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APPLICATION NUMBER:

213260Orig1s000

NON-CLINICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 213260
Supporting document/s:	SDN 1 and SDN 2
Applicant's letter date:	01/13/2020 and 02/13/2020
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Product:	Atorvastatin Oral Suspension
Indication:	Treatment of adults with primary hyperlipidemias, homozygous familial hypercholesterolemia and heterozygous familial hypercholesterolemia in adult and pediatric patients (10 to 17 years)
Applicant:	CMP development LLC
Review Division:	Division of Diabetes, Lipid Disorders, and Obesity
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1 Executive Summary

1.1 Introduction

The Applicant, CMP Development LLC, seeks approval of atorvastatin calcium oral suspension, 4 mg/mL (proposed tradename (b) (4)®) for the treatment of adults with primary, mixed 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), which was initially approved in 1996. The Applicant obtained a written 'right of reference' to Drug Master File (b) (4) for the atorvastatin drug substance.

1.2 Brief Discussion of Nonclinical Findings

Physiochemical characterization and clinical oral bioequivalence studies in healthy adult human subjects with atorvastatin calcium oral suspension (4 mg/mL at dose of 80 mg) compared to Lipitor® (80 mg tablets) provide the critical scientific data to support reliance on the safety of approved Lipitor® tablets. From a pharmacology/toxicology perspective, the Applicant's reliance on the nonclinical safety information described in the current label for Lipitor®, is reasonable pending acceptable CMC information, and in the absence of any new safety concerns (e.g., due to unqualified impurities and degradants, or concerns regarding the formulation).

In forced degradation studies with atorvastatin oral suspension, (b) (4) degradation product was formed, which was present at (b) (4)% in the drug product. This level exceeds the qualification threshold of 0.5% described in ICH Q3B(R2). To address the safety of (b) (4) and to support the proposed drug product specification of NMT (b) (4)%, the Applicant conducted a 90-day oral repeat-dose toxicity study in rats to compare th toxicity of atorvastatin containing (b) (4) impurity compared to atorvastatin administered with minimal levels of the impurity. Atorvastatin spiked with (b) (4) impurity and atorvastatin alone caused similar effects in rats when administered at doses up to 10 mg/kg/day, which represent exposures equivalent to the maximum human dose of 80 mg/day, based on body surface area comparison. Based on

the absence any new safety concerns with the degradant at clinically relevant exposures, the [redacted] degradant is considered qualified and the Applicant's proposed drug product specification limit for the [redacted] degradant (NMT [redacted]%) is considered acceptable.

The composition of the to-be-marketed atorvastatin drug product formulation, an oral suspension, differs from that of the listed drug product Lipitor®, an oral tablet. Three excipients, methylparaben, ethylparaben, and propylparaben, were identified as potentially exceeding the amounts present in prior FDA approved drug products for the same route of administration (oral) and duration of use (chronic) per the FDA inactive ingredients guide (IIG). Methyl, ethyl and propylparaben were added as [redacted] in atorvastatin oral suspension and their daily intake levels at the maximum human recommended human dose of atorvastatin (80 mg) are [redacted] mg/day, respectively. The individual and total amounts of methylparaben and ethylparaben included in atorvastatin oral suspension are within the group acceptable daily intake (ADI) established ([redacted] mg/day) for the total paraben (the sum of methyl and ethylparaben) suggested by the Joint FAO/WHO Expert Committee on Food Additives (JFECA)[1]. Propylparaben was excluded from the group ADI due to concerns over its potential estrogenic activity and adverse male reproductive toxicities reported at doses below the group ADI[2]. However, the amount of propylparaben present in atorvastatin oral suspension [redacted] mg/day) is well below a suggested permitted daily exposure (PDE) of [redacted] mg (i.e., [redacted] mg/kg/day assuming a body weight of 60 kg)[3] based on a well-conducted juvenile rat toxicity study, and is lower than the daily amount commonly consumed in foods[4], and also is below the level in one approved drug products indicated for a serious chronic indication ([redacted] mg/day). Therefore, the safety of all excipients in atorvastatin oral suspension are equately justified.

Nonclinical studies that addressed drug product-related safety issues (i.e., a [redacted] degradant), along with scientific rationale to support the safety of paraben excipients, are adequate to support the marketing of the proposed product [redacted]® (atorvastatin calcium oral suspension 4 mg/mL) from the Pharm/Tox perspective.

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[1]Evaluation of certain food additives and contaminants. Seventeenth report of the joint FAO/WHO expert committee on food additives. World Health Organ Tech Rep Ser 1974; No. 539.
[2]Evaluation of certain food additives and contaminants. Sixty-seventh report of the joint FAO/WHO expert committee on food additives. World Health Organ Tech Rep Ser 2006; No. 940.
[3]European Medicines Agency. Committee for Medicinal Products for Veterinary Use. European public MRL assessment report (EPMAR): Propyl 4-hydroxybenzoate and its sodium salts (all food producing species). EMA/CVMP/632934/2014, September 2015.
[4]M.G Soni., Safety assessment of esters of p-hydroxybenzoic acid (parabens). Food Chem Toxicol, 2005; 43 (7): 985-1015.

1.3 Recommendations

1.3.1 Approvability

This NDA is approvable from a pharmacology/toxicology perspective. We note that the clinical pharmacology and CMC reviewers recommended a complete response because the Applicant failed to establish clinical bioequivalence between atorvastatin oral suspension and Lipitor® and for deficiencies related to process and facilities, respectively. However, no additional nonclinical studies are recommended, because the risks associated with atorvastatin under or overdosing are established, and the CMC deficiencies do not have any nonclinical component. If the Applicant chooses to reformulate their product to address clinical bioequivalence issues, additional nonclinical studies might be necessary to establish the safety of novel excipients or as part of the process of evaluating the altered absorption/pharmacokinetic properties of a reformulated product. Nonclinical studies might also be warranted to qualify any changes in the impurity/degradant profile associated with reformulation, consistent with ICH thresholds.

1.3.2 Additional NonClinical Recommendations

None

1.3.3 Labeling

No labelling changes compared to the approved atorvastatin labeling (Lipitor® NDA 020702) are recommended.

2 Drug Information

2.1 Drug

CAS Registry Number
344423-98-9

Generic Name
Atorvastatin oral suspension

Code Name
N/A

Chemical Name
1H-pyrrole-1-heptanoic acid, 2-(4-fluorophenyl)-β, δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenyl-amino) carbonyl], calcium salt (2:1), trihydrate [R-(R*, R*)]

Reference ID: 4681694

Molecular Formula/Molecular Weight
$(C_{33}H_{34}FN_2O_5)_2Ca.3H_2O/1209.41$

Structure or Biochemical Description

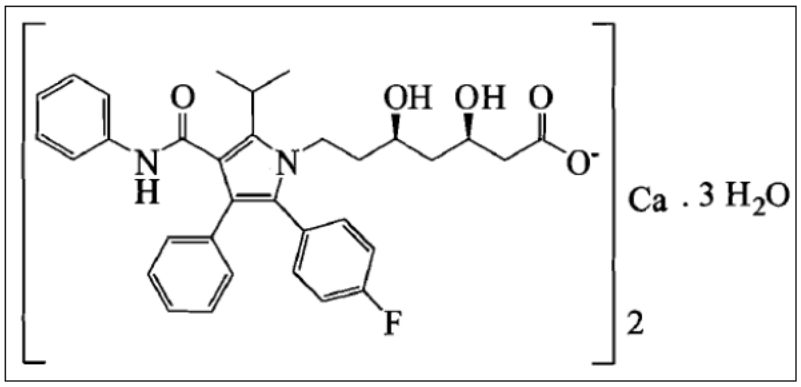


Figure 1. Structure of atorvastatin

Pharmacologic Class
HMG CoA-reductase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

NDA 020702 Atorvastatin calcium tablet; Pfizer
DMF (b) (4) Atorvastatin drug substance manufacturer; (b) (4)
DMF (b) (4) Orange flavor (b) (4) manufacturer; (b) (4)

2.3 Drug Formulation

The composition of the atorvastatin oral suspension (4 mg/mL) is given in the **Table 1** below.

Table 1. Composition of atorvastatin oral suspension 4 mg/ mL

Ingredient	Quality Standard	Function	% w/v	Quantity/mL (mg/mL)
Atorvastatin (as Atorvastatin Calcium Trihydrate)	USP	Active Pharmaceutical Ingredient	0.400	4.000
Carboxymethylcellulose Sodium	USP	(b) (4)		
Magnesium Aluminum Silicate	NF			
Methylparaben	NF			
Ethylparaben	NF			
Propylparaben	NF			
Sucralose	NF			
Acesulfame Potassium	NF			
Orange Flavor ((b) (4)	N/A			
(b) (4) Water	USP			
Total			100.0%	1 mL

[Applicant]

The composition of the orange flavoring agent is shown in the **Table 2** below:

Table 2. Quantitative composition of orange flavor ((b) (4)

Component	% w/w
(b) (4)	

[Applicant]

2.4 Comments on Novel Excipients

All the excipients included in the atorvastatin oral suspension are present in approved drug products and are listed in the FDA Inactive Ingredients Guide (IIG). The Applicant's comparison of the total daily intake of all the components of atorvastatin oral suspension (4 mg/mL) at the maximum recommended human dose (MRHD) of atorvastatin (80 mg/day ~ 20 mL) concluded that none exceed levels found in approved products listed in FDA IIG (**Table 3**). However, three excipients added as (b) (4) methylparaben, ethylparaben and propylparaben are present at higher level compared to IIG amounts for chronic oral administration. (b) (4)

(b) (4)

Therefore, the maximum potencies of methyl, ethyl and propylparaben listed in IIG are not adequate to support their inclusion in atorvastatin oral suspension, because the durations of use are not supported.

Table 3. Applicant's comparison of quantity of excipients to maximum limit specified in the IIG

Excipients	% w/v	Quantity/dose (mg/mL)	Quantity in mg per MDD (20 mL)	IIG limit from FDA Database	Route, Dosage Form	Justification
Carboxymethylcellulose Sodium, USP	(b) (4)			450 mg	Oral, Suspension	Meets IIG Limit
Magnesium Aluminum Silicate, NF				5000 mg/5 mL	Oral, Suspension	Meets IIG Limit
Methylparaben, NF				1000 mg/5 mL	Oral, Suspension	Meets IIG Limit
Ethylparaben, NF				50 mg/1 mL	Oral, Solution	Meets IIG Limit
Propylparaben, NF				200 mg/5 mL	Oral, Suspension	Meets IIG Limit
Sucralose, NF				230 mg	Oral, Solution	Meets IIG Limit
Acesulfame Potassium, NF				200 mg	Oral, Solution	Meets IIG Limit
Orange Flavor (b) (4)				N/A		
(b) (4)				*N/A*	*N/A*	Flavor used is less than (b) (4)% and does not need further justification
				N/A	*N/A*	Flavor used is less than (b) (4)% and does not need further justification
				N/A	*N/A*	Flavor used is less than (b) (4)% and does not need further justification
				(b) (4)		Meets IIG Limit
						Meets IIG Limit
				N/A	*N/A*	N/A

[Applicant]

Moreover, the daily intake of all the three parabens in the atorvastatin oral suspension is 2-times higher than those found simvastatin oral suspension (NDA 213260), recently for similar duration of use and indication (**Table 4**).

Table 4. Comparison of total daily intake of parabens in proposed atorvastatin oral suspension and approved simvastatin oral suspension

Component	Atorvastatin oral suspension (NDA 213260)	Simvastatin oral suspension (NDA 206679)
	4 mg/ mL	20 mg/5 mL and 40 mg/5 mL
Methylparaben, NF	(b) (4)	
Ethylparaben, NF		
Propylparaben, NF		

Parabens

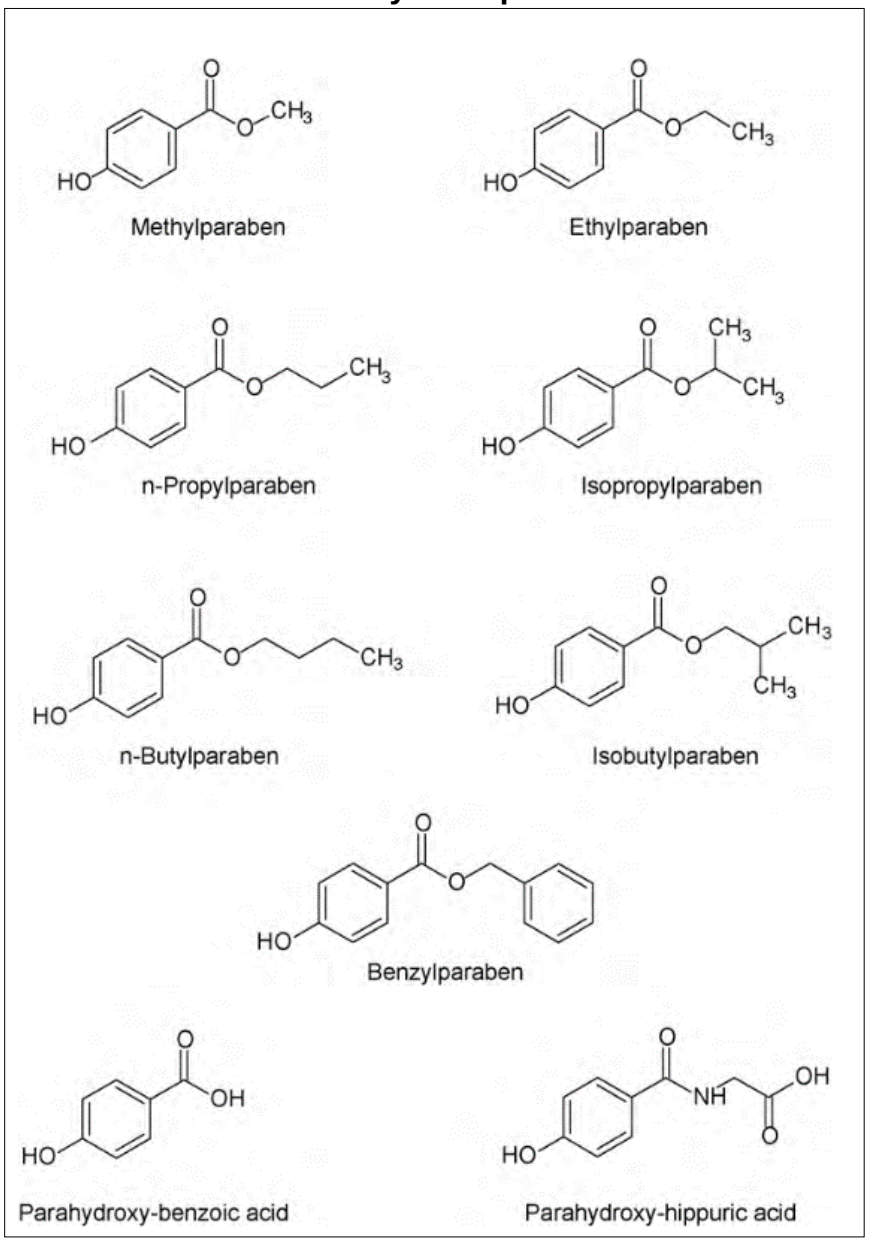
Parabens are family of alkyl esters of para-hydroxybenzoic acid that differ at the para position of the benzene ring by various chemical substitutions[5]. Within this family, methylparaben, ethylparaben, propylparaben and butylparaben are the most commonly used members, independently and in combination with each other. Parabens possess antimicrobial activity over a wide range of pH hence they are widely used as antimicrobial preservatives in foods, cosmetics, oral, and topical pharmaceutical formulations.

Parabens are rapidly absorbed through the skin and gastrointestinal tract, metabolized by esterases to P-hydroxybenzoic acid and excreted in urine, with a biological half-life of less than 24 hours. There is no solid evidence of accumulation within the body tissues or organs.

[5]Cashman AL and Warshaw EM Parabens: A review of Epidemiology, Structure, Allergenicity, and hormonal properties. Dermatitis, 2005;16(2): 57-66.

Reference ID: 4681694

Figure 2. Structures of commonly used parabens and their metabolites



[Reference: Boberg J *et al*][6]

In general, parabens show very limited effects in chronic oral studies, are negative in genotoxicity testing and are non-carcinogenic. Parabens have not been shown to produce fetal anomalies in animal studies even at levels that produce maternal toxicity[6]. The major nonclinical safety concerns identified with respect to parabens include disruption of endocrine function and male reproductive toxicity in juvenile animals.

[6]Boberg J *et al*., Possible endocrine disrupting effects of parabens and their metabolites. Reproductive Toxicol, 2010; 30(2):301-12.

Parabens are potential endocrine disruptors due to their ability to mimic estrogen[7]. In cell-based studies, all parabens are shown to bind rodent and human estrogen receptors (ERα and ERβ), albeit very weakly, with potencies between 10^4 and 10^7-fold lower than 17β-estradiol[8]. Estrogenic activity increases with increasing length of the alkyl chain with the order of potency (butyl>propyl>ethyl>methyl paraben) and their main metabolite p-hydroxybenzoic acid (PHBA) is inactive.

Most parabens were without any estrogenic effect in the in vivo uterotrophic assays in immature and ovariectomized animals, except butylparaben (which is not found in the to-be-marketed product) produced a small increase in uterus weights when given orally at dose levels from 800 to 1200 mg/kg/day[6,8]. In addition to the weak estrogenic activity, some studies reported potential adverse effects on male reproduction system including, low testosterone levels, and reduced sperm count and sperm production in juvenile male rats with oral dietary doses of propylparaben at ≥ 10 mg/kg/day and butylparaben at ≥ 15 mg/kg/day[9,10]. Neither methylparaben nor ethylparaben showed any effect on male reproductive organs when given at dietary doses of up to 1000 mg/kg/week for 8 weeks[11]. The exact mechanism and human relevance of these reproductive effects are unknown.

Safety assessment of parabens

The FDA granted GRAS status to methylparaben and propylparaben as a preservative for its intended use as an addition to foods with a limit of 0.1% (21 CFR 184.1490). The Joint FAO/WHO Expert Committee on Food Additives (JECFA) evaluated the safety of parabens in 1972, issued a recommendation on the group acceptable daily intake (ADI) of the sum of methyl, ethyl and propylparabens and their sodium salts up to 10 mg/kg/day (600 mg for 60 kg individual)[1]. Later, propylparaben was withdrawn from the group ADI in view of the concerning estrogenic activity and adverse male reproductive effects in juvenile rats at doses within the range of the group ADI[2].

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[7]Darbre PD *et al*., Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. J Appl Toxicol, 2008;28(5): 561-78.

[8]Routledge EJ *et al*., Some alkyl hydroxy benzoate preservatives (paraben) are estrogenic. Toxicol Appl Pharmacol, 1998; 153(1):12-9.

[9]Oishi S., Effects of propyl paraben on the male reproductive system. Food Chem Toxicol, 2002;40(12):1807-13.

[10]Oishi, S., Effects of butyl paraben on the male reproductive system in mice. Arch Toxicol, 2002; 76(7):423-9.

[11]Oishi S., Lack of spermatotoxic effects of methyl and ethyl esters of p-hydroxybenzoic acid in rats. Food Chem Toxicol, 2004;42(11):1845-9.

Reference ID: 4681694

Methylparaben
The total daily intake of methylparaben in atorvastatin oral suspension would be (b) (4) mg when this product is used at the MRHD and this amount exceeds the maximum daily intake listed in IIG (**Table 3**). However, the proposed level of methylparaben is below the established group ADI 600 mg/day (0-10 mg/kg/day for 60 kg individual) and it only represent (b) (4)% of the ADI. Likewise, the sum of methyl-and ethylparaben (b) (4) mg) did not exceed th group ADI. Therefore, the level of methylparaben (b) (4) mg) in atorvastatin oral suspension is considered acceptable.

Ethylparaben
The total daily intake of ethylparaben would be (b) (4) mg when atorvastatin oral suspension is consumed at the MRHD and this level exceeds the value listed in the IIG (**Table 3**). Nevertheless, the proposed level of ethylparaben alone or summed up with methylparaben ((b) (4) mg) in the atorvastatin oral suspension is much below the group ADI of 600 mg/day. Therefore, the amount of ethylparaben is considered acceptable.

Propylparaben
The total daily intake of propylparaben is (b) (4) mg from the product. In 2007, JECFA excluded propylparaben from the group ADI of 600 mg/day due to adverse effects on male reproductive parameters in juvenile rats[2]. In receptor binding assays, propylparaben produced weak (30,000-fold less than endogenous ligand estradiol) transactivation of the estrogen receptors and it was inactive in uterotrophic assays in immature or ovariectomized female rats. Administration of propylparaben in the diet to 3 weeks old juvenile male rats (postnatal day (PND) 19-21) at doses of 0.01, 0.1 and 1% (equivalent to 0.1, 1, 10 mg/kg/day) for 4 weeks caused reduction in epididymal sperm reserve, daily sperm production in the testis at all doses and dose-related low serum concentration of testerone at ≥ 1 mg/kg/day[9]. No NOAEL was established in this study and the doses which were associated with adverse male reproductive effects are within the JECFA group ADI (0-10 mg/kg/day). However, extensive and GLP studies conducted subsequently with propylparaben did not reproduce the adverse reproductive toxicity noted in juvenile male rats[12,13].

In 2015, the European Medicines Agency (EMA) released a reflection paper and assigned permitted daily exposure (PDE) value of 2 mg/kg/day (120 mg for ~120 mg assuming a patient weighing 60 kg) for the use of propylparaben in adult and pediatric patients[3]. The

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[12]Gazin V, et al., Oral propylparaben administration to juvenile male Wistar rats did not induce toxicity in reproductive organs. 2013; 136(2): 392-401.

[13]Sivaraman L *et al*., Safety assessment of propylparaben in juvenile rats. Regul Toxicol Pharmacol, 2018; 92:370-381.

Reference ID: 4681694

PDE was calculated based on a conservative oral NOEL of 100 mg/kg/day identified in the study that showed propylparaben-related estrogenic effect (i.e., earlier onset of puberty and increased weight of uterus) in juvenile female rats treated at 1000 mg/kg/day from PND 4 through PND 90. The level of propylparaben in the to be marketed atorvastatin oral suspension (b) (4) mg/day) is approximately (b) (4)-times lower than the PDE value established by EMA.

Propylparaben is found in numerous foods, especially in cakes, pie-crusts, pastries, icings, toppings and fillings, and the average daily intake of propylparaben may be as high as 238 mg in adults, which greatly exceeds the (b) (4) mg daily human exposure from atorvastatin oral suspension **(Table 5)**.

This reviewer also found one U.S.-approved product, (b) (4) that contains propylparaben at (b) (4) mg/5 mL level. At the maximum recommended human dose of (b) (4) mg/day), the daily exposure to propylparaben will be (b) (4) mg/day, which exceeds the amount contained in atorvastatin oral suspension.

Taken together, the level of propylparaben in atorvastatin oral suspension is considered reasonably safe based on a toxicity study in juvenile rats, higher daily exposures to parabens reported from food, and greater amounts found in at least one U.S.-approved product indicated for chronic use.

Table 5. Possible average daily intake methyl and propylparaben

Table 2
Possible average daily intake of methyl and propyl paraben (LSRO/FASEB (1972)

Age group	Possible daily intake in mg							
	Total				Per kg body weight[a]			
	Average		Maximum		Average		Maximum	
	Methyl	Propyl	Methyl	Propyl	Methyl	Propyl	Methyl	Propyl
0–5 months	5	5	9	10	1	1	2	2
6–11 months	49	56	108	124	6	7	14	16
12–23 months	93	105	155	179	8	10	14	16
2–65+ years	222	238	347	381	4	4	6	6

[a] Calculations based on an average body weight of 60 kg for an adult. For infants the estimated body weights by age group were 0–5 months, 5 kg; 6–11 months, 8 kg; 12–23 months, 11 kg.

[Reference: M.G Soni., Food Chem Toxicol, 2005; 43 (7): 985-1015][4]

Orange Flavor ((b) (4)
Orange flavor (b) (4) is manufactured under DMF (b) (4), which is held by (b) (4). The flavoring substances used in the orange flavor are considered GRAS and are present below (b) (4)%, and (b) (4) are found in approved drug products. The amounts present in atorvastatin oral suspension are below listed in IIG levels for chronic oral administration.

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In conclusion, the levels of all excipients in the atorvastatin oral suspension formulation when ingested at the maximum recommended human dose are considered acceptable from the pharmacology/toxicology perspective and do not pose any significant toxicologic concerns.

2.5 Comments on Impurities/Degradants of Concern

Drug substance impurities

The Applicant references DMF [(b) (4)] ([(b) (4)] for atorvastatin drug substance. No drug substance-related impurities of concern were identified.

Drug product impurities/degradants

Forced degradation studies with atorvastatin oral suspension identified, [(b) (4)] [(b) (4)] degradant present in the finished product at [(b) (4)]%. This level exceeds the ICH Q3B (R2) threshold of 0.5% (**Table 6**).

In order to qualify this degradant and support the proposed drug product specification for [(b) (4)] of NMT [(b) (4)]%, the Applicant conducted the 90-day repeat dose rat comparative toxicity study with atorvastatin enriched with the [(b) (4)] impurity versus atorvastatin lacking the impurity. The rat study did not identify any safety concern for the [(b) (4)] degradant (see the general toxicology section 6.2). Therefore, the currently proposed drug product specification of NMT [(b) (4)]% [(b) (4)] is acceptable.

Table 6. Justification of specified identified degradation product of drug product

Chemical Name	Code #	MDD of Drug (mg)	QT (%)	QT (TDI)	Regulatory QT Threshold (%)	Proposed Release AC (%)	Justification if proposed AC (%) > Regulatory QT Threshold (%)
(b) (4)							

[Applicant]

2.6 Proposed Clinical Population and Dosing Regimen

Atorvastatin oral suspension's proposed indication is the same as for Lipitor® tablets, which is for the treatment of adult patients with primary hyperlipidemia (heterozygous familial and nonfamilial), mixed dyslipidemia, homozygous familial hypercholesterolemia, reduction of cardiovascular event risk and in pediatric patients (10-17%) with HeFH.

2.7 Regulatory Background

The Applicant submitted a Type-B meeting (Pre-IND 137915) on 02/05/2018 to request FDA guidance on their clinical and non-clinical development plans for the proposed liquid formulation of atorvastatin. The Applicant conducted two clinical bioequivalence studies, performed CMC characterization, and completed one impurity/degradant qualification study in rats as bridging studies for NDA for atorvastatin oral suspension (NDA 213260) via the 505(b)(2) pathway.

3 Studies Submitted

3.1 Studies Reviewed

Repeated Dose (90 Days) Oral Toxicity Study of Atorvastatin Calcium spiked with (b) (4) Impurity in Wistar Rats

3.2 Studies Not Reviewed

None

3.3 Previous Reviews Referenced

NDA 206679 (simvastatin oral suspension)

4 Pharmacology

4.1 Primary Pharmacology

No new pharmacology studies were submitted by the Applicant NDA 213260 for atorvastatin oral suspension. The Applicant refers to the existing pharmacological information from the label for Lipitor® (NDA 020702).

Atorvastatin is a selective and competitive inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, the rate-limiting enzyme that converts HMG-CoA to mevalonate, a precursor of sterols, including cholesterol.

In animal models, atorvastatin lowers plasma cholesterol and lipoprotein levels by inhibiting HMG-CoA reductase and cholesterol synthesis in the liver and by increasing the number of hepatic low-density lipoprotein (LDL) receptors on the cell surface to enhance update and catabolism of LDL; atorvastatin also reduces LDL production and the number of LDL particles.

5 Pharmacokinetics/ADME/Toxicokinetics

Atorvastatin pharmacokinetics and toxicokinetics are extensively characterized in nonclinical studies completed and reviewed to support the approval of Lipitor® (NDA 020702). The clinical pharmacology of atorvastatin is described in detail in the section 12 of Lipitor label® (NDA 020702).

6 General Toxicology

6.2 Repeat-Dose Toxicity+

6.2.1 Repeated Dose (90 Days) Oral Toxicity Study of Atorvastatin Calcium spiked with (b) (4) Impurity in Wistar Rats

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Study no.:	(b) (4)/0918/G/T069
Study report location:	EDR: SDN1
Study initiation date:	June 20, 2019
Conducting laboratory and location:	(b) (4)
Duration:	90
Duration Units:	days
GLP compliance:	Y
Drug, lot #, and % purity:	Atorvastatin Calcium, AC1m0600614, (b) (4)% (b) (4)

Key Findings

- With NDA 213260, the Applicant submitted one toxicology study to qualify a drug product impurity ((b) (4)) since the level of (b) (4) in the atorvastatin drug product (b) (4)%) exceeded qualification specification set (0.5%) in accordance with ICH Q3B (R2) qualification threshold.
- Wistar rats (10 animals/sex/group, 6 to 8 weeks of age) were orally administered vehicle, atorvastatin spiked with up to (b) (4) impurity at 2.5, 5 and 10 mg/kg/day or atorvastatin alone (10 mg/kg/day) by once-daily oral gavage for 90 days.
- Oral administration of atorvastatin calcium spiked with (b) (4) impurity and atorvastatin alone were found to be well tolerated and were devoid of any obvious signs of toxicity up to the maximum tested dose of 10 mg/kg/day with (b) (4) or alone.
- Atorvastatin calcium spiked with (b) (4) impurity demonstrated a comparable safety profile with that of Atorvastatin Calcium at similar dose levels.
- Based on the findings, the no observed adverse effect level (NOAEL) of atorvastatin calcium spiked with the (b) (4) impurity in Wistar rat following oral administration for 90 consecutive days is 10 mg/kg/day.

Methods

Doses:	Spiked: 0, 2.5, 5 and 10 mg/kg/day Unspiked: 10 mg/kg/day
Frequency of dosing:	Daily
Number/Sex/Group:	10/sex/group
Dose volume:	10 mL/kg
Formulation/Vehicle:	0.5 % w/v Sodium Carboxy Methyl Cellulose
Route of administration:	ORAL GAVAGE
Species:	RAT
Strain:	WISTAR
Age / Sexual Maturity:	6 to 8 weeks
Comment on Study Design and Conduct:	None
Dosing Solution Analysis:	Acceptable (Assay means fall within 100 ±15%)

Reference ID: 4681694

Observations and Results

All the animals were normal and were free from all visible clinical signs throughout the study period. Neurobehavioral observations carried out during the last week of exposure period revealed normal home cage, handling and open field behavior in all animals. No abnormalities were detected in the ophthalmoscopic examination of animals before treatment and also during the last week of exposure. Weekly body weight and food consumption of all test and reference item treated groups were comparable to the vehicle control group. Atorvastatin calcium spiked with (b) (4) did not reveal any treatment related changes in any of the hematology, clinical chemistry and urinalysis parameters at all dose levels tested. No treatment related changes were observed in the absolute and relative organ weights of animals treated with the test items. Gross and histopathological observations did not reveal any lesions attributable either to atorvastatin or (b) (4) impurity.

7 Genetic Toxicology

The genotoxic potential of atorvastatin was studied previously (NDA 020702) and summarized in the Section 13 of Lipitor® label as follows:

Atorvastatin was not mutagenic or clastogenic in the following in vitro tests with and without metabolic activation: the Ames test with Salmonella typhimurium and Escherichia coli, the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the in vivo mouse micronucleus test.

8 Carcinogenicity

The carcinogenicity potential of atorvastatin was evaluated previously (NDA 020702) and summarized in the Section 13 of Lipitor® label as follows:

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma $AUC_{(0\text{-}24)}$ value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma $AUC_{(0\text{–}24)}$ values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose.

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9 Reproductive and Developmental Toxicology

The reproductive toxicology of atorvastatin was characterized previously (NDA 020702) and is summarized in the Section 8 of Lipitor® label as follows:

Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was aplasia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m^2). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day.

Atorvastatin is present the in rat milk.

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/s/

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10/06/2020 01:04:14 PM

CALVIN L ELMORE
10/06/2020 01:28:54 PM
Concur with recommendation.