CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213260Orig1s000

SUMMARY REVIEW

Cross-Discipline Team Leader Review

Date	1/24/2023
From	Jayabharathi Vaidyanathan, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 213260
Applicant	CMP Development LLC
Date of Submission	7/31/2022
PDUFA Goal Date	2/1/2023
Proprietary Name / Established (USAN) names	ATORVALIQ (Atorvastatin Calcium) Oral Suspension
Dosage forms / Strength	Suspension 4 mg/mL
Proposed Indication(s)	Treatment of adults with primary hyperlipidemia, homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia in adult and pediatric patients (10 to 17 years)
Recommendation	Approval

1. Introduction

On January 13, 2020, the applicant (CMP Development LLC) submitted NDA 213260 through the 505(b)(2) pathway for atorvastatin oral suspension, 4 mg/mL referencing Lipitor® (NDA 020702, atorvastatin calcium tablets) as the listed drug. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. The proposed indications are the same as the listed drug, prevention of cardiovascular disease (CVD) in adults (with multiple risk factors for CVD, diabetes and multiple risk factors for CVD, and with clinically evident CVD), and for the treatment of adults with primary and mixed hyperlipidemia, elevated triglyceride levels, dysbetalipoproteinemia, homozygous familial hypercholesterolemia (HoFH), and for heterozygous familial hypercholesterolemia (HeFH) in adults and pediatric patients (10-17 years).

A Complete Response (CR) was issued on 10/16/2020 due to inadequate bioavailability data to bridge to the efficacy and safety data of the listed drug Lipitor®. In addition, significant deficiencies were identified in the manufacturing process and facility inspection.

The applicant resubmitted their NDA on 7/31/2022.

2. Background

On 1/12/2018, the applicant submitted a Type B (Pre-IND 137915) meeting request to seek guidance on their development plan for their atorvastatin oral suspension. A Written Response was granted, and the Agency agreed to the applicant's plan to conduct the two relative

bioavailability studies (see COR-MEET-09 (Final Written Response) dated 3/8/2018 in DARRTS under IND 137915) – a fasting study comparing the bioavailability of the proposed product to Lipitor® and a food effect study with the proposed atorvastatin oral suspension.

The applicant submitted an initial pediatric study plan (iPSP) on 3/26/2019. The Division discussed the iPSP with the Pediatric Review Committee (PeRC) and an agreement letter was sent to the applicant on 9/12/2019 (see FRM-MINUTES-01 (Internal Meeting Minutes) dated 9/20/2019 in DARRTS under IND 137915).

The applicant submitted the NDA on 1/13/2020 and included the results of two relative 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."*

The clinical pharmacology review concluded that the data submitted to bridge the efficacy and safety data of the listed product, Lipitor® were unacceptable to support the approval of the NDA (see REV-CLINPHARM-21 (Primary Review) dated 9/8/2020 in DARRTS).

Study 18-VIN-0235 results indicated that the relative bioavailability between atorvastatin oral suspension and Lipitor® did not meet the conventional 80 ─125% criteria. The 90% confidence interval for the geometric mean ratios (GMRs) between atorvastatin oral suspension and the reference product for all primary PK parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) were outside the 80-125% limits for all moieties measured (atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin) under fasting conditions. In addition, Study 18-VIN-0236 showed that atorvastatin oral suspension had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in C_{max}) compared to the reported values of 9% reduction in AUC and 25% reduction in C_{max} for Lipitor® when administered with food.

Since the application did not contain clinical efficacy and safety data for the proposed formulation, relative bioavailability results were the fundamental bridge to the efficacy and safety data of the innovator product, Lipitor®. There was a wide fluctuation in atorvastatin and metabolite levels following administration of atorvastatin oral suspension compared to Lipitor® under both fasting and fed conditions. This variability could lead to loss of efficacy if atorvastatin oral suspension were administered under the fed condition since the magnitude of the decrease in atorvastatin and metabolites exposure was greater for atorvastatin oral suspension compared to Lipitor®. On the other hand, if the product were administered under fasting conditions, the large increase in atorvastatin and metabolites exposure following atorvastatin oral suspension compared to Lipitor® could lead to a safety issue. Thus, the clinical pharmacology and other relevant findings of Lipitor® could not be relied upon for the proposed atorvastatin oral suspension product.

The sponsor was recommended to either reformulate the proposed product and conduct additional relative bioavailability studies to demonstrate bioequivalence to the reference listed drug, Lipitor® or conduct a clinical efficacy study to support the effective and safe use of the proposed atorvastatin oral suspension. Refer to the CDTL memo in DARRTS (REV-SUMMARY-09 (CDTL Review)).

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

3. Quality (CMC/Device)

The final overall recommendation for this NDA resubmission from the Office of Pharmaceutical Quality (OPQ) is approval. OPQ review team has determined that the NDA meets all applicable standards to support the identity, strength, quality, and purity that the drug product purports to have (see REV-QUALITY-25 (Integrated Quality Review) dated 12/8/2022 in DARRTS).

Drug Substance:

The drug substance information was found to be adequate to support the approval of the NDA in the first cycle. The resubmission included updated drug substance specification to include particle size distribution justification and validated analytical method that was requested by the drug substance reviewer. The review concluded that the CMC information provided in the NDA resubmission and drug master files (DMF) was adequate.

Drug Product:
There were no pending issues from a drug product perspective that were included in the CR letter. The proposed product is a white to brown white, non-sterile, oral suspension packaged in a 150 mL amber glass bottle sealed with a child resistant closure. Each mL of atorvastatin calcium oral suspension contains the equivalent of 4 mg atorvastatin. The applicant included additional CMC data from a newly manufactured drug product batch (dosed in the new bioavailability study) in the NDA resubmission. The drug product reviewer concluded that the formulation composition, manufacturing process, quality standards, as well as the particle size distribution of the drug substance (used in the new study) remains unchanged. Overall, the drug product information is adequate.

Microbiological control information:
There was no change in the microbiology information. The microbiology quality was deemed adequate in the first review cycle and remains as adequate.

Biopharmaceutics:
The dissolution method information, method development information (i.e., method's discriminating ability to detect changes in critical material attributes and formulation variables), and dissolution acceptance criteria were acceptable in the first review cycle. The resubmission review concludes that the proposed quality control dissolution specification

remains unchanged, and the review concluded that the NDA contains adequate biopharmaceutics information.

Manufacturing process and facility:
The applicant satisfactorily responded to the Office of Pharmaceutical Manufacturing Assessment (OPMA/OPQ) deficiencies in the CR letter and updated the commercial batch records with respect to the process parameters, in-process control ranges, and equipment to be used for the commercial manufacturing.

The applicant transferred to a new facility, (b) (4) and withdrew the objectionable facility ((b) (4) The new facilities are compliant and OPMA/OPQ recommends approval for these newly listed facilities.

I concur with the OPQ review team's conclusion.

4. Nonclinical Pharmacology/Toxicology

No nonclinical pharmacology/toxicology information was included in the NDA resubmission. The nonclinical review concluded that there were no nonclinical concerns in the first review cycle and recommended 'approvable' action (see REV-NONCLINICAL-21 (Primary Review) dated 10/6/2020 in DARRTS).

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review has concluded that the submitted data are acceptable to support approval. The relative bioavailability study provides the scientific bridge to reference the effectiveness and safety of ATORVALIQ (atorvastatin calcium) oral suspension to the FDA's findings of the effectiveness and safety of the listed drug, Lipitor®. Due to the significant effect of food on the exposure of atorvastatin calcium suspension, it should be taken only on an empty stomach (see REV-CLINPHARM-21 (Primary Review) dated 1/20/2023 in DARRTS).

The applicant conducted two pilot and one pivotal (Study C1B1024) relative bioavailability studies to compare the bioavailability of atorvastatin oral suspension to Lipitor®. Study C1B1024 was an open label, randomized, 2-treatment, 4-period, 2-sequence, fully replicated, crossover, single dose study. A 7-day washout separated the 2 oral administrations. A total of 52 healthy men received treatments under fasting conditions, out of which 51 completed the study. The within subject standard deviation of the atorvastatin Cmax was > 0.294 and the atorvastatin Cmax was assessed via reference scaled bioequivalence approach, whereas the atorvastatin AUCt and AUCinf were assessed via the 2-way average bioequivalence approach (within subject standard deviations of AUCt and AUCinf were < 0.294).

The 95% upper confidence interval (critical bound) for the atorvastatin Cmax is -0.03395 (< 0). The 90% confidence interval of the ratio for atorvastatin AUCt and AUCinf between atorvastatin oral suspension and Lipitor® tablet was within 80% – 125%. Thus, the 80 mg/20 mL atorvastatin calcium oral suspension is bioequivalent to the 80 mg Lipitor® tablet.

To address the inconsistencies between the results of the two pilot studies (Study C1B1021 and Study C1B1023), the current pivotal study (Study C1B1023), and the pivotal study in the original submission (Study 18-VIN-0235), the review team checked the data integrity using the Data Anomalies in BioEquivalence R Shiny (DABERS) tool and did not find any issues. The review further explored the reasons behind the first failed pivotal study and found that the previous study had unusually low atorvastatin AUC values for both the reference and test treatment periods as compared to the pilot study as well as data from studies from literature. The applicant conducted the new study in a different clinical study site and this study site, appears reliable and within the surveillance period of the last FDA inspection.

The applicant did not conduct a food-effect study to respond to the CR letter. Instead, the applicant used the publicly available redacted review of Lipitor® and compared the % reduction observed after food administration in Study 18-VIN-0236 calculated via natural log-transformed least square mean values with the innovator's reported % reduction after food administration (natural log-transformed parameters). (b) (4) The innovator's food effect study was published in the *European Journal of Drug Metabolism and Pharmacokinetics* 2000;25:97-101." The article clearly shows that the food effect of Lipitor® was not assessed after natural log transformed least square mean values of atorvastatin Cmax and AUC(0-24). (b) (4) Thus, the results of the Study 18-VIN-0236 indicates that the atorvastatin oral suspension had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in Cmax) compared with the reported values of 9% reduction in AUC and 25% reduction in Cmax for Lipitor® when administered with food. Therefore, atorvastatin oral suspensions should be administered only on an empty stomach.

6. Clinical Efficacy & Safety

There are no new clinical efficacy or safety data essential for the risk/benefit assessment of atorvastatin oral suspension. The atorvastatin oral suspension development program included 2 pivotal bioavailability studies and a food effect study that examined single oral administration of a 4 mg/mL dose to a total of 125 subjects. The clinical reviewer concludes that no adverse events were included in the submission that would change the risk-benefit assessment of atorvastatin administered as an oral suspension (See Primary Review (REV-CLINICAL-21) dated 1/23/2023 in DARRTS).

7. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

8. Pediatrics

The safety and efficacy of atorvastatin calcium to treat HeFH in patients 10 to 17 years of age and to treat HoFH in patients 6 years of age and older has been established, as reflected in the Lipitor® packaging information. The applicant requested partial waivers for studies of HeFH in patients 0 to 9 years and for studies of HoFH in patients aged 0 to 5 years. Full waivers were also requested for pediatric studies in patients with cardiovascular disease (CVD), mixed dyslipidemia, familial hypertriglyceridemia, and dysbetalipoproteinemia.

The applicant's pediatric plan was discussed with PeRC, and the Agency agreed with the plan to request a full waiver for pediatric studies birth to less than 18 years of age with CVD, mixed dyslipidemia, familial hypertriglyceridemia, and dysbetalipoproteninemia 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 (see FRM-MINUTES-01 (Internal Meeting Minutes) dated 9/20/2019 in DARRTS under IND 137915).

9. Other Relevant Regulatory Issues

OSIS inspection

An Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and bioanalytical sites of the pivotal clinical pharmacology study, C1B01024. The Division of New Drug Study Integrity (DNDSI) within OSIS determined that an inspection was not warranted for the clinical and bioanalytical sites. The Office of Regulatory Affairs (ORA) inspected the clinical site in (b) (4), which falls within the surveillance interval. OSIS conducted a Remote Regulatory Assessment (RRA) for the analytical site in (b) (4) which also falls within the surveillance interval (see CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) in DARRTS dated 11/1/2022).

Financial Disclosure

FDA 3454 form was submitted confirming that the applicant of the submitted studies did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trial.

Proprietary name

Division of Medication Error Prevention and Analysis (DMEPA) has reviewed and concluded that the proposed proprietary name ATROVALIQ is acceptable (see REV-SURVEPI-10 (Proprietary Name Review) in DARRTS dated 10/24/2022).

10. Labeling

The labeling was revised for consistency with the listed drug, Lipitor®. In addition, the following labeling comments were included:

- Section 2: Take ATROVALIQ orally once daily at any time of the day, only on an empty stomach (1 hour before or 2 hours after a meal)
- Section 2, Missed dosing: Advise patients to take a missed dose as soon as possible. If the dose was missed by more than 12 hours, patients should not take the missed dose and resume with the next scheduled dose.
- Edit to use the established name (atorvastatin) when discussing the PK (e.g., plasma concentrations of atorvastatin), for risks reported with atorvastatin, and for efficacy data from clinical trials with atorvastatin.
- Section 12.3: Administration of ATORVALIQ with high fat meal resulted in a 30% and 63% decrease in atorvastatin AUC and Cmax, respectively, compared with what was observed in the fasted state. The decrease in exposure can be clinically significant, and therefore ATORVALIQ should be taken only on an empty stomach (1 hour before or 2 hours after a meal).
- Included 'linkage' statements in sections 6, 14, 8.4 to indicate that the data were derived from atorvastatin trials, not ATORVALIQ. Linkage statements have been included in 505b2 labeling to assist with clarifying when the data were not obtained with the 505b2 drug. Inclusion of linkage statements may be particularly helpful when the 505b2 drug has a different dosage form from the listed drug (as is the case for this labeling). For example, when discussing clinical data from the listed drug (Sections 6 and 14), the complete nonproprietary name of the listed drug should be used. Including linkage statements before the data from atorvastatin calcium tablets, will provide context to the healthcare provider as to why the labeling is discussing data from the tablet dosage form (as opposed to data from the oral solution).
- Added information that patients should always use a calibrated oral syringe or other oral dosing device, with metric units of measurements (i.e., mL), to correctly measure the prescribed amount of medication.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAYABHARATHI VAIDYANATHAN
01/25/2023 02:26:22 PM

JOHN M SHARRETTS
01/25/2023 02:28:10 PM

Cross-Discipline Team Leader Review

Date	10/15/2020
From	Jayabharathi Vaidyanathan, Ph.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 213260
Applicant	CMP Development LLC
Date of Submission	1/13/2020
PDUFA Goal Date	11/13/2020
Proprietary Name / Established (USAN) names	Atorvastatin Calcium Oral Suspension
Dosage forms / Strength	Oral Suspension 4 mg/mL
Proposed Indication(s)	Treatment of primary hyperlipidemia and homozygous familial hypercholesterolemia
Recommendation	Complete Response

1. Introduction

On January 13, 2020, the applicant (CMP Development LLC) submitted NDA 213260 via the 505(b)(2) pathway for atorvastatin oral suspension, 4 mg/mL referencing Lipitor® (NDA 020702, atorvastatin calcium tablets) as the listed drug. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, an enzyme that catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. The proposed indications are the same as the listed drug, prevention of cardiovascular disease (CVD) in adults (with multiple risk factors for CVD, diabetes and multiple risk factors for CVD, and with clinically evident CVD), and for the treatment of adults with primary and mixed hyperlipidemia, elevated triglyceride levels, dysbetalipoproteinemia, homozygous familial hypercholesterolemia (HoFH), and for heterozygous familial hypercholesterolemia (HeFH) in adults and pediatric patients (10-17 years).

The NDA will receive a Complete Response due to inadequate bioavailability data to bridge to the efficacy and safety data of the listed drug Lipitor®. In addition, significant deficiencies were identified in the manufacturing process and facility inspection.

2. Background

On 1/12/2018, the applicant submitted a Type B (Pre-IND 137915) meeting request to seek guidance on their development plan for their atorvastatin oral suspension. A Written Response was granted, and the Agency agreed to the applicant's plan to conduct the two relative bioavailability studies (see COR-MEET-09 (Final Written Response) dated 3/8/208 in DARRTS under IND 137915) – a fasting study comparing the bioavailability of the proposed product to Lipitor® and a food effect study with the proposed atorvastatin oral suspension.

The applicant submitted an initial pediatric study plan (iPSP) on 3/26/2019. The Division discussed the iPSP with the Pediatric Review Committee (PeRC) and an agreement letter was sent to the applicant on 9/12/2019 (see FRM-MINUTES-01 (Internal Meeting Minutes) dated 9/20/2019 in DARRTS under IND 137915). Refer to Section 8 of this review for details of the pediatric study plan.

3. Quality (CMC/Device)

The recommendation from the Office of Pharmaceutical Quality (OPQ) is a Complete Response action due to deficiencies related to process and facilities (specifically related to (b) (4) the drug product manufacturing site and (b) (4)., the drug substance testing site) (see REV-QUALITY-25 (Integrated Quality Review) dated 10/5/2020 in DARRTS).

Drug Substance:

The drug substance information was found to be adequate to support the approval of the NDA. The review concluded that the proposed atorvastatin calcium release testing is consistent with the USP monograph. The applicant's additional testing and stability data were found to be adequate.

Drug Product:
The proposed product is a white to brown white, non-sterile, oral suspension packaged in a 150 mL amber glass bottle sealed with a child resistant closure. Each mL of atorvastatin calcium oral suspension contains the equivalent of 4 mg atorvastatin. The composition of the proposed commercial product is the same as the one used in the relative bioavailability studies. The drug product was tested for appearance, identity, (b) (4) content, pH, assay, purity and impurities, deliverable volume, uniformity of dosage units, sedimentation volume, and zeta potential, and the proposed drug product specification was determined to be adequate.

Microbiological control information:
The microbiological controls information including drug product specification, was concluded to be adequate.

Biopharmaceutics:
The dissolution method information, method development information (i.e., method's discriminating ability to detect changes in critical material attributes and formulation variables), and dissolution acceptance criteria were acceptable, and the review concluded that the NDA contains adequate biopharmaceutics information.

Manufacturing process and facility:
The proposed commercial batch size is (b) (4) The composition of the drug product, the drug product manufacturing process, and the packaging system used to manufacture the drug

product used in the relative bioavailability studies are the same as that proposed for commercial use. The manufacturing process involves [redacted] Review of the manufacturing process controls and master batch records indicated that the proposed commercial [redacted] batch records are inadequate to support the NDA. The applicant will need to revise the submitted [redacted] batch records to address the process deficiency.

The facility review team concluded that the compliance status of the drug substance manufacturing facility ([redacted] – FDA Establishment Identifier (FEI)# [redacted]) is acceptable. The facility review team recommended withhold approval recommendation to [redacted], the drug substance testing facility and [redacted] the drug product manufacturing facility for the following reasons:

(1) [redacted] is currently under Official Action Indicated (OAI).

(2) [redacted] Based on the review of records obtained from [redacted] through 704(a)(4) records request process, the facility review team identified deficiencies related to [redacted]

The facility review team concluded that a satisfactory pre-approval inspection and/or adequate facility responses addressing these conditions are needed before this application may be approved.

I concur with the OPQ review team's conclusion.

4. Nonclinical Pharmacology/Toxicology

As per Pharmacology/Toxicology reviewers, the nonclinical studies submitted with this NDA and the applicant's reliance on the nonclinical safety information described for the listed drug is reasonable pending acceptable CMC information and in absence of any new safety concerns (e.g., due to unqualified impurities and degradants).

In the forced degradation studies with atorvastatin oral suspension, a degradation product ([redacted] was formed and was present at [redacted]% in the drug product. As it exceeded the qualification threshold of 0.5% described in the ICH Q3B(R2), and to address its safety, the applicant conducted a 90-day repeat -dose toxicity study in rats and compared the toxicity of atorvastatin containing [redacted] impurity compared to atorvastatin administered with minimal levels of the impurity. The study results showed that there were no new safety concerns with the degradant at clinically relevant exposures, and the [redacted] is considered qualified, and the applicant's proposed drug product specification limit for the degradation product is considered acceptable. The safety of all other excipients (methylparaben, ethylparaben, and propylparaben) in atorvastatin oral suspension was adequately justified.

Overall, the nonclinical review concluded that there are no nonclinical concerns and the NDA is approvable (see REV-NONCLINICAL-21 (Primary Review) dated 10/6/2020 in DARRTS). I concur with reviewer's assessment that there are no nonclinical pharmacology/toxicology issues that would preclude approval, and if the applicant chooses to reformulate their product to address clinical bioequivalence, additional nonclinical studies might be necessary to establish the safety of novel excipients or if there are any changes to the impurity/degradant profile of the reformulated product.

5. Clinical Pharmacology/Biopharmaceutics

The clinical pharmacology review has concluded that the data submitted to bridge the efficacy and safety data of the listed product, Lipitor® is unacceptable to support the approval of this NDA (see REV-CLINPHARM-21 (Primary Review) dated 9/8/2020 in DARRTS).

The applicant's submission included the results of two relative bioavailability studies – Study 18-VIN-0235, a crossover relative bioavailability study comparing the bioavailability of the atorvastatin oral suspension to that of the listed drug, Lipitor® under fasting conditions, and Study 18-VIN-0236, conducted to evaluate the effect of food on the pharmacokinetics (PK) of atorvastatin following administration of atorvastatin oral suspension under fasting and fed conditions.

Study 18-VIN-0235 results indicated that the relative bioavailability between atorvastatin oral suspension and Lipitor® did not meet the conventional 80 —125% criteria. The 90% confidence interval for the geometric mean ratios (GMRs) between atorvastatin oral suspension and the reference product for all primary PK parameters (AUC_{0-t}, $AUC_{0-\infty}$ and C_{max}) were outside the 80-125% limits for all moieties measured (atorvastatin, 2-hydroxy atorvastatin and 4-hydroxy atorvastatin) under fasting conditions. The exposure of atorvastatin, 2-hydroxy atorvastatin, and 4-hydroxy atorvastatin were (b) (4) , respectively following administration of atorvastatin oral suspension as compared to those following administration of Lipitor®.

In addition, Study 18-VIN-0236 showed that atorvastatin oral suspension had a greater magnitude of food effect (30% reduction in AUC and 63% reduction in C_{max}) compared to the reported values of 9% reduction in AUC and 25% reduction in C_{max} for Lipitor® when administered with food.

Since the application does not contain clinical efficacy and safety data for the proposed formulation, relative bioavailability results are the fundamental bridge to the efficacy and safety data of the innovator product, Lipitor®. The Sponsor's arguments (b) (4) are not adequate to overcome the failed bioequivalence study results.

There is a wide fluctuation in atorvastatin and metabolite levels following administration of atorvastatin oral suspension compared to Lipitor® under both fasting and fed conditions. This could lead to loss of efficacy when atorvastatin oral suspension is administered under the fed condition since the magnitude of the decrease in atorvastatin and metabolites exposure is greater for atorvastatin oral suspension compared to Lipitor®. On the other hand, if the product is administered under fasting conditions, the large increase in atorvastatin and metabolites exposure following atorvastatin oral suspension compared to Lipitor® will lead to a safety issue. Thus, the clinical pharmacology and other relevant findings of Lipitor® cannot be relied upon for the proposed atorvastatin oral suspension product.

I concur with the clinical pharmacology review conclusions, and the sponsor is recommended to either reformulate the proposed product and conduct additional relative bioavailability studies to demonstrate bioequivalence to the reference listed drug, Lipitor® or conduct a clinical efficacy study to support the effective and safe use of the proposed atorvastatin oral suspension.

6. Clinical Efficacy & Safety

There are no new clinical efficacy or safety data essential for the risk/benefit assessment of atorvastatin oral suspension.

7. Advisory Committee Meeting

There was no Advisory Committee Meeting for this application.

8. Pediatrics

The safety and efficacy of atorvastatin calcium to treat HeFH in patients 10 to 17 years of age and to treat HoFH in patients 6 years of age and older has been established, as reflected in the Lipitor® packaging information. The applicant requested partial waivers for studies of HeFH in patients 0 to 9 years and for studies of HoFH in patients aged 0 to 5 years. Full waivers were also requested for pediatric studies in patients with cardiovascular disease (CVD), mixed dyslipidemia, familial hypertriglyceridemia, and dysbetalipoproteinemia.

The applicant’s pediatric plan was discussed with PeRC, and the Agency agreed with the plan to request a full waiver for pediatric studies birth to less than 18 years of age with CVD, mixed dyslipidemia, familial hypertriglyceridemia, and dysbetalipoproteninemia 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 (see FRM-MINUTES-01 (Internal Meeting Minutes) dated 9/20/2019 in DARRTS under IND 137915).

9. Other Relevant Regulatory Issues

OSIS inspection

The Office of Study Integrity and Surveillance (OSIS) inspection was requested for the clinical and bioanalytical sites of the pivotal clinical pharmacology studies 18-VIN-0235 and 18-VIN-0236. The Division of New Drug Study Integrity (DNDSI) within OSIS determined that an inspection was not warranted for the clinical and bioanalytical sites. The rationale for this decision was that the most recent clinical and analytical inspections of these sites occurred in (b) (4) which fell within the requested surveillance interval. The final classification for the inspections was No Action Indicated (NAI), and therefore, an inspection was not warranted at this time (see CONSULT REV-DSI-05 (Bioequivalence Establishment Inspection Report Review) in DARRTS dated 03/19/2020).

Financial Disclosure

FDA 3454 form was submitted confirming that the applicant of the submitted studies did not enter into any financial arrangement with the listed clinical investigators that could influence the outcome of the trial.

Proprietary name

Division of Medication Error Prevention and Analysis (DMEPA) has reviewed and concluded that the proposed proprietary name is not acceptable from a safety perspective. The proposed proprietary name, (b) (4) could result in medication errors due to confusion with the applicant's proposed proprietary name for another product ((b) (4)) (see REV-SURVEPI-10 (Proprietary Name Review) in DARRTS dated 10/13/2020), due to similarity in spelling, orthographic and phonetic similarities and overlapping product characteristics.

10. Labeling

Since the application will be receiving a Complete Response, labeling will not be discussed in this review cycle.

11. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Complete Response

The information provided in this application does not provide adequate bioavailability data for the atorvastatin oral suspension to bridge to the efficacy and safety data of the listed drug Lipitor®. In addition, significant deficiencies were identified in the manufacturing process and facility inspection.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JAYABHARATHI VAIDYANATHAN
10/15/2020 02:42:30 PM

JOHN M SHARRETTS
10/15/2020 09:59:16 PM
I concur