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APPLICATION NUMBER:

213260Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	505(b)(2)
Application Number(s)	213260
Priority or Standard	Standard
Submit Date(s)	07/31/2022
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PDUFA Goal Date	02/01/2023
Division/Office	Division of Diabetes, Lipid Disorders, and Obesity of the Office of Cardiology, Hematology, Endocrinology, and Nephrology
Reviewer Name(s)	Ovidiu Galescu
Review Completion Date	01/23/2023
Established/Proper Name	Atorvastatin Oral Suspension
(Proposed) Trade Name	ATORVALIQ
Applicant	CMP Development LLC
Dosage Form(s)	Suspension; 4 mg/mL
Applicant Proposed Dosing Regimen(s)	**Recommended Dosage in Adult Patients** The recommended starting dose of ATORVALIQ is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily. Patients who require reduction in LDL-C greater than 45% may be started at 40 mg once daily. **Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HeFH** The recommended starting dosage of ATORVALIQ is 10 mg once daily. The dosage range is 10 mg to 20 mg once daily. **Recommended Dosage in Pediatric Patients 10 Years of Age and Older with HoFH** The recommended starting dosage of ATORVALIQ is 10 mg to 20 mg once daily. The dosage range is 10 mg to 80 mg once daily.
Applicant Proposed Indication(s)/Population(s)	Treatment of adults with primary hyperlipidemias, homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia in adult and pediatric patients (10 to 17 years)
Recommendation on Regulatory Action	Approval

BACKGROUND

The Applicant, CMP Development LLC, seeks approval of atorvastatin calcium oral suspension, 4 mg/mL (proposed tradename ATORVALIQ ®) for the treatment of adults with primary hyperlipidemia, homozygous familial hypercholesterolemia, and for heterozygous familial hypercholesterolemia in adults and pediatric patients (10-17 years).

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme in the de novo cholesterol biosynthesis pathway that converts 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols. Inhibition of cholesterol biosynthesis leads to upregulation of LDL-R expression in the liver and decreased plasma LDL-cholesterol.

This is a 505(b)(2) application relying on the FDA's previous findings of safety and effectiveness of the listed drug Lipitor® (NDA 020702, atorvastatin calcium tablets).

The reference listed drug (RLD), Lipitor, is indicated as an adjunct therapy to diet to:

- To reduce the risk of:
    - Myocardial infarction (MI), stroke, revascularization procedures, and angina in adults with multiple risk factors for coronary heart disease (CHD) but without clinically evident CHD
    - MI and stroke in adults with type 2 diabetes mellitus with multiple risk factors for CHD but without clinically evident CHD
    - Non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in adults with clinically evident CHD

- As an adjunct to diet to reduce low-density lipoprotein cholesterol (LDL-C) in:
    - Adults with primary hyperlipidemia.
    - Adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).

- As an adjunct to other LDL-C-lowering therapies, or alone if such treatments are unavailable, to reduce LDL-C in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).

- As an adjunct to diet for the treatment of adults with:
    - Primary dysbetalipoproteinemia
    - Hypertriglyceridemia

REGULATORY HISTORY

On March 8, 2019, under associated IND 137915, a type B meeting was held where the Agency agreed to Applicant's plan to conduct the following studies:
▪ Open-label, randomized, reference replicate, single oral dose, two treatment, three period, three-way crossover relative bioavailability study of 10mls of atorvastatin oral suspension, 40mg/5ml versus 80mg LIPITOR tablets in healthy adults under fasting conditions.
▪ Open-label, randomized, single oral dose, one-treatment, two period, two-way crossover food effect study of 10mls of [atorvastatin] oral suspension, 40mg/5ml, administered under fed versus fasted conditions in healthy adults.

On July 15, 2019, the Pediatric Review Committee (PeRC) agreed with the Applicant's plan to request partial waiver for studies of HeFH in pediatrics birth to 10 years of age because studies are impossible or highly impracticable and assessment in pediatrics 10 to 17 years of age. Additionally, the PeRC agreed with the plan to request partial waiver for studies of HoFH in pediatrics birth to 6 years of age because studies are impossible or highly impracticable and assessment in pediatrics 6 to 17 years of age.

On September 20, 2019, the PeRC agreed with the plan to request a full waiver for pediatric studies birth to less than 18 years of age with cardiovascular disease (CVD), mixed dyslipidemia, familial hypertriglyceridemia and dysbetalipoproteinemia because studies are impossible or highly impracticable; partial waiver for pediatric studies for pediatrics 0 to less than 9 years of age with HeFH and pediatrics 0 to 5 years of age with HoFH because studies are impossible or highly impracticable; and assessment for pediatrics 10 to less than 17 years of age with HeFH and pediatrics 6 to less than 17 years of age with HoFH.

On January 13, 2020, the Applicant submitted the current initial application under NDA 213260 for atorvastatin calcium oral suspension (4 mg/mL) via the 505(b)(2) pathway using LIPITOR (atorvastatin calcium) oral tablets 80 mg, as the reference listed drug.

At that time the application was primarily supported by two in-vivo bioavailability studies: Study 18-VIN-0235 - *"An open label, balanced, randomized, single-dose, two-treatment, three-sequence, three period, partial replicate, crossover, oral bioequivalence study of Atorvastatin oral suspension 20 mg/5mL at a dose of 80 mg (20 mL) of* (b) (4) *and LIPITOR® (Atorvastatin calcium) 80 mg film-coated tablets of Parke-Davis, Division of Pfizer Inc. NY, NY 10017, in healthy, adult, human subjects under fasting condition"* and Study 18-VIN-0236 - *"An open label, balanced, randomized, single-dose, one-treatment, two-sequence, two period, crossover, oral bioavailability (pharmacokinetic comparison) study of Atorvastatin oral suspension 20 mg/5 mL at a dose of 80 mg (20 mL) of* (b) (4) *in healthy, adult, human subjects under fasting and fed condition."*

In addition, the submission relied on the Agency's previous findings of safety and effectiveness in accordance with section 505(b)(2) for the Federal Food, Drug and Cosmetic Act for the listed drug LIPITOR® (atorvastatin calcium) tablets (NDA 020702). LIPITOR tablets 10, 20, 40 mg strengths were initially approval on Dec 17, 1996, and the 80 mg strength was approved on April

On October 16, 2020, the initial submission received a complete response (CR) (DARRTS Reference ID: 4687276), after the review team identified several product quality, facilities, and clinical pharmacology issues.

The Chemistry, Manufacturing, and Controls (CMC) issues identified during the initial submission included objectionable conditions at the manufacturing facility namely, (b) (4) (b) (4) and commercial manufacturing concerns.

The Clinical Pharmacology team identified concerning issues with the relative bioavailability between the proposed product and the listed drug. The results from Study 18-VIN-0235 did not meet conventional 80 – 125% bioavailability criteria. Since the application did not contain clinical efficacy and safety data for the proposed atorvastatin calcium oral suspension (proposed product), relative bioavailability results were the fundamental bridge to the efficacy and safety data of the listed drug product.

It was determined that the deficiency could not be addressed with labeling, because there was no condition of use that would ensure safety and effectiveness of the product. When the proposed product was administered under fed conditions, the magnitude of the decrease in atorvastatin and its metabolites exposure was much greater for the proposed product compared to the listed drug, which could lead to loss of efficacy. On the other hand, if the product was administered under fasting conditions, the large increase in atorvastatin and its metabolites exposure compared to the listed drug was a safety issue. Additionally, there was a wide fluctuation in atorvastatin and metabolite levels following administration of the proposed product compared to the listed drug under both fasting and fed conditions. Thus, the clinical pharmacology and other relevant findings of the listed drug could not be relied upon for the proposed atorvastatin product and the data did not support its approval.

The FDA recommendations were to reformulate the proposed product and conduct additional relative bioavailability studies to demonstrate the bioequivalence (BE) to the listed drug or conduct a clinical study to support the effective and safe use of the proposed atorvastatin oral suspension product.

The current submission is the Applicant's complete response to the complete response letter.

STUDIES SUBMITTED TO NDA

To address the complete response letter, the applicant conducted 3 relative bioavailability studies. Studies C1B01021 and C1B01023 are pilot studies, whereas Study C1B01024 serves as the pivotal bridging study to reference the efficacy and safety of the RLD, LIPITOR.

Study C1B1021 is an open label, randomized, three-period, two-treatment, three-sequence, reference replicate, crossover, balanced, single dose oral bioequivalence study. The primary

objective of this study was to compare and evaluate the oral bioavailability of Atorvastatin oral suspension 4 mg/mL (40 mg/ 10 mL) with that of 'LIPITOR®' (Atorvastatin calcium) tablets 40 mg in healthy, adult, human subjects under fasting conditions.

A total of 15 healthy male subjects, age 20-43 years, were dosed, out of which 14 completed the study.

The reported results showed a 95% upper confidence interval (critical bound) for the atorvastatin Cmax of -0.0084 (< 0). The 90% confidence interval of the ratio for atorvastatin AUC between atorvastatin suspension and LIPITOR tablet is 94.54% – 113.82% (within the 80% – 125%).

The interpretation of these results by our ClinPharm team is that the 40 mg/10 mL atorvastatin calcium oral suspension is bioequivalent to the 40 mg LIPITOR tablet.

Study C1B1023 is an open label, randomized, four-period, two-treatment, two-sequence, fully replicate, crossover, balanced, single dose oral bioequivalence study. The primary objective of this study was to compare and evaluate the oral bioavailability of Atorvastatin oral suspension 4 mg/mL (80 mg/ 20 mL) with that of 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg in healthy, adult, human subjects under fasting conditions.

A total of 16 healthy male subjects, age 24-43 years, were dosed, out of which 16 completed the study.

The reported results showed a 95% upper confidence interval (critical bound) for the atorvastatin Cmax of 0.0239 (not < 0). The 90% confidence interval of the ratio for atorvastatin AUC between atorvastatin suspension and LIPITOR tablet is 95.44% – 113.97% (within the 80% – 125%).

The interpretation of these results by our ClinPharm team is that the 80 mg/20 mL atorvastatin calcium oral suspension is not bioequivalent to the 80 mg LIPITOR tablet.

Study C1B1024 is an open label, randomized, four-period, two-treatment, two-sequence, fully replicated, crossover, balanced, single dose oral comparative bioavailability design. The objective of this study was to compare and evaluate the oral comparative bioavailability of Atorvastatin oral suspension 4 mg/mL (80 mg/ 20 mL) with that of 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg in healthy, adult, human subjects under fasting conditions. The main secondary objective was to prove the bioequivalence between Atorvastatin oral suspension 4 mg/mL (80 mg/ 20 mL) and 'LIPITOR®' (Atorvastatin calcium) tablets 80 mg in healthy, adult, human subjects under fasting condition.

A total of 52 healthy male subjects, age 20-44 years, were dosed, out of which 51 completed the study.

The reported results showed a 95% upper confidence interval (critical bound) for the atorvastatin Cmax of -0.03395 (< 0). The 90% confidence interval of the ratio for atorvastatin AUC between atorvastatin suspension and LIPITOR tablet is 107.71% – 121.12% (within the 80% – 125%).

The interpretation of these results by our ClinPharm team is that , the 80 mg/20 mL atorvastatin calcium oral suspension is bioequivalent to the 80 mg LIPITOR tablet.

SAFETY

The Atorvastatin Oral Suspension development program included 3 bioavailability studies that examined single oral administration of a 4 mg/mL dose to a total of 125 subjects.

Drug Exposure

Table 1: Atorvastatin Oral Suspension Clinical Studies – Extent of Exposure

Type of Study	Study Identifier	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
Comparative Bioavailability	18-VIN-0235	Test Atorvastatin Oral Suspension 4 mg/mL, Suspension; Single dose; Oral Reference LIPITOR® (atorvastatin calcium) 80 mg tablet; Single dose (one tablet); Oral	59	Healthy Adult Male	Single Dose 3-period, 2-treatment, 3-sequence, Partially Replicated, Crossover
Comparative Bioavailability	18-VIN-0236	Atorvastatin Oral Suspension 4 mg/mL, 20 mL suspension (80 mg); Single dose; Oral	14	Healthy Adult Male	Single Dose 2-period, 1-treatment, 2-sequence, Crossover
Comparative Bioavailability	C1B01024	Test Atorvastatin Oral Suspension 4 mg/mL, Suspension; Single dose; Oral Reference LIPITOR® (atorvastatin calcium) 80 mg Tablet; Single dose (1 tablet); Oral	52	Healthy Adult Male	Single Dose 4-period, 2-treatment, 2-sequence, Fully Replicated, Crossover

* Source: Applicant's Table 1 in Summary of Clinical Safety Summary

Adverse Events

Per Applicant's submission there were 5 adverse events reported for Study 18-VIN-0235, none reported for Study 18-VIN-0236, and 3 adverse events reported for Study C1B01024. Of these 8 total adverse events, 4 occurred after administration of Atorvastatin Oral Suspension 4 mg/mL,

and 4 occurred after administration of LIPITOR 80 mg film-coated tablet. There were no clinically significant or serious adverse events. There were no adverse events involving Atorvastatin Oral Suspension that require safety narratives (i.e., there were no deaths, other serious adverse events, or other significant adverse events in either study).

Medical Officer's Safety Conclusion: No adverse events were included in this submission that would change the risk-benefit assessment of atorvastatin, administered as an oral suspension. No pattern suggestive of previously unknown adverse drug effect of atorvastatin was noted.

CLINICAL-PHARMACOLOGY
(Source: Review in DARRTS, submitted January 20, 2023 , Reference ID: 5113162)

Team Summary and Recommendations:
To address the inconsistencies between the results of studies C1B1021, C1B1023 (showed bioequivalence for the AUC but did not show bioequivalence for Cmax), and C1B1024 which show bioequivalence and studies 18-VIN-0236 and 18-VIN-0235 (original submission) that failed to demonstrate bioequivalence, the clinical pharmacology team has conducted Data Anomalies in BioEquivalence R Shiny (DABERS) analyses to rule out data integrity issues. None were identified. The team has also reproduced all BE analyses (for pivotal as well as pilot studies) and agrees with the statistical results presented by the Applicant. The Clinical Pharmacology team further explored the reasons behind the failed 1st pivotal BE study and feel they can now reject the results of the 1st study and accept those from the 2nd study. Specifically, the 1st pivotal study has a low value for AUC for both test and reference relative to the other studies conducted by the Applicant. Furthermore, the AUC value for the reference was low compared to the value for AUC for the reference reported in the literature. The AUC value of the test product under fasting conditions in the food effects study was comparable to the AUC in the 2nd pivotal study and higher than value in 1st pivotal study. This suggests that there was incorrect dosing in the 1st pivotal study. The 2nd pivotal study was conducted with a different contract research organization (CRO); this site/vendor is familiar to the Office of Generic Drugs (OGD), appears reliable, and has submitted a number of studies to FDA.

CMC/QUALITY

(Source: Review in DARRTS, submitted December 8, 2022, Reference ID: 5090559)

Per the Office of Pharmaceutical Quality (OPQ) review, the current submission addresses all previously identified issues and meets all applicable standards to support the identity, strength, quality, and purity that the drug product purports to have. For details, please refer to the OPQ review from December 8, 2022.

Benefit-Risk Integrated Assessment

Hyperlipidemia is a highly prevalent condition in the U.S. and around the world with significant associated morbidity and mortality and a large socio-economic impact. It has been linked with an increased risk of cardiovascular disease and lipid lowering is a staple in the prevention of CVD.

There are currently many FDA approved therapies for lipid lowering.

Atorvastatin is a selective, competitive inhibitor of HMG-CoA reductase, initially approved to treat hyperlipidemia under the brand name Lipitor (NDA 020702: approved on December 17, 1996).

There are no major clinical concerns regarding Atorvaliq. This product is bioequivalent to the FDA approved Lipitor formulations and may be approved from a clinical standpoint.

The proposed Atorvastatin Oral Solution (Atorvaliq) may improve compliance for patients struggling with the solid oral dosage forms.

Due to the significant effect of food on the exposure of atorvastatin calcium suspension, ATORVALIQ needs to be administered on an empty stomach.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Hyperlipidemia: • Clinical dyslipidemia includes, but is not limited to, patients with abnormal levels of low-density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol, triglycerides, or lipoprotein(a). • Hyperlipidemia is defined as total cholesterol or LDL-C levels above the 90th percentile for the general population. • The prevalence of one or more abnormal lipid fractions varies with the population being studied. It is highest in populations of patients with	• Hyperlipidemia is a highly prevalent condition in the U.S. adult population and carries an extremely high burden of morbidity and mortality. • It is related to an increased risk of atherosclerotic cardiovascular disease which is recognized as the number 1 cause of mortality in the U.S.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	premature coronary heart disease (CHD), which can be defined as occurring before 55 to 60 years of age in men and before 65 years in women. In this setting, the prevalence of dyslipidemia is as high as 75 to 85 percent compared with approximately 40 to 48 percent in age-matched controls without CHD. • Most hyperlipidemia is caused by genetic polymorphism in the context of dietary and other lifestyle factors. • Having hyperlipidemia increases the risk of developing CHD which is the leading cause of death in the U.S.	• Aggressive therapy aimed at lowering LDL-C, especially in at-risk populations, has been associated with decreased morbidity and mortality in these patients.
Current Treatment Options	• The cornerstone of therapy of hyperlipidemia is focusing on reduction of atherosclerotic cardiovascular disease (ASCVD) risk. • In order to determine which patients should make an attempt to lower their LDL-C, their risk for the development of cardiovascular disease (CVD) events needs to be assessed using risk evaluation tools that take into account more than the baseline LDL-C. Cardiovascular risk should be calculated using validated risk models/calculators. • The American Heart Association/American College of Cardiology (AHA/ACC)[1] identified the following groups that benefit from LDL-C lowering therapy despite associated risks: adults with ASCVD; adults ≥20 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes); adults aged 40 to 75 years without ASCVD, but with diabetes and with LDL-C 70 to 189 mg/dL; and adults ages 40 to 75 years without ASCVD or diabetes, with LDL-C	LDL-C lowering therapy (statins) in patients with and without manifest CVD leads to reductions in CVD events . Statin therapy leads to important reductions in myocardial infarction and in CHD mortality; reductions in stroke are somewhat smaller in magnitude but also clinically important.

[1] 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines.
Grundy SM, Stone NJ, Bailey AL, et al. J Am Coll Cardiol. 2019 Jun 25;73(24):3168-3209. doi: 10.1016/j.jacc.2018.11.002. Epub 2018 Nov 10.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	70 to 189 mg/dL, and an estimated 10-year risk for ASCVD of ≥7.5% as determined by the Pooled Cohort Equations. • For patients identified at risk the first step in management is lifestyle modification with dietary intervention and increased exercise. • The initial pharmacological intervention is statin therapy	
Benefit	• LIPITOR tablets have the strengths of 10, 20, 40, and 80 mg atorvastatin per tablet and is approved for lipid lowering treatment of adults with primary hyperlipidemias, adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia or heterozygous familial hypercholesterolemia.	• ATORVALIQ 4 mg/mL suspension is bioequivalent to the RLD, however, due to the significant effect of food on the exposure of atorvastatin calcium suspension, it needs to be administered on an empty stomach.
Risk and Risk Management	• The newly proposed formulation has the same active ingredient as the currently approved Lipitor formulation, however absorption of the solution seems to be impacted by food.	• The effect of food on the efficacy of Atorvaliq should be addressed in labeling.

Therapeutic Context

Analysis of Condition

Dyslipidemias are disorders of lipoprotein metabolism that include abnormal levels of low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides, or lipoprotein(a). In adults, dyslipidemia is an established risk factor for CVD, and correcting dyslipidemia reduces the risk of CVD. Dyslipidemia begins as early as childhood or adolescence.

In the United States, CHD is the leading cause of death, killing about half a million men and women annually. In addition, some 12 million adults in the United States live with CHD, including angina, heart attacks and other forms of the disease.[2] Increased blood cholesterol levels, or, more specifically, increased levels of LDL-C, are causally related to an increased risk of CHD.[3]

The prevalence of one or more abnormal lipid fractions varies with the population being studied. It is highest in populations of patients with premature CHD, which can be defined as occurring before 55 to 60 years of age in men and before 65 years in women. In this setting, the prevalence of dyslipidemia is as high as 75 to 85 percent compared with approximately 40 to 48 percent in age-matched controls without CHD.[4,5] In one study, for example, 54 percent of all patients with premature CHD (and 70 percent of those with a lipid abnormality) had a familial disorder.[1,3] In the great majority of patients, inheritance is polygenic, and the expression of dyslipidemia is strongly influenced by factors such as obesity (particularly central obesity) and the saturated fat and cholesterol content of the diet.

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[2] Younus, A., E. C. Aneni, E. S. Spatz, C. U. Osondu, L. Roberson, O. Ogunmoroti, R. Malik, S. S. Ali, M. Aziz, T. Feldman, S. S. Virani, W. Maziak, A. S. Agatston, E. Veledar and K. Nasir (2016). "A Systematic Review of the Prevalence and Outcomes of Ideal Cardiovascular Health in US and Non-US Populations." Mayo Clin Proc 91(5): 649-670.

[3] (2002). "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." Circulation 106(25): 3143-3421.

[4] Genest, J. J., Jr., S. S. Martin-Munley, J. R. McNamara, J. M. Ordovas, J. Jenner, R. H. Myers, S. R. Silberman, P. W. Wilson, D. N. Salem and E. J. Schaefer (1992). "Familial lipoprotein disorders in patients with premature coronary artery disease." Ibid. 85(6): 2025-2033.

[5] Roncaglioni, M. C., L. Santoro, B. D'Avanzo, E. Negri, A. Nobili, A. Ledda, F. Pietropaolo, M. G. Franzosi, C. La Vecchia, G. A. Feruglio and et al. Ibid."Role of family history in patients with myocardial infarction. An Italian case-control study. GISSI-EFRIM Investigators." 2065-2072.

Hyperlipidemia is defined as total cholesterol or LDL-C levels above the 90th percentile for the general population. Elevation of LDL-C is common in the general population. Most of these individuals have one or more genetic abnormalities rather than a secondary cause (such as liver or kidney disease). For individuals with LDL-C above 190 mg/dL, the genetic defects that lead to familial hypercholesterolemia (FH) are the most common underlying cause.

Most hyperlipidemia is caused by genetic polymorphism in the context of dietary and other lifestyle factors. Identifiable familial forms account for only a fraction of all hyperlipidemias yet carry the highest cardiovascular risk.

Familial hypercholesterolemia (FH) is the most common autosomal dominant genetic disease. It affects up to 0.2% of the United States population; is the most common cause of marked hypercholesterolemia in children and in adolescents and is associated with early onset of CHD.[6] The clinical syndrome (phenotype) is characterized by extremely elevated levels of LDL-C and a propensity to early onset ASCVD. In general, homozygotes manifest the disease at a much earlier age than heterozygotes and the disease is more severe. Intense LDL-C lowering in individuals with heterozygous or homozygous FH decreases progression of angiographically demonstrated coronary artery disease, and reduces cardiovascular disease events (myocardial infarction), coronary heart disease mortality, and all-cause mortality.[7,8,9,10] For homozygous FH patients, who often have untreated LDL-C of >500 mg/dL (>13 mmol/L) there is no agreement on LDL-C goal. Generally intensive LDL-C lowering, with a minimal target of <150 mg/dL (3.9 mmol/L) is accepted across guidelines and practices. The vast majority of adult patients with FH encountered in clinical practice will be heterozygotes and will usually have an untreated LDL-C ≥190 mg/dL.

Familial combined hyperlipidemia (FCHL) is a relatively common lipid disorder. It occurs in 1 to 2 percent of the general population and accounts for one-third to one-half of familial causes

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[6] Liyanage, K. E., J. R. Burnett, A. J. Hooper and F. M. van Bockxmeer (2011). "Familial hypercholesterolemia: epidemiology, Neolithic origins and modern geographic distribution." Crit Rev Clin Lab Sci 48(1): 1-18.
[7] Kane, J. P., M. J. Malloy, T. A. Ports, N. R. Phillips, J. C. Diehl and R. J. Havel (1990). "Regression of coronary atherosclerosis during treatment of familial hypercholesterolemia with combined drug regimens." JAMA 264(23): 3007-3012.
[8] Versmissen, J., D. M. Oosterveer, M. Yazdanpanah, J. C. Defesche, D. C. Basart, A. H. Liem, J. Heeringa, J. C. Witteman, P. J. Lansberg, J. J. Kastelein and E. J. Sijbrands (2008). "Efficacy of statins in familial hypercholesterolaemia: a long term cohort study." BMJ 337: a2423.
[9] Neil, A., J. Cooper, J. Betteridge, N. Capps, I. McDowell, P. Durrington, M. Seed and S. E. Humphries (2008). "Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study." Eur Heart J 29(21): 2625-2633.
[10] Raal, F. J., G. J. Pilcher, V. R. Panz, H. E. van Deventer, B. C. Brice, D. J. Blom and A. D. Marais (2011). "Reduction in mortality in subjects with homozygous familial hypercholesterolemia associated with advances in lipid-lowering therapy." Circulation 124(20): 2202-2207.

of CHD[11] and 10 percent of cases of premature CHD.[12] In affected families, some individuals will have hypertriglyceridemia, some hypercholesterolemia, some both, and some neither.

The clinical manifestations of hyperlipidemia include premature CHD (particularly in patients with concurrent hypertriglyceridemia), xanthelasma (in 10 percent of cases), and obesity. Coexisting diabetes mellitus or impaired glucose tolerance is more common in patients who also have hypertriglyceridemia.

Most people will have no symptoms, but having hyperlipidemia increases the risk of developing CHD which is the leading cause of death in the U.S. In familial, or inherited, hyperlipidemia, there may be yellowish fatty growths (called xanthomas) around the eyes or the joints.

Multiple meta-analyses of randomized clinical trials (RCT) of LDL-C lowering therapy in patients with and without manifest CVD found strong evidence of reductions in CVD events and CVD mortality.[13,14,15] Other meta-analyses have also found a reduction in the risk of all-cause mortality. In terms of individual components, all have found important reductions in myocardial infarction and in CHD mortality; reductions in stroke are somewhat smaller in magnitude but also clinically important.[16]

Analysis of Current Treatment Options

For LDL-C lowering, regardless of weight status, the AHA/ACC guidelines recommend consuming a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; including low-fat dairy products, poultry, fish, legumes, nontropical vegetable oils, and nuts; and limiting intake of sweets, sugar-sweetened beverages, and red meats. This dietary pattern should be adapted to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes). Patients can achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the

[11] Williams, R. R., P. N. Hopkins, S. C. Hunt, L. L. Wu, S. J. Hasstedt, J. M. Lalouel, K. O. Ash, B. M. Stults and H. Kuida (1990). "Population-based frequency of dyslipidemia syndromes in coronary-prone families in Utah." Arch Intern Med 150(3): 582-588.
[12] Goldstein, J. L., H. G. Schrott, W. R. Hazzard, E. L. Bierman and A. G. Motulsky (1973). "Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia." J Clin Invest 52(7): 1544-1568.
[13] Mihaylova, B., J. Emberson, L. Blackwell, A. Keech, J. Simes, E. H. Barnes, M. Voysey, A. Gray, R. Collins and C. Baigent (2012). "The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials." Lancet 380(9841): 581-590.
[14] Ray, K. K., S. R. Seshasai, S. Erqou, P. Sever, J. W. Jukema, I. Ford and N. Sattar (2010). "Statins and all-cause mortality in high-risk primary prevention: a meta-analysis of 11 randomized controlled trials involving 65,229 participants." Arch Intern Med 170(12): 1024-1031.
[15] Taylor, F., M. D. Huffman, A. F. Macedo, T. H. Moore, M. Burke, G. Davey Smith, K. Ward and S. Ebrahim (2013). "Statins for the primary prevention of cardiovascular disease." Cochrane Database Syst Rev(1): CD004816.
[16] Chou, R., T. Dana, I. Blazina, M. Daeges and T. L. Jeanne (2016). "Statins for Prevention of Cardiovascular Disease in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force." JAMA 316(19): 2008-2024.

AHA Diet. Patients should aim for a dietary pattern that achieves 5%–6% of calories from saturated fat and reduce percent of calories from saturated fat as well as reduce percent of calories from trans-fat.[17]

In 2019, the ACC identified the following groups that benefit from LDL-C lowering therapy despite associated risks: adults with clinical ASCVD; adults ≥20 years of age with LDL-C ≥190 mg/dL (not due to secondary modifiable causes); adults aged 40 to 75 years without ASCVD, but with diabetes and with LDL-C 70 to 189 mg/dL; and adults ages 40 to 75 years without ASCVD or diabetes, with LDL-C 70 to 189 mg/dL, and an estimated10-year risk for ASCVD of ≥7.5% as determined by the Pooled Cohort Equations.[18]

Based on their 2017 assessment, the U.S. Preventive Services Task Force (USPSTF) recommends that adults without a history of CVD (i.e., symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: (1) they are aged 40 to 75 years; (2) they have 1 or more CVD risk factors (i.e., dyslipidemia, diabetes, hypertension, or smoking); and (3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater.[19]

The following drugs are currently approved for patients with primary hyperlipidemia or mixed dyslipidemia:

- atorvastatin, simvastatin, pitavastatin, lovastatin, fluvastatin, pravastatin, rosuvastatin, atorvastatin/ezetimibe and simvastatin/ezetimibe, niacin extended-release, fenofibrate (as an adjunct to diet to reduce low-density lipoprotein cholesterol in adults with primary hyperlipidemia).
- Praluent (Alirocumab) as an adjunct to diet, alone or in combination with other low density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C.

  As an adjunct to other LDL-C-lowering therapies in adult patients with homozygous familial hypercholesterolemia (HoFH) to reduce LDL-C.
- Repatha (evolocumab) was approved as an adjunct to diet, alone or in combination with other low-density lipoprotein cholesterol (LDL-C)-lowering therapies, in adults with primary hyperlipidemia, including heterozygous familial hypercholesterolemia (HeFH), to reduce LDL-C

[17]http://www.onlinejacc.org/content/accj/63/25_Part_B/2960.full.pdf?_ga=2.134080011.486408902.1510851575-2003018969.1472140967
[18] Grundy SM, Stone NJ, Bailey AL, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73: e285–e350..
[19] https://www.aafp.org/afp/2017/0115/od1.pdf

As an adjunct to diet and other LDL-C-lowering therapies in pediatric patients aged 10 years and older with HeFH, to reduce LDL-C
As an adjunct to other LDL-C-lowering therapies in adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH), to reduce LDL-C.

Other lipid lowering therapies available are listed in Table 1.

Table 1 FDA Approved Drugs for Treatment of Hyperlipidemia

Product Name	Class	Year of Approval	Route and Frequency of Administration	Important Safety and Tolerability Issues
Atorvastatin	HMG-CoA reductase Inhibitors	June 15, 2015	10 to 80 mg/day	Headache; nausea; sleep disturbance; elevations in hepatocellular enzymes and alkaline phosphatase. Myositis and rhabdomyolysis, primarily when given with gemfibrozil or cyclosporine; myositis is also seen with severe renal insufficiency (CrCl <30 mL/min). Lovastatin, atorvastatin, rosuvastatin, and simvastatin potentiate effect of warfarin; this interaction is not seen with pravastatin, fluvastatin, or pitavastatin. Most statins can also affect digoxin metabolism and levels.
Fluvastatin		May 8, 1999	IR: 20 to 80 mg/day XR: 80 mg/day	
Lovastatin		September, 1987	IR: 20 to 80 mg/day XR: 20 to 60 mg/day	
Pitavastatin		August 3, 2009	1 to 4 mg/day	
Pravastatin		February 10, 2000	10 to 80 mg/day	
Rosuvastatin		August 13, 2003	5 to 40 mg/day	
Simvastatin		July 10, 1998	5 to 40 mg/day	
Alirocumab	PCSK9 Inhibitors	July 24, 2015	75 to 150 mg every two weeks SQ	Injection site reactions
Evolocumab		August 27, 2015	140 mg every two weeks or 420 mg every month SQ Homozygous familial hypercholesterolemia: 420 mg every month to 420 mg every two weeks SQ	
Inclisiran		December 22, 2021	284 mg administered as a single subcutaneous injection initially, again at 3 months,	Injection site reaction, arthralgia, urinary tract infection, diarrhea, bronchitis, pain in extremity, and dyspnea.

			and then every 6 months, in combination with maximally tolerated statin therapy	
Fenofibrate	Fibric acid derivatives	September 4, 2001	Nanocrystal 145 mg/day Micronized 160 to 200 mg/day	Skin rash, gastrointestinal (nausea, bloating, cramping) myalgia; lowers blood cyclosporine levels; potentially nephrotoxic in cyclosporine treated patients. Avoid in patients with CrCl <30 mL/min.
Gemfibrozil		November 20, 1986	600 mg twice per day	Potentiates warfarin action. Absorption of gemfibrozil diminished by bile acid sequestrants.
Niacin	Nicotinic acid	July 28, 1997	IR: 1 to 6 g/day XR (Niaspan): 0.5 to 2 g/day	Prostaglandin-mediated cutaneous flushing, headache, warm sensation, and pruritus; hyperpigmentation (particularly in intertriginous regions); acanthosis nigricans; dry skin; nausea; vomiting; diarrhea; and myositis
Cholestyramine	Bile acid sequestrants	August 3, 1973	4 to 24 g/day PO	Nausea, bloating, cramping, and constipation; elevations in hepatic transaminases and alkaline phosphatase. Impaired absorption of fat-soluble vitamins and coadministered medications including: Amiodarone, digoxin, warfarin, thiazides, beta blockers, levothyroxine, others; interaction can be minimized by taking other medications at least one hour before or four hours after bile acid sequestrant.
Colestipol		April 4, 1977	5 to 30 g/day PO	
Colesevelam		May 26, 2000	3.75 g/day PO	
Ezetimibe	Cholesterol absorption inhibitors	October 25, 2002	10 mg/day	Increased transaminases in combination with statins
Bempedoic acid	adenosine triphosphate -citrate lyase (ACL) inhibitors	February 21, 2020	180 mg/day	Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Bempedoic acid is associated with increased risk of tendon rupture or injury.
bempedoic acid and ezetimibe	(ACL) inhibitor and cholesterol absorption inhibitor combination	Feb 26, 2020	180 mg bempedoic acid/10 mg ezetimibe /day	Upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, elevated liver enzymes, diarrhea, arthralgia, sinusitis, fatigue, and influenza. Bempedoic acid is associated with increased risk of tendon rupture or injury.

* (b) (4)

**Liptruzet (ezetimibe / atorvastatin) was discontinued on June 2, 2015 and is no longer available in the United States.

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I agree with the findings and conclusions in Dr. Galescu’s review and concur with the approval recommendation. (Acting) Clinical Team Lead