Effectiveness of Statins for Prevention of Recurrent Myocardial Infarction in 12156 Typical Older Patients: A Quasi-Experimental Study. Journals of Gerontology: Medical Sciences. 2016 May 4;72(2):243-50.

74. Lloyd-Jones DM, Morris PB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, et al. 2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. Journal of the American College of Cardiology. 2016 Mar 28. Doi:10.1016/j.jacc.2016.03.519.

75. Kellick KA, Bottorff M, Toth PP. A clinician's guide to statin drug-drug interactions. Journal of Clinical Lipodology. 2014;(8):S30-S46.

76. Paiva H, Thelen KM, Van Coster R, Smet J, De Paepe B, Mattila KM et al. High-dose statins and skeletal muscle metabolism in humans: a randomized, controlled trial. Clinical Pharmacology and Therapeutics. 2005;(78):60–8.

77. Parker BA, Capizzi JA, Grimaldi AS, Clarkson PM, Cole SM, Keadle J, et al. Effect of statins on skeletal muscle function. Circulation. 2013;(127):96–103.

78. Apostolopoulou M, Corsini A, Roden M. The role of mitocondria in statind-induced myopathy. European Journal of Clinical Investigation. 2015; 45(7):745–54.

79. Sattar N, Preiss D, Murry HM, Weish P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trial. Lancet. 2010 feb 27;375(9716):735-42.

80. Stitziel NO, Won HH, Morrison AC, Peloso GM, Do R, Lange LA, et al. Inactivating mutations in NPC1L1 and protection from coronary heart disease. New England Journal of Medicine. 2014;(371):2072-82.

81. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al; IMPROVE-IT Investigators. Ezetimiba Added to Statin Therapy after Acute Coronary Syndromes. New England Journal of Medicine. 2015 Jun 18;372(25):2387-97.

82. Ross S, D'Mello M, Anand SS, Eikelboom J, Stewart AF, Samani NJ, et al. Effect of Bile Acid Sequestrants on the Risk of Cardiovascular Events: A Mendelian Randomization Analysis. Circulation: Cardiovascular Genetics. 2015 Aug;8(4):618-27.

83. Schoonjans K, Martin G, Staels B, Auwerx J. Peroxisome proliferator-activated receptor (PPAR) in mediating the effects of fibrates and fatty acids on gene expression. Journal of Lipid Research. 1996 37:907-925.

84. Stanulovic V, Deric M, Popovic J. Clinical trials of statins and fibrates --a meta-analysis. Medicinsky Pregled. 2006;59(5-6): p. 213-8.

85. Vogt A. Hyperlipoproteinemia-apheresis and emergin therapes. Clinical Research in Cardiology. 2017;12(Suppl1):12-17.

86. Navarese EP, Kolodziejczak M, Schulze V, Gurbel PA, Tantry U, Lin Y, et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. Annals of Internal Medicine. 2015 Jul 7;163(1):40-51.

87. Brass EP. Supplemental carnitine and exercise. American Journal of Clinical Nutrition. 2000;72(Suppl2):618-23.

88. Compound Summary for L. Carnitine, U.S. National Library of Medicine, National Center for Biotechnology Iformation, NIH. Fecha de Creación 01 Jun 2005, última modificación 12.febrero 2017.

89. Thomson/Micromedex. Drug Information for the Health Care Professional. Greenwood Village, CO. 2007;(1):1819.

90. Coates PM, Blackman MR, Cragg GM, Levine M, Moss J, White JD. (Ed), Encyclopedia of Dietary Supplements. Marcel Dekker, New York, NY, p. 76-78 (2005).

91. Serban MC, Sahebkar A, Mikhaidilis DP, Toth PP, Jones SR, Muntner P, et al. Impact of L-carnitine on plasma lipoprotein (a) concentrations: A systematic review and meta-analysis of randomized controlled trials. Scientific reports. 6, 19188; doi: 10.1038/srep19188 (2016).

92. Naini AE, Sadeghi M, Mortazavi M, Moghadasi M, Harandi AA. Oral carnitine supplementation for dyslipidemia in chronic hemodialysis patients. Saudi Journal of Kidney Diseases and Transplantation. 2012;23:484–8.

93. Naini AE, Moradi M, Mortazavi M, Amini Harandi A, Hadizadeh M, Shirani F, et al. Effects of oral L-carnitine supplementation on lipid Profile, anemia, and quality of life in chronic renal disease patients under hemodialysis: a randomized, double-blinded, placebo-controlled trial. Journal of Nutrition and Metabolism. 2012; 2012:510483.

94. NIH/ODS; DIetary Supplement Fact Sheets on Carnitine- 15 jun 2006.

95. Ferrari R, Merli E, Cicchitelli G, Mele D, Fucili A, Ceconi C. Therapeutic Effects of L-carnitine and Propionyl-L-carnitine on Cadiovascular Diseases: A Review. New York Academy of Sciences. 2004;1033:79-91.

96. McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2002. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2002 (Plus Supplements), p. 1762.

97. Tiwari A, Bansal V, Chugh A, Mookhtiar K. Statins and myotoxicity: a therapeutic limitation. Expert Opinion on Drug Safety. 2006;(5):651-66.

98. Anfossi G, Massucco P, Bonomo K, Trovati M. Prescription of statins to dyslipidemic patients affected by liver diseases: a subtle balance between risks and benefits. Nutrition, Metabolism and Cardiovascular Diseases. 2004;(14):215-24.

99. McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2002. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2002 (Plus Supplements), p. 1763.

100. McEvoy, G.K. (ed.). American Hospital Formulary Service- Drug Information 2002. Bethesda, MD: American Society of Health-System Pharmacists, Inc. 2002 (Plus Supplements), p. 1762-63.

101. Chatzizisis YS, Koskinas KC, Misirli G, et al. Risk factors and drug interactions predisposing to statin-induced myopathy: implications for risk assessment, prevention and treatment. Drug Safety. 2010;(33):171-87.

102. Arora R, Liebo M, Maldonado F. Statin-induced myopathy: the two faces of Janus. Journal of Cardiovascular Pharmacology and Therapeutics. 2006;(11):105-12.

103. Owczarek J, Jasinska M, Orszulak-Michalak D. Drug-induced myopathies. An overview of the posible mechanisms. Pharmacological Reports. 2005;(57):23-34.

104. Hardman, J.G., L.E. Limbird, P.B. Molinoff, R.W. Ruddon, A.G. Goodman (eds.). Goodman and Gilman's The Pharmacological Basis of Therapeutics. 11th ed. New York, NY: McGraw-Hill, 2006. p. 951-52.

105. Armitage J. The safety of statins in clinical practice. Lancet. 2007;(370):1781-90.

106. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. British Medical Journal. 2003;(326):1423-9.

107. Arca M. Atorvastatin. A safety and tolerability profile. Drugs. 2007;67(Suppl 1):63-9.

108. Sever PS, Dahlof B, Poulter NR, Wedel H, Beevers G, Culfield M, et al. ASCOT investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm (ASCOT-LLA): a multicenter randomised controlled trial. Lancet. 2003;(361):1149-58.

109. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone S, et al. on behalf of the CARDS investigators. Primary prevention of cardiovascular disease with

atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomized placebo-controlled trial. Lancet. 2004;(364):685-96.

110. Schwartz GG, Olsson AG, Ezekowitz MD, Ganz P, Oliver MF, Waters D, et al.; Myocardial ischemia reduction with aggressive cholesterol lowering (MIRACL) Study Investigators. Effects of atorvastatin on early recurrent ischemic events in acute coronary syndromes: the MIRACL study: a randomized controlled trial. Journal of American Medical Association. 2001;(285):1711-8.

111. Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al.; Pravastatin or atorvastatin evaluation and infection therapy-thrombolysis in myocardial infarction 22 investigators. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. New England Journal of Medicine. 2004; (350):1495-504.

112. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart JC, et al.; For the Treating to New Targets (TNT) Investigators. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. New England Journal of Medicine. 2005;(352):1425-35.

113. Athyros VG, Tziomalos K, Karagianis A, Michailidis DP. Atorvastatin: safety and tolerability. Expert Opinion. Drug Safety Evaluation. 2010;9(4):667-74.

114. Restrepo CA, Castaño JA. Eficacia y seguridad de la atorvastatina en dosis altas en pacientes con enfermedad renal crónica estadio 5 en terapia de diálisis peritoneal. Revista Colombiana de Cardiología. 2014;21(6):382-91.

115. HSDB®, Hazardous Substances Data Bank, Compiled by the National Library of Medicine, an agency of the Department of Health and Human Services. It contains copyrighted materials. All Rights Reserved. , I.c.c.m.A.R. Reserved., Editor. 1988-2012.

116. Parke-Davis, Lipitor® (atorvastatin calcium) tablets prescribing information. Nov 2007: New York, NY.

117. Escobar C, Echarri R, Barrios V. Relative safety profiles of high dose statin regimens. Vascular Health and Risk Management. 2008;(4):525-33.

118. Newman CB, Palmer G, Silbershatz H, Szarek M. Safety of atorvastatin derived from analysis of 44 completed trials in 9,416 patients. American Journal of Cardiology. 2003;(92):670-6.

119. Newman C, Tsai J, Szarek M, Luo D, Gibson E. Comparative safety of atorvastatin 80 mg versus 10 mg derived from analysis of 49 completed trials in 14,236 patients. American Journal of Cardiology. 2006;(97):61-7.

120. Athyros VG, Papageorgiou AA, Symeonidis AN, Didangelos TP, Pehlivanidis AN, et al.; GREACE Study Collaborative Group. Early benefit from structured care with atorvastatin in patients with coronary heart disease and diabetes mellitus. Angiology. 2003;(54):679-90.

121. Patel SS, Kimmel PL, Singh A. New clinical practice guidelines for chronic kidney disease: a framework for K/DOQI. Seminars in Nephrology. 2002;(22):449-58.

122. Wanner C, Krane V, Marz W, Olschewki M, Mann JFE, Ruf G, et al.; German Diabetes and Dialysis Study Investigators. Atorvastatin in patients with type 2 diabetes mellitus undergoing hemodialysis. New England Journal of Medicine. 2005;(353):238-48.

123. MICROMEDEX Thomson Health Care. USPDI - Drug Information for the Health Care Professional. 22nd ed. Volume 1. MICROMEDEX Thomson Health Care, Greenwood Village, CO. 2002. Content Reviewed and Approved by the U.S. Pharmacopeial Convention, Inc., p.1653.

124. Carter AL, Abney TO, Lapp DF. Biosynthesis and metabolism of carnitine. Journal of Child Neurology. 1995;10(Suppl 2):S3-S7.

125. Lee MS, Lee HJ, Lee HS, Kim Y. L-carnitine stimulates lipolysis via induction of the lipolytic gene expression and suppression of the adipogenic gene expression in 3T3-L1 adipocytes. Journal of Medicinal Food. 2006;9(4):468-73.

126. Stephens FB, Constantin-Teodosiu D, Laitwaite D, Simpson EJ, Greenhaff PL. A threshold exists for the stimulatory effect of insulin on plasma L-carnitine clearance in humans. American Journal of Physiology – Endocrinology and Metabolism journal. 2007;292(2):637-41.

127. Poorabbas A, Bagdadchi J, Fallah F, Mahdavi R, Aliasgarzadeh A, Asadi Y, et al. Assessment of free L-carnitine levels in Type 2 diabetic women with and withouth complications. Asia Pacific Journal of Clinical Nutrition. 2004.;(13):s155.

128. Anuradha C. L-carnitine: implications in the treatment of the metabolic syndrome and Type 2 diabetes. Expert Review of Endocrinology and Metabolism journal. 2008;3(6):777-83.

129. Rajasekar P, Anuradha CV. Effect of L-carnitine on skeletal muscle lipids and oxidative stress in rats fed high-fructose diet. Experimental Diabetes Research. 2007: 1-8.

130. Evans AM, Fornasini G. Pharmacokinetics of L-carnitine. Clinical Pharmacokinetics. 2003;42(11):941-67.

131. Irat AM, Aktan F, Ozansoy G. Effects of L-carnitine treatment on oxidant/antioxidant state and vascular reactivity of streptozotocin-diabetic rat aorta. Journal of Pharmacy and Pharmacology. 2003;55(10):1389-95.

132. Sayed-Ahmed MM, Khattab MM, Gad MZ, Mostafa N. L-carnitine prevents the progression of atherosclerotic lesions in hypercholesterolaemic rabbits. Pharmacologial Research. 2001;44(3):235-42.

133. Derosa G, Cicero AF, Gaddi A, Mugellini A, Ciccarelli L, Fogari R. The effect of L-carnitine on plasma lipoprotein(a) levels in hypercholesterolemic patients with type 2 diabetes mellitus. Clinical Therapeutics. 2003;25:1429–39.

134. Bartel LL, Hussey JL, Shrago E. Perturbation of serum carnitine levels in human adults by chronic renal disease and dialysis therapy. American Journal of Clinical Nutrition. 1981;34:1314–20.

135. Thomson HealthCARE. Pdr FOR Nutritional Supplements. Thomson Helth Care Inc. Montvale, NJ. P. 257 (2001).

136. Abdoli N, Azarmi Y, Eghbal MA. Mitigation of statins-induced cytotoxicity and mitochondrial dysfunction by L-carnitine in freshly-isolated rat hepatocytes. Research in Pharmaceutical Sciences. 2015;10(2):143-151.

137. DiNicolantino JJ, Experts Review. CpQ10 and L-carnitine for statin mialgia? Expert Review of Cardiovascular Therapy. 2012;10(10):1329-33.

138. Galvano F,Li Volti G, Malaguarnera M, Avitabile T, Antic T, Vacante M, Malaguarnera M. Effects of simvastatin and carnitine versus simvastatin on lipoprotein(a) and apoprotein(a) in type 2 diabetes mellitus, Expert Opinion on Pharmacotherapy. 2009;10(12):1875-82.

139. Malaguarnera M, Vocant M, Motta M, Malaguarnera M, Volti GL, Galvano F. Effect of L-carnitine on the size of low-density lipoprotein particles in type 2 diabetes mellitus patients treated with simvastatin. Metabolism Clinical and Experimental. 2009; (58):1618-1623.

140. Solfrizzi V, Capurso C, Colacicco AM, DÍntrono A, Fontana C, Capurso SA, et al. Efficacy and tolerability of combined treatment with L-carnitine and simvastatin in lowering lipoprotein(a) serum levels in patients with type 2 diabetes mellitus. Atherosclerosis. 2006;(188):455-461.

141. Shojaei M, Djalali M, Khatami M, Siassi F, Eshraghian M. Effects of Carnitine and Conzyme Q10 on Lipid Profile and Serum Levels of Lipoprotein(a) in Maintenance Hemodialysis Patients ond Statin Therapy. Iranian Journal of Kidney Diseases. March 2001;5(2): 114-118.

142. Rtveladze K, Marsh T, Barquera S, Sanchez Romero LM, Levy D, Melendez G, et al. Obesity prevalence in Mexico: impact on health and economic burden. Public Health Nutrition. 2014 Jan;17(1):233-9.

143. Viera AJ, Sheridan SL. Global risk of coronary heart disease: assessment and application. American Academy of Family Physicians. 2010 Aug 1;82(3):265-74.

144. Ajufo E, Rader DJ. Recent advances in the pharmacological management of hypercholesterolaemia. Lancet Diabetes and Endocrinology. 2016 May;4(5):436-46.

145. Collins R, Reith C, Emberson J, Armitage J, Baigent C, Blackwell L, et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet. 2016;(388):2532–61.

146. Lazcano E, Salazar E, Gutiérrez P, Angeles A, Hernández A, Viramontes JL. Ensayos clínicos aleatorizados: variantes, métodos de aleatorización, análisis, consideraciones éticas y regulación. Salud Pública de México. Nov-Dic 2004;46(6):569-84.

147. Piaggio G, Elbourne DR, Pocock SJ, Stephen JWE, Altman DG, for the CONSORT Group. Reporting of Noninferiority and Equivalence Randomized Trials Extension of the CONSORT 2010 Statement. Journal of American Medical Association. 2012;308(24):2594-604.

148. Armitage P, Berry G. Statistical methods in medical research. 3rd ed. Oxford: Blackwell; 1994.

149. Rosas M, Santos LE, Magaña J, Valencia JS, Garrido M, Pérez G. Metodología para los estudios clínicos de superioridad frente a los de equivalencia y estudios de no inferioridad. Una revisión aplicada. Revista Médica del Instituto Mexicano del Seguro Social. 2016;54(3):344-53.

150. Camacho J. Tamaño de muestra en estudios clínicos. Nota estadística. Ene-mar 2008;50(1):20-21.

151. International Conference on Harmonisation, Guideline for Good Clinical Practice. Federal Register, 9 May 1997; 62 (90): 25691-709.

152. Secretaría de Salud/Comisión Nacional de Bioética. Guía nacional para la integración y el funcionamiento de los Comités de Bioética. 6 ed. México: 2016.

153. Asociación Médica Mundial, Declaración de Helsinki. Principios éticos para las investigaciones médicas en seres humanos. Fortaleza, Brasil. 64ª asamblea de octubre de 2013.

154. Altman DG. Comparability of randomized groups. Journal od the Royal Statistical Society. 1985;(34):125-136.

155. Martin JD. Algorithms for assessing the probability of an Adverse Drug Reaction, Respiratory Medicine CME. 2009; (2):63-67. ISSN 1755-0017.

156. De Vivo DC, Bohan TP, Coulter DL, Dreifuss FE, Greenwood RS, Nordli DR Jr., et al. L-carnitine supplementation in childhood epilepsy. Current perspectives. Epilepsia. 1998; (39):1216-1225.

157. Van Oudheusden LJ, Scholte HR. Efficacy of carnitine in the treatment of children with attentiondeficit hyperactivity disorder. Prostaglandins, Leukotrienes and Essential Fatty Acids. 2002; 67(1):33-38.

158. Rizos I. Three-year survival of patients with heart failure caused by dilated cardiomyopathy and Lcarnitine administration. American Heart Journal. 2000;(139):S120-S123.

159. Ellaway C, Williams K, Leonard H, Higgins G, Wilcken B, Christodoulou J. Rett syndrome: randomized controlled trial of L-carnitine. Journal of Child Neurology.1999;14(3):162-167.

160. Plioplys AV, Plioplys S. Amantadine and L-carnitine treatment of chronic fatigue syndrome. Neuropsychobiology 1997; (35):16-23.

161. Campos Y, Huertas R, Lorenzo G, Bautista J, Gutierrez E, Aparicio M. Plasma carnitine insufficiency and effectiveness of Lcarnitine therapy in patients with mitochondrial myopathy. Muscle and Nerve. 1993; 16(2):150-153.

162. Cherchi A, Lai C, Angelino F, Trucco G, Caponnetto S, Mereto PE, et al. Effects of L-carnitine on exercise tolerance in chronic stable angina: a multicenter, double blind, randomized, placebo controlled crossover study. International Journal of Clinical Pharmacology, Therapy and Toxocology. 1985; 23(10):569-572.

163. Harper P, Elwin CE, Cederblad G. Pharmacokinetics of intravenous and oral bolus doses of Lcarnitine in healthy subjects. European Journal of Clinical Pharmacology. 1988; 35(5):555-562.

164. Product Information: CARNITOR ® injection, levocarnitine injection. Sigma-Tau Pharmaceuticals, Gaithersburg, MD, 2004.

Legislative annex

[L1] Secretaría de Salud. Norma oficial mexicana NOM- 037-SSA2-2012, para la prevención, tratamiento y control de las dislipidemias. Diario Oficial de la Federación del 13 de julio de 2012.

[L2] Secretaría de Salud, Norma Oficial Mexicana NOM-030-SSA2-2009, para la prevención, detección, diagnóstico, tratamiento y control de la hipertensión arterial sistémica. Diario Oficial de la Federación del 24 de noviembre de 2009.

[L3] Secretaría de Salud, Norma Oficial Mexicana NOM-015-SSA2-2010, para la prevención, tratamiento y control de la diabetes mellitus. Diario Oficial de la Federación del 05 de agosto del 2010.

[L4] Gobierno de la República de los Estados Unidos Mexicanos, Plan Nacional de Desarrollo 2013-2018. Diario Oficial de la Federación del 20 de mayo de 2013.

[L5] Secretaría de Salud, Norma Oficial Mexicana NOM-012-SSA3-2012, Que establece los criterios de proyectos de investigación para la salud en seres humanos. Diario Oficial de la Federación del 04 de enero de 2013.

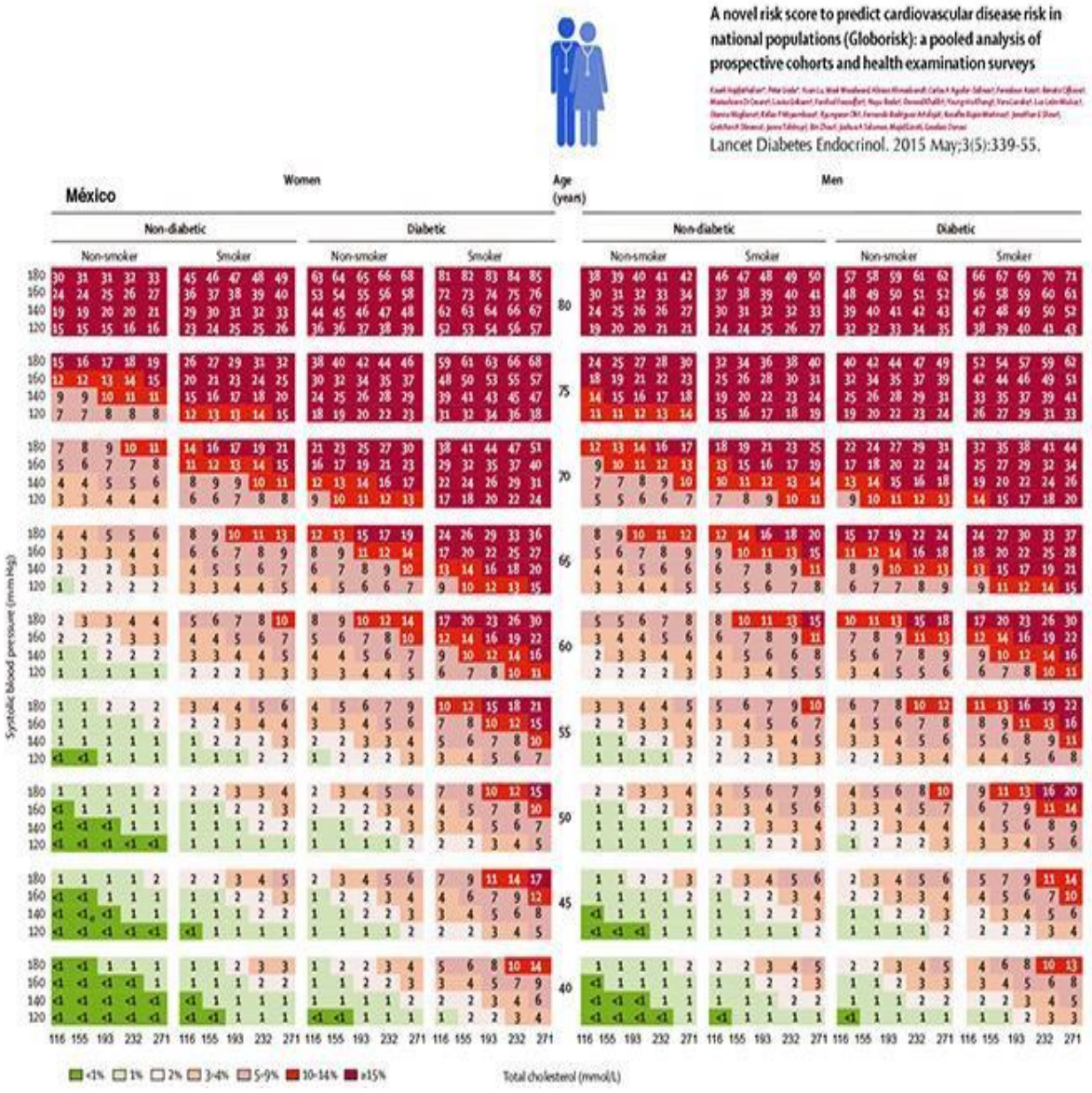
[L6] Honorable Congreso de la Unión, Ley General de Salud, Título Quinto. Investigación para la Salud, Capítulo único. Diario Oficial de la Federación del 27 de enero de 2017.

[L7] Presidencia de la República de los Estados Unidos Mexicanos, Reglamento de la Ley General de Salud en Materia de Investigación para la Salud. Diario Ofical de la Federación del 7 de febrero de 1984.

[L8] Secretaría de Salud, Norma Oficial Mexicana NOM-004-SSA3-2012, Del expediente clínico. Diario Oficial de la Federación del 29 de junio de 2012.

[L9] Secretaría de Salud, Norma Oficial Mexicana NOM-220-SSA1-2012, Instalación y operación de la farmacovigilancia. Diario Oficial de la Federación del 07 de enero de 2013.

Annex 1. Globorisk Scale



Annex 2.Control Card of Treatment of the Patient, Basal Visit

LOGO OF THE SITE OF INVESTIGATION

NAME OF THE SITE OF INVESTIGATION

"PHASE III CLINICAL STUDY TO EVALUATE THE THERAPEUTIC EFFICACY IN MEXICAN PATIENTS WITH DYSLIPIDEMIA THROUGH THE ORAL ROUTE USE OF L-CARNITINE + ATORVASTATIN COMPARED WITH ATORVASTATIN

CONTROL CARD OF TREATMENT OF THE PARTICIPANT

BASAL VISIT

NAME OF THE PARTICIPANT	
TREATMENT CODE	
NUMBER OF TABLETS PROVIDED	
DATE OF COMMENCEMENT OF TREATMENT	
DATE OF NEXT VISIT	

CONTACT DATA OF THE SITE OF INVESTIGATION:

Site telephones:

01 (Lada) XXX-XXX-X.

Mobile telephone 24/7:

Contact name: XXXX-XXX-XXX

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Basal Visit

VALEANT
Pharmaceuticals International, Inc.

Code of the Subject:
Site of Investigation:

DATA TO BE FILLED BY THE PERSONNEL OF THE SITE OF INVESTIGATION WHEN CARD IS PROVIDED

Initials of the subject	Date	Hour	Assigned treatment Code	Initials of the person who provides treatment
	___/___/____ (DD / MMM / YYYY	___:___ (HH : MM)		

Number of Tablets Provided:

66 ☐ Another amount ☐ Specify: _____

Number of Days of Treatment Provided:

33 ☐ Another amount ☐ Specify: _____

Observations:

DATA TO BE FILLED BY THE PERSONNEL OF THE SITE OF INVESTIGATION WHEN CARD IS PROVIDED

Initials, date and hour of person who receives the card:

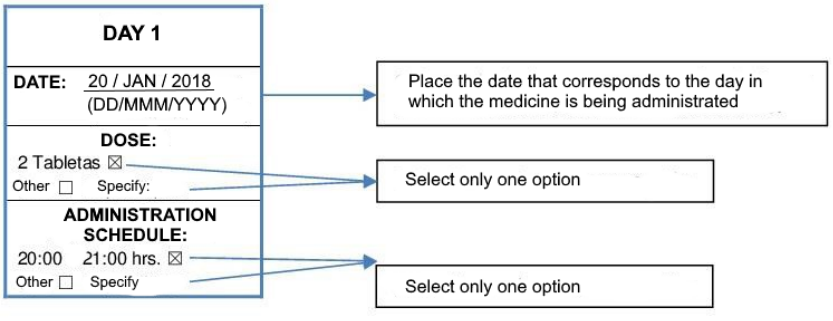
DATA TO BE FILLED BY THE PATIENT

Administration Instructions

- **At least 30 minutes before dinner.**
- **Medicine must be administered through oral route with the aid of 1 glass of water of approximately 250 ml.**
- **Always take 2 tablets only once a day, between 20:00 and 21:00 hours (8-9 o'clock at night).**
- **THE MEDICINE MUST NOT BE ADMINISTERED WITH OTHER MEDICINES**

Instruction for Filling

The filling must be made with blue ink pen, do it at the same time that the medicine is administered.
Choose only one option per square; if the option you desire isn't there, select the answer "other" and place it where it says "Specify". In the sections where you must place letters or numbers do it in print letters.
If someone assists you with the filling of the card state it in the section of observations and notify your physician in the next visit.
If a mistake is made when introducing the data don't use corrector, cross out or hide the data. Place the correction referencing with the date the mistake was made in the section of observations and notify it to the physician of the study in the next visit.



THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Basal Visit

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 1	**DAY 2**	**DAY 3**	**DAY 4**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 5	**DAY 6**	**DAY 7**	**DAY 8**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 9	**DAY 10**	**DAY 11**	**DAY 12**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 13	**DAY 14**	**DAY 15**	**DAY 16**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Basal Visit

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 17	**DAY 18**	**DAY 19**	**DAY 20**
DATE: __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 21	**DAY 22**	**DAY 23**	**DAY 24**
DATE: __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 25	**DAY 26**	**DAY 27**	**DAY 28**
DATE: __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 29	**DAY 30**	**DAY 31**	**DAY 32**
DATE: __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)	**DATE:** __/____/_____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Basal Visit

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 33			
DATE: ___/____/_____ (DD / MMM / ____)			
DOSE: 2 Tablets ☐ Other ☐ Specify:			
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:			
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Annex 3. Control Card of the Treatment of the Patient Visit 1

LOGO OF THE SITE OF INVESTIGATION

NAME OF THE SITE OF INVESTIGATION

"PHASE III CLINICAL STUDY TO EVALUATE THE THERAPEUTIC EFFICACY IN MEXICAN PATIENTS WITH DYSLIPIDEMIA THROUGH THE ORAL ROUTE USE OF L-CARNITINE + ATORVASTATIN COMPARED WITH ATORVASTATINE"

CONTROL CARD OF TREATMENT OF THE PARTICIPANT

VISIT 1

NAME OF THE PARTICIPANT	
TREATMENT CODE	
NUMBER OF TABLETS PROVIDED	
DATE OF COMMENCEMENT OF TREATMENT	
DATE OF NEXT VISIT	

CONTACT DATA OF THE SITE OF INVESTIGATION:

Telephones of the site:

01 (Lada) XXX-XXX-X.

Mobile telephone 24/7:

Contact name: XXXX-XXX-XXX

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant

VALEANT Pharmaceuticals International, Inc.

Visit 1

Code of the Subject:
Site of Investigation:

DATA TO BE FILLED BY THE PERSONNEL OF THE SITE OF INVESTIGATION WHEN CARD IS PROVIDED				
Initials of the subject	**Date**	**Hour**	**Assigned treatment Code**	**Initials of the person who provides treatment**
	____/____/____ (DD / MMM / YYYY	____:____ (HH : MM)		

Number of Tablets Provided:
66 ☐ Another amount ☐ Specify: _____

Number of Days of Treatment Provided:
33 ☐ Another amount ☐ Specify: _____

Observations:

DATA TO BE FILLED BY THE PERSONNEL OF THE SITE OF INVESTIGATION WHEN CARD IS PROVIDED

Initials, date and hour of person who receives the card:

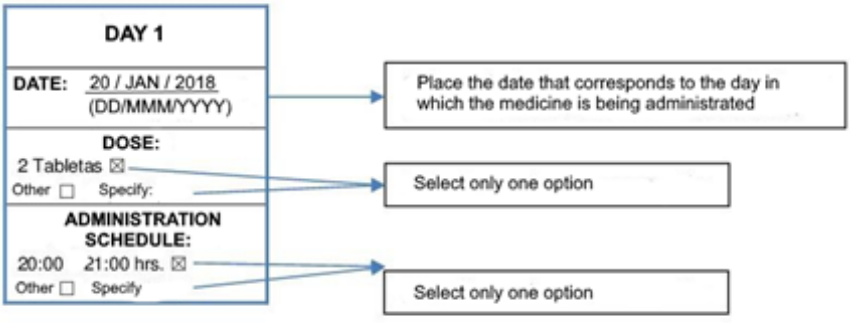
DATA TO BE FILLED BY THE PATIENT

Administration Instructions

- **At least 30 minutes before dinner.**
- **Medicine must be administered through oral route with the aid of 1 glass of water of approximately 250 ml.**
- **Always take 2 tablets only once a day, between 20:00 and 21:00 hours (8-9 o'clock at night).**
- **THE MEDICINE MUST NOT BE ADMINISTERED WITH OTHER MEDICINES**

Instruction for Filling

The filling must be made with blue ink pen, do it at the same time that the medicine is administered.
Choose only one option per square; if the option you desire isn't there, select the answer "other" and place it where it says "Specify". In the sections where you must place letters or numbers do it in print letters.
If someone assists you with the filling of the card state it in the section of observations and notify your physician in the next visit.
If a mistake is made when introducing the data don't use corrector, cross out or hide the data. Place the correction referencing with the date the mistake was made in the section of observations and notify it to the physician of the study in the next visit.



THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant
Visit 1

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 1	**DAY 2**	**DAY 3**	**DAY 4**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 5	**DAY 6**	**DAY 7**	**DAY 8**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 9	**DAY 10**	**DAY 11**	**DAY 12**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 13	**DAY 14**	**DAY 15**	**DAY 16**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 17	**DAY 18**	**DAY 19**	**DAY 20**
DATE: __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 21	**DAY 22**	**DAY 23**	**DAY 24**
DATE: __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 25	**DAY 26**	**DAY 27**	**DAY 28**
DATE: __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 29	**DAY 30**	**DAY 31**	**DAY 32**
DATE: __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)	**DATE:** __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 1

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 33	**DAY 34**	**DAY 35**	**DAY 36**
DATE: __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 37	**DAY 38**	**DAY 39**	**DAY 40**
DATE: __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 41	**DAY 42**	**DAY 43**	**DAY 44**
DATE: __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 45	**DAY 46**	**DAY 47**	**DAY 48**
DATE: __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)	**DATE:** __/__/__ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 1

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 49	**DAY 50**	**DAY 51**	**DAY 52**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 53	**DAY 54**	**DAY 55**	**DAY 56**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 57	**DAY 58**	**DAY 59**	**DAY 60**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 61	**DAY 62**	**DAY 63**	**DAY 64**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 1

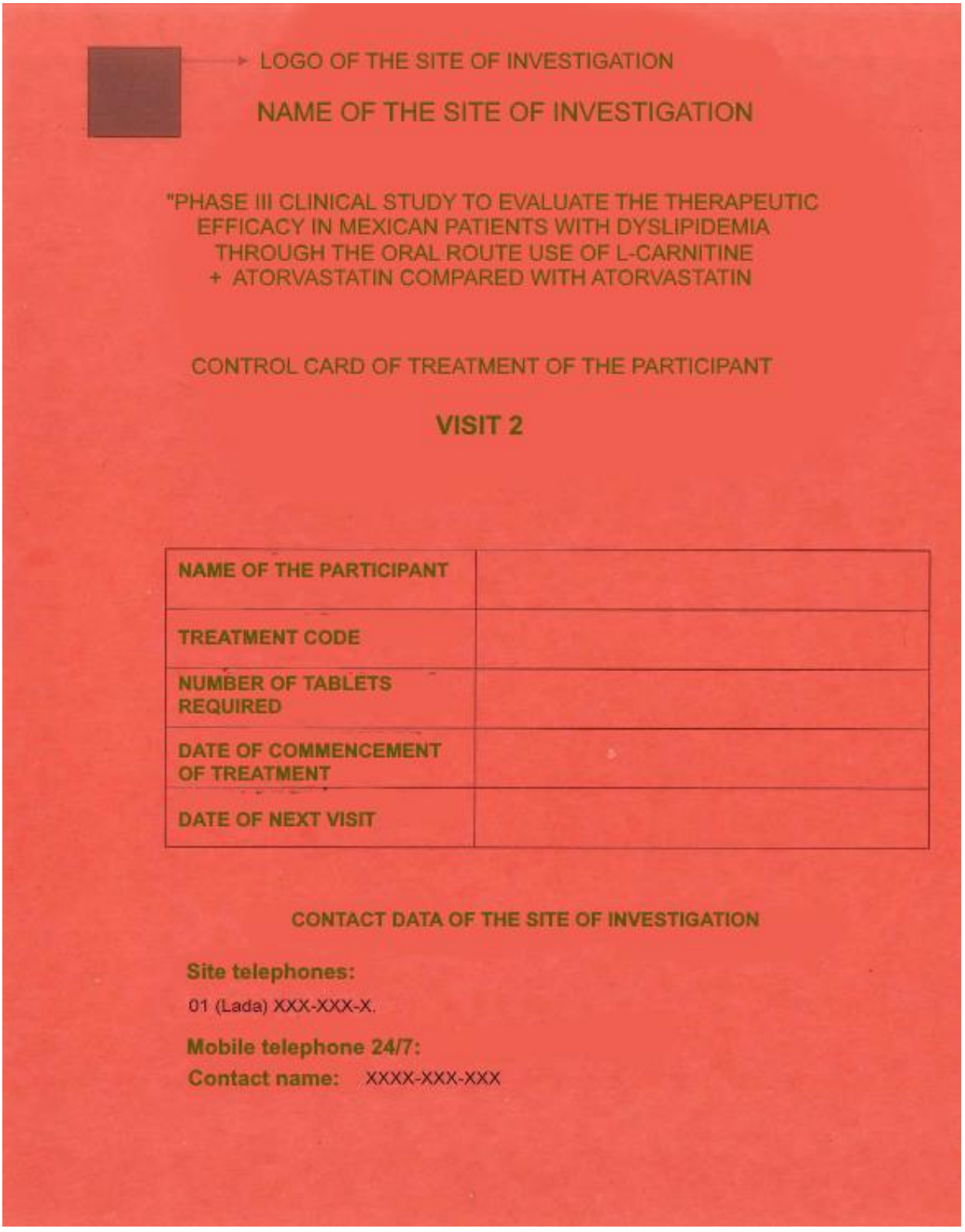
VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1		
DAY 65	**DAY 66**	
DATE: __/__/_____ (DD / MMM /)	**DATE:** __/__/_____ (DD / MMM /)	
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	
Observations:		

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Annex 4. Control Card of Treatment of the Participant, Visit 2



LOGO OF THE SITE OF INVESTIGATION

NAME OF THE SITE OF INVESTIGATION

"PHASE III CLINICAL STUDY TO EVALUATE THE THERAPEUTIC EFFICACY IN MEXICAN PATIENTS WITH DYSLIPIDEMIA THROUGH THE ORAL ROUTE USE OF L-CARNITINE + ATORVASTATIN COMPARED WITH ATORVASTATIN

CONTROL CARD OF TREATMENT OF THE PARTICIPANT

VISIT 2

NAME OF THE PARTICIPANT	
TREATMENT CODE	
NUMBER OF TABLETS REQUIRED	
DATE OF COMMENCEMENT OF TREATMENT	
DATE OF NEXT VISIT	

CONTACT DATA OF THE SITE OF INVESTIGATION

Site telephones:

01 (Lada) XXX-XXX-X.

Mobile telephone 24/7:

Contact name: XXXX-XXX-XXX

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant

VALEANT
Pharmaceuticals International, Inc.

Visit 2

Code of the Subject:
Site of Investigation:

DATA TO BE FILLED BY THE PERSONNEL OF THE SITE OF INVESTIGATION WHEN CARD IS PROVIDED

Initials of the subject	Date	Hour	Assigned treatment Code	Initials of the person who provides treatment
	___/___/___ (DD / MMM / YYYY	___:___ (HH : MM)		

Number of Tablets Provided:

66 ☐ Another amount ☐ Specify: _____

Number of Days of Treatment Provided:

33 ☐ Another amount ☐ Specify: _____

Observations:

DATA TO BE FILLED BY THE PERSONNEL OF THE SITE OF INVESTIGATION WHEN CARD IS PROVIDED

Initials, date and hour of person who receives the card:

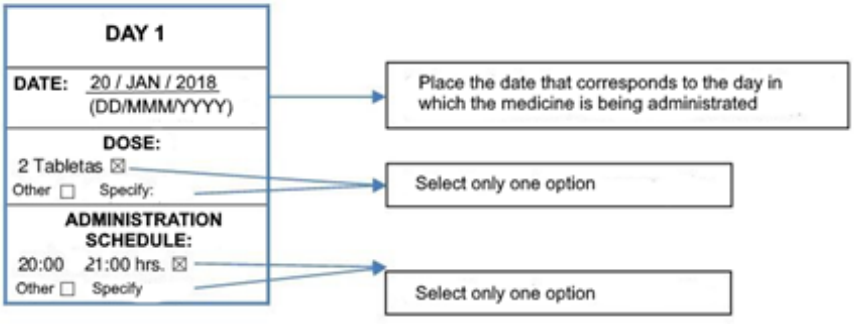
DATA TO BE FILLED BY THE PATIENT

Administration Instructions

- **At least 30 minutes before dinner.**
- **Medicine must be administered through oral route with the aid of 1 glass of water of approximately 250 ml.**
- **Always take 2 tablets only once a day, between 20:00 and 21:00 hours (8-9 o'clock at night).**
- **THE MEDICINE MUST NOT BE ADMINISTERED WITH OTHER MEDICINES**

Instruction for Filling

The filling must be made with blue ink pen, do it at the same time that the medicine is administered.
Choose only one option per square; if the option you desire isn't there, select the answer "other" and place it where it says "Specify". In the sections where you must place letters or numbers do it in print letters.
If someone assists you with the filling of the card state it in the section of observations and notify your physician in the next visit.
If a mistake is made when introducing the data don't use corrector, cross out or hide the data. Place the correction referencing with the date the mistake was made in the section of observations and notify it to the physician of the study in the next visit.



THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 1	**DAY 2**	**DAY 3**	**DAY 4**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 5	**DAY 6**	**DAY 7**	**DAY 8**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 9	**DAY 10**	**DAY 11**	**DAY 12**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 13	**DAY 14**	**DAY 15**	**DAY 16**
DATE: __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)	**DATE:** __/__/____ (DD / MMM / .)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 17	**DAY 18**	**DAY 19**	**DAY 20**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 21	**DAY 22**	**DAY 23**	**DAY 24**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 25	**DAY 26**	**DAY 27**	**DAY 28**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 29	**DAY 30**	**DAY 31**	**DAY 32**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 33	**DAY 34**	**DAY 35**	**DAY 36**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 37	**DAY 38**	**DAY 39**	**DAY 40**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 41	**DAY 42**	**DAY 43**	**DAY 44**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 45	**DAY 46**	**DAY 47**	**DAY 48**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 49	**DAY 50**	**DAY 51**	**DAY 52**
DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 53	**DAY 54**	**DAY 55**	**DAY 56**
DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 57	**DAY 58**	**DAY 59**	**DAY 60**
DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 61	**DAY 62**	**DAY 63**	**DAY 64**
DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)	DATE: __/__/____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

CONFIDENTIAL

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 65	**DAY 66**	**DAY 67**	**DAY 68**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 69	**DAY 70**	**DAY 71**	**DAY 72**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 73	**DAY 74**	**DAY 75**	**DAY 76**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 77	**DAY 78**	**DAY 79**	**DAY 80**
DATE: __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)	**DATE:** __/____/_____ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 81	**DAY 82**	**DAY 83**	**DAY 84**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 85	**DAY 86**	**DAY 87**	**DAY 88**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 89	**DAY 90**	**DAY 91**	**DAY 92**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
DAY 93	**DAY 94**	**DAY 95**	**DAY 96**
DATE: ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)	**DATE:** ___/___/___ (DD / MMM /)
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Version 01.
August 2, 2017
Code of the study: GMX-001-2017

Control Card of the Treatment of the Participant Visit 2

VALEANT
Pharmaceuticals International, Inc.

FILL IN THE DATA WITH THE INFORMATION FOUND ON PAGE 1			
DAY 97	**DAY 98**	**DAY 99**	
DATE: __/__/_____ (DD / MMM /)	**DATE:** __/__/_____ (DD / MMM /)	**DATE:** __/__/_____ (DD / MMM /)	
DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	DOSE: 2 Tablets ☐ Other ☐ Specify:	
ADMINISTRATION SCHEDULE: 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	**ADMINISTRATION SCHEDULE:** 20:00 to 21:00 hrs. ☐ Other ☐ Specify:	
Observations:			

THIS DOCUMENT MUST BE FILLED BY THE DELEGATE PERSONNEL THAT PERFORMS THE PROCEDURE, IN PRINT AND BLUE INK

Annex 5. Format for the Evaluation of Causality

Naranjo Algorithm for the evaluation of the Causality	Yes	No	N/D	Score
1) Is there conclusive previous evidence about this reaction?	1	0	0	
2) Did the adverse reaction appear after the administration of the implied medicine?	2	-1	0	
3) Was there an improvement of the adverse reaction when the medicine was suspended or when a specific antagonist was administered?	1	0	0	
4) Did the adverse reaction reappear when the medicine was re-administered?	2	-1	0	
5) Are there alternative causes that may have caused the reaction?	-1	2	0	
6) Did this reaction occur after administrating placebo?	-1	1	0	
7) Was the presence of the medicine proven in the corporal fluids in concentrations known as toxic?	1	0	0	
8) Was there a variation in the severity of the reaction when the dose of the medicine was varied?	1	0	0	
9) Has the patient experienced a similar reaction in previous expositions to the medicine or to similar medicines?	1	0	0	
10) Has the adverse reaction been confirmed through some objective evidence?	1	0	0	
TOTAL SCORE				

TOTAL SCORE	CLASSIFICATION
Less than 0	Doubtful
From 1 to 4	Possible
From 5 to 8	Probable
9 or more	Certain

References:

Martin J. Doherty, Algorithms for assessing the probability of an Adverse Drug Reaction, Respiratory Medicine CME, Volume 2, Issue 2, 2009, Pages 63-67, ISSN 1755-0017.