Table 96 Primary Hypercholesterolemia Long-term Ezetimibe Experience Summary Of Adverse Events

Event	Number and (Percent) of Patients: All Reported After Assignment of Ezetimibe[a] (n=1624)	Number and (Percent) of Patients: Reported During Ezetimibe Monotherapy (n=1624/1094)[b]
Total Deaths in Long-Term Experience	4	3
[Previously Reported Death During P00474][c]	[1]	[1]
Serious Adverse Events Present During Entirety of Long-Term Experience	136 (8)	75 (7)[b]
[Subjects With Serious Adverse Events Previously Reported Present During P00474 and P00475]	[26]	[26]
Discontinuations Due to Adverse Events	172 (11)	146 (13)[b]
[Previously Reported Discontinuations Due to Adverse Events During P00474 and P00475]	[51]	[51]
Treatment-Emergent Adverse Events of Any Intensity	1353 (83)	1256 (77)
Severe, Treatment-Emergent Adverse Event	187 (12)	153 (9)
Life-Threatening, Treatment-Emergent Adverse Event	20[d] (1)	13[d] (<1)

NOTE: The median duration of participation is 12.8 months for "All Reported After Assignment of Ezetimibe" and 9.0 months for "Reported During Ezetimibe Monotherapy."

a: Including coadministration with statin, and ezetimibe experience in subjects whose statin dosing record subsequently stopped.

b: For deaths, serious adverse events, and discontinuation because of adverse event, this represents the "pure ezetimibe monotherapy data subset (no statin administered)," for which n = 1094 and median duration of participation is 12.1 months.

c: See Section 4.1.1.1.2.1..

d: The fatal myocardial infarction suffered by Subject P00476-048/0417 was not included in the data base as an adverse event because it occurred after the cut-off date for inclusion in the interim evaluation. The death was captured, however, and is noted in this table

Table 97 Primary Hypercholesterolemia
Long-term Ezetimibe Experience
Serious Adverse Events (SAEs)

Number and (Percent) of Patients

Body System/Organ Class and Adverse Event	All Reported After Assignment of Ezetimibe[a] (n=1624)	Reported in Pure Ezetimibe Monotherapy Subset (n=1094)
ANY ADVERSE EVENT	**136 (8)**	**75 (7)**
BENIGN AND MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)	**24 (1)**	**14 (1)**
BARRETT'S ESOPHAGUS	1 (<1)	0
BASAL CELL CARCINOMA	7 (<1)	3 (<1)
BREAST NEOPLASM MALIGNANT FEMALE	2 (<1)	1 (<1)
COLON CARCINOMA	1 (<1)	1 (<1)
ESOPHAGEAL CARCINOMA	1 (<1)	1 (<1)
HODGKIN'S DISEASE NOS	1 (<1)	1 (<1)
NEOPLASM NOS	1 (<1)	1 (<1)
NON-HODGKIN'S LYMPHOMA NOS	1 (<1)	0
PROSTATIC CANCER	4 (<1)	3 (<1)
RECTAL CARCINOMA	1 (<1)	1 (<1)
RECURRENT CANCER	1 (<1)	1 (<1)
RENAL CARCINOMA	1 (<1)	0
SKIN CARCINOMA	1 (<1)	0
SQUAMOUS CELL CARCINOMA	5 (<1)	2 (<1)
BODY AS A WHOLE - GENERAL DISORDERS	**19 (1)**	**9 (<1)**
ANOREXIA	1 (<1)	0
CHEST PAIN	9 (<1)	5 (<1)
DEATH	2 (<1)	1 (<1)
DIZZINESS	2 (<1)	1 (<1)
EDEMA LEGS	1 (<1)	1 (<1)
FATIGUE	1 (<1)	0
FLANK PAIN	1 (<1)	0
RIGORS	1 (<1)	0
SYNCOPE	3 (<1)	1 (<1)

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Table 97 Continued.

Body System/Organ Class and Adverse Event	Number And (Percent) Of Patients: All Reported After Assignment of Ezetimibe[a] (n=1624)	Number And (Percent) Of Patients: Reported in Pure Ezetimibe Monotherapy Subset (n=1094)
CARDIOVASCULAR DISORDERS, GENERAL	**23 (1)**	**7 (<1)**
ANGINA PECTORIS	6 (<1)	1 (<1)
ANGINA PECTORIS AGGRAVATED	3 (<1)	1 (<1)
AORTIC STENOSIS	2 (<1)	1 (<1)
CORONARY ARTERY DISORDER	7 (<1)	2 (<1)
HYPERTENSION	1 (<1)	0
HYPERTENSION AGGRAVATED	1 (<1)	0
HYPOTENSION	1 (<1)	0
HYPOTENSION POSTURAL	1 (<1)	1 (<1)
MYOCARDIAL INFARCTION	7 (<1)	2 (<1)
PERICARDITIS	1 (<1)	1 (<1)
CENTRAL AND PERIPHERAL NERVOUS SYSTEM DISORDERS	**8 (<1)**	**4 (<1)**
ATAXIA	1 (<1)	1 (<1)
AUTONOMIC NEUROPATHY	1 (<1)	0
CEREBRAL INFARCTION	1 (<1)	0
CEREBROVASCULAR ACCIDENT NOS	1 (<1)	1 (<1)
HYPOESTHESIA	1 (<1)	0
MENINGITIS	1 (<1)	1 (<1)
SPINAL STENOSIS NOS	1 (<1)	1 (<1)
TRANSIENT ISCHEMIC ATTACK	2 (<1)	0
DISORDERS OF THE EAR AND LABYRINTH	**3 (<1)**	**2 (<1)**
CHOLESTEATOMA	1 (<1)	1 (<1)
LABYRINTHINE DISORDER	1 (<1)	0
SENSATION OF BLOCK IN EAR	1 (<1)	1 (<1)
VERTIGO	1 (<1)	1 (<1)
VESTIBULAR DISORDER	1 (<1)	0
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST	**5 (<1)**	**4 (<1)**
ENDOMETRIOSIS	1 (<1)	0
HYSTERECTOMY	1 (<1)	0
OVARIAN CYST	1 (<1)	1 (<1)
UTERINE FIBROID	3 (<1)	3 (<1)
UTERINE PROLAPSE	1 (<1)	1 (<1)
ENDOCRINE DISORDERS	**1 (<1)**	**1 (<1)**
DIABETES MELLITUS	1 (<1)	1 (<1)

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Table 97 Continued.

Body System/Organ Class and Adverse Event	Number And (Percent) Of Patients: All Reported After Assignment of Ezetimibe[a] (n=1624)	Number And (Percent) Of Patients: Reported in Pure Ezetimibe Monotherapy Subset (n=1094)
GASTROINTESTINAL SYSTEM DISORDERS	**10 (<1)**	**4 (<1)**
ABDOMINAL PAIN	4 (<1)	1 (<1)
ABDOMINAL PAIN AGGRAVATED	1 (<1)	0
APPENDICITIS	3 (<1)	0
COLONIC POLYP	1 (<1)	1 (<1)
DYSPHAGIA	1 (<1)	1 (<1)
GASTRITIS	1 (<1)	0
GASTROINTESTINAL DISORDER NOS	1 (<1)	1 (<1)
GASTROESOPHAGEAL REFLUX	1 (<1)	1 (<1)
NAUSEA	3 (<1)	1 (<1)
PEPTIC ULCER	1 (<1)	0
HEART RATE AND RHYTHM DISORDERS	**5 (<1)**	**4 (<1)**
FIBRILLATION ATRIAL	4 (<1)	3 (<1)
PALPITATION	1 (<1)	1 (<1)
INFECTION AND INFESTATIONS	**7 (<1)**	**3 (<1)**
EAR INFECTION NOS	1 (<1)	1 (<1)
OTITIS MEDIA	1 (<1)	1 (<1)
PNEUMONIA	3 (<1)	0
TOOTH ABSCESS	1 (<1)	1 (<1)
WOUND INFECTION	1 (<1)	0
INJURY AND POISONING	**11 (<1)**	**9 (<1)**
COMPRESSION FRACTURE	1 (<1)	1 (<1)
CONCUSSION	2 (<1)	2 (<1)
CONTUSION	2 (<1)	2 (<1)
FRACTURE	2 (<1)	2 (<1)
FRACTURE, BONE	5 (<1)	4 (<1)
INJURY ACCIDENTAL	4 (<1)	3 (<1)
LACERATION, SKIN	1 (<1)	1 (<1)
LIVER AND BILIARY SYSTEM DISORDERS[b]	**16 (<1)**	**9 (<1)**
CHOLECYSTITIS	8 (<1)	2 (<1)
CHOLELITHIASIS	5 (<1)	2 (<1)
GALLBLADDER DISEASE	2 (<1)	2 (<1)
GAMMA-GT INCREASED	1 (<1)	1 (<1)
HEPATIC ENZYMES INCREASED	1 (<1)	0
HEPATIC FUNCTION ABNORMAL	1 (<1)	1 (<1)
SGOT INCREASED	4 (<1)	4 (<1)
SGPT INCREASED	3 (<1)	3 (<1)

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Table 97 Continued.

Body System/Organ Class and Adverse Event	Number And (Percent) Of Patients: All Reported After Assignment of Ezetimibe[a] (n=1624)	Number And (Percent) Of Patients: Reported in Pure Ezetimibe Monotherapy Subset (n=1094)
METABOLIC AND NUTRITIONAL DISORDERS	**3 (<1)**	**2 (<1)**
CALCINOSIS	1 (<1)	1 (<1)
CREATINE PHOSPHOKINASE INCREASED	1 (<1)	1 (<1)
HYPOKALEMIA	1 (<1)	0
MUSCULOSKELETAL SYSTEM DISORDERS	**15 (<1)**	**9 (<1)**
ARTHRALGIA	1 (<1)	0
ARTHRITIS	2 (<1)	1 (<1)
ARTHRITIS AGGRAVATED	1 (<1)	1 (<1)
BACK PAIN	3 (<1)	3 (<1)
BACK PAIN, AGGRAVATED	1 (<1)	0
HERNIA	1 (<1)	1 (<1)
HERNIA AGGRAVATED	1 (<1)	0
JOINT DISLOCATION	1 (<1)	1 (<1)
MUSCULOSKELETAL PAIN	3 (<1)	3 (<1)
SPINAL DISORDER	3 (<1)	0
TENDON RUPTURE	1 (<1)	1 (<1)
PLATELET, BLEEDING AND CLOTTING DISORDERS	**2 (<1)**	**2 (<1)**
HEMATOMA	1 (<1)	1 (<1)
HEMORRHAGE NOS	1 (<1)	1 (<1)
PSYCHIATRIC DISORDERS	**1 (<1)**	**1 (<1)**
AMNESIA	1 (<1)	1 (<1)
RENAL AND URINARY SYSTEM DISORDERS	**2 (<1)**	**0**
BLADDER CALCULUS	1 (<1)	0
HEMATURIA	1 (<1)	0
RENAL CALCULUS	1 (<1)	0
URETHRAL STRICTURE NOS	1 (<1)	0
RESPIRATORY SYSTEM DISORDERS	**7 (<1)**	**3 (<1)**
ASTHMA	1 (<1)	1 (<1)
COPD AGGRAVATED	1 (<1)	1 (<1)
DYSPNEA	3 (<1)	0
DYSPNEA AGGRAVATED	1 (<1)	0
EMPHYSEMA	1 (<1)	1 (<1)
PULMONARY EDEMA	1 (<1)	1 (<1)

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Table 97 Continued.

Body System/Organ Class and Adverse Event	All Reported After Assignment of Ezetimibe[a] (n=1624) Number And (Percent) Of Patients	Reported in Pure Ezetimibe Monotherapy Subset (n=1094) Number And (Percent) Of Patients
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	**3 (<1)**	**3 (<1)**
CELLULITIS	2 (<1)	2 (<1)
PANNICULITIS	1 (<1)	1 (<1)
SURGICAL AND MEDICAL PROCEDURES	**30 (2)**	**13 (1)**
CHOLECYSTECTOMY	10 (<1)	5 (<1)
PROCEDURE	2 (<1)	2 (<1)
PROCEDURE (NO ADVERSE EVENT)	20 (1)	8 (<1)
VASCULAR (EXTRACARDIAC) DISORDERS	**6 (<1)**	**2 (<1)**
AORTIC ANEURYSM	2 (<1)	1 (<1)
ARTERIAL OCCLUSION NOS	1 (<1)	0
PERIPHERAL ISCHEMIA AGGRAVATED	1 (<1)	0
THROMBOPHLEBITIS DEEP	1 (<1)	1 (<1)
VASCULAR DISORDER	1 (<1)	0

NOTE: The median duration of participation is 12.8 months for "All Reported After Assignment of Ezetimibe" and 12.1 months for "Reported in Pure Ezetimibe Monotherapy Subset."

a: Including coadministration with statin, and ezetimibe experience in subjects whose statin was subsequently discontinued.

b: SGOT = AST; SGPT = ALT.

NOS = not otherwise specified.

Table 98 Primary Hypercholesterolemia
Long-term Experience With
Ezetimibe Coadministered With A Statin
Summary Of Adverse Events

Number and (Percent) of Patients

Event	Reported During Coadministration[a] (n=1281)
Total Deaths During Long-Term Coadministration	2 (0.16)
[Previously Reported Death During Coadministration in P00476]	[1]
Serious Adverse Events	75 (5.9)
[Subjects With Serious Adverse Events Previously Reported Present During Coadministration in P00476]	[44]
[Subjects With Serious Adverse Events Previously Reported Present During Coadministration in P00691]	[1]
Discontinuation Due to Adverse Events	64 (5.0)
[Previously Reported Discontinuations During Coadministration in P00476]	[23]
[Previously Reported Discontinuations During Coadministration in P00691]	[9]
Treatment-Emergent Adverse Events	885 (69.1)
Severe/Life-Threatening, Treatment-Emergent Adverse Events	19 (1.5)

NOTE: The median duration of participation is 5.6 months for "Reported During Coadministration."

a: All subjects who were assigned to receive ezetimibe plus a statin in P00476, P00691/P01416, or P02134. Reports were included up to 30 days after discontinuation of statin while continuing ezetimibe (when that occurred).

Table 99 Primary Hypercholesterolemia
Long-term Experience With Ezetimibe Coadministered With A Statin
Serious Adverse Events (SAEs)

Number and (Percent) of Patients

Body System/Organ Class and Adverse Events	Reported During Coadministration (n=1281)
SUBJECTS REPORTING ANY ADVERSE EVENT	**75 (5.9)**
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)	**14 (1.1)**
BARRETT'S ESOPHAGUS	1 (0.1)
BASAL CELL CARCINOMA	3 (0.2)
BREAST NEOPLASM MALIGNANT FEMALE	3 (0.4)
CARCINOMA	1 (0.1)
NONHODGKIN'S LYMPHOMA NOS	1 (0.1)
PROSTATIC CANCER	1 (0.1)
RENAL CARCINOMA	1 (0.1)
SKIN CARCINOMA	1 (0.1)
SQUAMOUS CELL CARCINOMA	4 (0.3)
BODY AS A WHOLE - GENERAL DISORDERS	**11 (0.9)**
ANOREXIA	1 (0.1)
CHEST PAIN	1 (0.1)
DEATH	1 (0.1)
DIZZINESS	1 (0.1)
FLANK PAIN	1 (0.1)
SYNCOPE	1 (0.1)

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Table 99 Continued.

Number And (Percent) Of Patients

Body System/Organ Class and Adverse Events	Reported During Coadministration[a] (n=1281)
CARDIOVASCULAR DISORDERS, GENERAL	**21 (1.6)**
ANGINA PECTORIS	6 (0.5)
ANGINA PECTORIS AGGRAVATED	2 (0.2)
AORTIC STENOSIS	1 (0.1)
CARDIAC FAILURE AGGRAVATED	1 (0.1)
CARDIAC TAMPONADE	1 (0.1)
CARDIO-RESPIRATORY ARREST	1 (0.1)
CORONARY ARTERY DISORDER	7 (0.5)
HYPERTENSION	1 (0.1)
HYPERTENSION AGGRAVATED	1 (0.1)
HYPOTENSION	1 (0.1)
MYOCARDIAL INFARCTION	6 (0.5)
CENTR AND PERIPH NERV SYST DISORDERS	**4 (0.3)**
AUTONOMIC NEUROPATHY	1 (0.1)
CEREBRAL INFARCTION	1 (0.1)
HYPERTONIA	1 (0.1)
TRANSIENT ISCHEMIC ATTACK	1 (0.1)
DISORDERS OF THE EAR & LABYRINTH	**1 (0.1)**
LABYRINTHINE DISORDER	1 (0.1)
VESTIBULAR DISORDER	1 (0.1)
DISORDERS OF THE IMMUNE SYSTEM	**1 (0.1)**
SCLERODERMA	1 (0.1)
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST	**2 (0.2)**
BREAST MASS	0
ENDOMETRIOSIS	1 (0.1)
HYSTERECTOMY	1 (0.1)
OVARIAN CYST	1 (0.1)
GASTRO-INTESTINAL SYSTEM DISORDERS	**4 (0.3)**
ABDOMINAL PAIN	3 (0.2)
ABDOMINAL PAIN AGGRAVATED	1 (0.1)
APPENDICITIS PERFORATED	1 (0.1)
DIARRHEA	1 (0.1)
GASTRITIS	1 (0.1)
NAUSEA	2 (0.2)
PEPTIC ULCER	1 (0.1)
PERITONITIS	1 (0.1)
HEART RATE AND RHYTHM DISORDERS	**3 (0.2)**
ARRHYTHMIA VENTRICULAR	1 (0.1)
ATRIAL FLUTTER	1 (0.1)
FIBRILLATION ATRIAL	2 (0.2)

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Table 99 Continued.

Number And (Percent) Of Patients

Body System/Organ Class and Adverse Events	Reported During Coadministration[a] (n=1281)
INFECTION AND INFESTATIONS	**4 (0.3)**
PNEUMONIA	4 (0.3)
INJURY AND POISONING	**2 (0.2)**
FRACTURE, BONE	1 (0.1)
INJURY ACCIDENTAL	1 (0.1)
LIVER AND BILIARY SYSTEM DISORDERS	**6 (0.5)**
CHOLECYSTITIS	3 (0.2)
CHOLELITHIASIS	3 (0.2)
HEPATIC ENZYMES INCREASED	4 (0.3)
METABOLIC AND NUTRITIONAL DISORDERS	**1 (0.1)**
HYPOKALEMIA	1 (0.1)
MUSCULO-SKELETAL SYSTEM DISORDERS	**6 (0.5)**
ARTHRALGIA	2 (0.2)
ARTHRALGIA AGGRAVATED	1 (0.1)
ARTHRITIS	1 (0.1)
BACK PAIN, AGGRAVATED	1 (0.1)
HERNIA AGGRAVATED	1 (0.1)
NECK STIFFNESS	1 (0.1)
SPINAL DISORDER	1 (0.1)
PSYCHIATRIC DISORDERS	**2 (0.2)**
DEPRESSION WORSENED	1 (0.1)
MANIC DEPRESSION	1 (0.1)
MANIC DEPRESSION AGGRAVATED	1 (0.1)
RENAL & URINARY SYSTEM DISORDERS	**1 (0.1)**
RENAL CALCULUS	1 (0.1)
URETHRAL STRICTURE NOS	1 (0.1)
RESPIRATORY SYSTEM DISORDERS	**7 (0.5)**
BRONCHITIS	2 (0.2)
COPD AGGRAVATED	2 (0.2)
DYSPNEA	3 (0.2)
DYSPNEA AGGRAVATED	1 (0.1)
RESPIRATORY INSUFFICIENCY	1 (0.1)
SURGICAL AND MEDICAL PROCEDURES	**11 (0.9)**
CHOLECYSTECTOMY	3 (0.2)
PROCEDURE (NO ADVERSE EVENT)	8 (0.6)
VASCULAR (EXTRACARDIAC) DISORDERS	**4 (0.3)**
AORTIC ANEURYSM	1 (0.1)
ARTERIAL OCCLUSION NOS	1 (0.1)
CAROTID ARTERY STENOSIS	1 (0.1)
PERIPHERAL ISCHEMIA AGGRAVATED	1 (0.1)

NOTE: The median duration of participation is 5.6 months for "Reported During Coadministration."

a: All subjects who were assigned to receive ezetimibe plus a statin in P00476, P00691/P01416, or P02134. Reports were included up to 30 days after discontinuation of statin while continuing ezetimibe (when that occurred).

Table 100 Homozygous Familial Hypercholesterolemia
Long-term Experience With
Ezetimibe Coadministered With A Statin
Summary Of Adverse Events

Number And (Percent) Of Patients

Event	EZ + Statin 40/80 mg[a] (n = 45)	EZ + Atorvastatin 40/80 mg (n = 33)	EZ + Simvastatin 40/80 mg (n = 12)
Deaths	0	0	0
Serious Adverse Event	8 (18)	6 (18)	2 (17)
Discontinuation Because of Adverse Event	2 (4)	1 (3)	1 (8)
Treatment-Emergent Adverse Event	32 (71)	25 (76)	7 (58)
Severe/Life-Threatening, Treatment-Emergent Adverse Event	11 (24)	10 (30)	1 (8)

a: Subjects who were assigned to receive ezetimibe 10 mg plus coadministered statin 40 or 80 mg P01030 and/or P01417. Reports were included up to 30 days after last recorded dose of statin while continuing ezetimibe 10 mg (when that occurred).

EZ = ezetimibe 10 mg.

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ON ORIGINAL

Table 101 Primary Hypercholesterolemia
Filter Coadministration Pool
Summary Of Adverse Events

Number And (Percent) Of Patients

Event	Statins (n=350)	EZ + Statins (n=371)	Atorva (n=316)	EZ + Atorva (n=305)	Simva (n=34)	EZ + Simva (n=66)
Death	1 (<1)	0	1 (<1)	0	0	0
Serious Adverse Event (SAE)	8 (2)	16 (4)	8 (3)	13 (4)	0	3 (5)
Treatment-Related[a] SAE	1 (<1)	2 (1)	1 (<1)	2 (1)	0	0
Discontinuation Because of Adverse Event	15 (4)	19 (5)	14 (4)	13 (4)	1 (3)	6 (9)
Discontinuation Because of Treatment-Related[a] Adverse Event	11 (3)	14 (4)	10 (3)	9 (3)	1 (3)	5 (8)
Treatment-Emergent Adverse Event (TEAE)	208 (59)	238 (64)	184 (58)	193 (63)	24 (71)	45 (68)
Treatment-Related[a] TEAE	80 (23)	94 (25)	68 (22)	72 (24)	12 (35)	22 (33)
Severe/LT TEAE	16 (5)	28 (8)	16 (5)	21 (7)	0	7 (11)
Treatment-Related[a] Severe/LT TEAE	5 (1)	9 (2)	5 (2)	7 (2)	0	2 (3)

a. Judged to be at least possibly related to treatment by the investigator.

EZ = ezetimibe 10 mg; Statins = all doses of atorvastatin or simvastatin; Atorva = all doses of atorvastatin; Simva = all doses of simvastatin; SAE = serious adverse event; TEAE = treatment-emergent adverse event; LT = life-threatening.

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Table 102 Primary Hypercholesterolemia/Mixed Dyslipidemia
Filter Coadministration Pool
Serious Adverse Events (SAEs) Reported With A Statin
Number And (Percent) Of Patients

Body System / Organ Class and Adverse Events	Statins (n=350)	EZ + Statins (n=371)	Atorva (n=316)	EZ + Atorva (n=305)	Simva (n=34)	EZ + Simva (n=66)
ANY SERIOUS ADVERSE EVENT	8 (2)	16 (4)	8 (3)	12 (4)	0	3 (5)
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)	0	2 (1)	0	1 (<1)	0	1 (2)
BASAL CELL CARCINOMA	0	1 (<1)	0	0	0	1 (2)
BREAST NEOPLASM MALIGNANT FEMALE	0	1 (1)	0	1 (1)	0	0
BODY AS A WHOLE - GENERAL DISORDERS	1 (<1)	3 (1)	1 (<1)	1 (<1)	0	2 (3)
CHEST PAIN	0	2 (1)	0	1 (<1)	0	1 (2)
DIZZINESS	1 (<1)	0	1 (<1)	0	0	0
HEADACHE	0	2 (1)	0	1 (<1)	0	1 (2)
CARDIOVASCULAR DISORDERS, GENERAL	1 (<1)	2 (1)	1 (<1)	2 (1)	0	0
ANGINA PECTORIS	0	1 (<1)	0	1 (<1)	0	0
MYOCARDIAL INFARCTION	1 (<1)	0	1 (<1)	0	0	0
MYOCARDIAL ISCHEMIA	0	1 (<1)	0	1 (<1)	0	0
CENTR AND PERIPH NERV SYST DISORDERS	0	1 (<1)	0	0	0	1 (2)
HEMORRHAGE INTRACRANIAL	0	1 (<1)	0	0	0	1 (2)
DISORDERS OF BLOOD AND LYMPHATIC SYSTEM	0	1 (<1)	0	1 (<1)	0	0
ANEMIA HEMOLYTIC	0	1 (<1)	0	1 (<1)	0	0
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST	0	2 (1)	0	0	0	0
HYSTERECTOMY	0	1 (1)	0	1 (1)	0	0
SALPINGITIS	0	1 (1)	0	1 (1)	0	0
GASTRO-INTESTINAL SYSTEM DISORDERS	3 (1)	1 (<1)	3 (1)	1 (<1)	0	0
ABDOMINAL PAIN	0	1 (<1)	0	1 (<1)	0	0
APPENDICITIS	1 (<1)	0	1 (<1)	0	0	0
HEMATEMESIS	1 (<1)	0	1 (<1)	0	0	0
NAUSEA	1 (<1)	0	1 (<1)	0	0	0
VOMITING	1 (<1)	0	1 (<1)	0	0	0
HEART RATE AND RHYTHM DISORDERS	0	1 (<1)	0	1 (<1)	0	0
BRADYCARDIA	0	1 (<1)	0	1 (<1)	0	0
INFECTION AND INFESTATIONS	0	1 (<1)	0	1 (<1)	0	0
SKIN INFECTION (NOS)	0	1 (<1)	0	1 (<1)	0	0
INJURY AND POISONING	1 (<1)	0	1 (<1)	0	0	0
FRACTURE, BONE	1 (<1)	0	1 (<1)	0	0	0
LIVER AND BILIARY SYSTEM DISORDERS	0	2 (1)	0	2 (1)	0	0
HEPATITIS	0	1 (<1)	0	1 (<1)	0	0
LIVER ABSCESS	0	1 (<1)	0	1 (<1)	0	0
MUSCULO-SKELETAL SYSTEM DISORDERS	0	3 (1)	0	3 (1)	0	0
MUSCULO-SKELETAL PAIN	0	2 (1)	0	2 (1)	0	0
MYALGIA	0	1 (<1)	0	1 (<1)	0	0
RENAL & URINARY SYSTEM DISORDERS	1 (<1)	0	1 (<1)	0	0	0
HYDRONEPHROSIS	1 (<1)	0	1 (<1)	0	0	0
RENAL CALCULUS	1 (<1)	0	1 (<1)	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (1)	0	2 (1)	0	0	0
CELLULITIS	1 (<1)	0	1 (<1)	0	0	0
PRURITUS	1 (<1)	0	1 (<1)	0	0	0
RASH MACULOPAPULAR	1 (<1)	0	1 (<1)	0	0	0
SURGICAL AND MEDICAL PROCEDURES	1 (<1)	2 (1)	1 (<1)	2 (1)	0	0
PROCEDURE	1 (<1)	0	1 (<1)	0	0	0
PROCEDURE (NO ADVERSE EVENT)	0	2 (1)	0	2 (1)	0	0
VASCULAR (EXTRACARDIAC) DISORDERS	1 (<1)	0	1 (<1)	0	0	0
VASCULITIS	1 (<1)	0	1 (<1)	0	0	0

EZ = ezetimibe 10 mg. Statins = all doses of atorvastatin or simvastatin; Atorva = all doses of atorvastatin; Simva = all doses of simvastatin. SAE = serious adverse event. NOS = not otherwise specified.

Table 103 Primary Hypercholesterolemia
Filter Coadministration Pool
Severe Or Life-threatening Adverse Events (AEs)

Number And (Percent) Of Patients

Body System / Organ Class and Adverse Events	Statins (n=350)	EZ + Statins (n=371)	Atorva (n=316)	EZ + Atorva (n=305)	Simva (n=34)	EZ + Simva (n=66)
SUBJECTS REPORTING ANY ADVERSE EVENT	16 (5)	28 (8)	16 (5)	21 (7)	0	7 (11)
BENIGN & MALIGNANT NEOPLASMS (INCLUDING CYSTS AND POLYPS)	0	1 (<1)	0	1 (<1)	0	0
BREAST NEOPLASM MALIGNANT FEMALE	0	1 (1)	0	1 (1)	0	0
BODY AS A WHOLE - GENERAL DISORDERS	1 (<1)	3 (1)	1 (<1)	3 (1)	0	0
DIZZINESS	1 (<1)	0	1 (<1)	0	0	0
FATIGUE	0	1 (<1)	0	1 (<1)	0	0
HEADACHE	0	2 (1)	0	2 (1)	0	0
CARDIOVASCULAR DISORDERS, GENERAL	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	0
MYOCARDIAL INFARCTION	1 (<1)	0	1 (<1)	0	0	0
MYOCARDIAL ISCHEMIA	0	1 (<1)	0	1 (<1)	0	0
CENTR AND PERIPH NERV SYST DISORDERS	0	2 (1)	0	1 (<1)	0	1 (2)
HEMORRHAGE INTRACRANIAL	0	1 (<1)	0	0	0	1 (2)
HYPERTONIA	0	1 (<1)	0	1 (<1)	0	0
DISORDERS OF BLOOD AND LYMPHATIC SYSTEM	0	1 (<1)	0	1 (<1)	0	0
ANEMIA HEMOLYTIC	0	1 (<1)	0	1 (<1)	0	0
DISORDERS OF THE EAR & LABYRINTH	1 (<1)	0	1 (<1)	0	0	0
VERTIGO	1 (<1)	0	1 (<1)	0	0	0
VESTIBULAR DISORDER	1 (<1)	0	1 (<1)	0	0	0
DISORDERS OF THE EYE	0	1 (<1)	0	1 (<1)	0	0
CORNEAL DISORDER (NOS)	0	1 (<1)	0	1 (<1)	0	0
DISORDERS OF THE IMMUNE SYSTEM	0	1 (<1)	0	0	0	1 (2)
ALLERGY	0	1 (<1)	0	0	0	1 (2)
DISORDERS OF THE REPRODUCTIVE SYSTEM AND BREAST	0	2 (1)	0	2 (1)	0	0
HYSTERECTOMY	0	1 (1)	0	1 (1)	0	0
PREGNANCY UNINTENDED	0	1 (1)	0	1 (1)	0	0
GASTRO-INTESTINAL SYSTEM DISORDERS	4 (1)	4 (1)	4 (1)	2 (1)	0	2 (3)
ABDOMINAL PAIN	0	1 (<1)	0	0	0	1 (2)
APPENDICITIS	1 (<1)	0	1 (<1)	0	0	0
DIARRHEA	0	2 (1)	0	1 (<1)	0	1 (2)
GASTRITIS	0	1 (<1)	0	1 (<1)	0	0
GASTROESOPHAGEAL REFLUX	0	1 (<1)	0	0	0	1 (2)
HEMATEMESIS	1 (<1)	0	1 (<1)	0	0	0
NAUSEA	2 (1)	0	2 (1)	0	0	0
VOMITING	1 (<1)	2 (1)	1 (<1)	1 (<1)	0	1 (2)
INFECTION AND INFESTATIONS	0	1 (<1)	0	0	0	1 (2)
UPPER RESP TRACT INFECTION	0	1 (<1)	0	0	0	1 (2)
INJURY AND POISONING	1 (<1)	2 (1)	1 (<1)	1 (<1)	0	1 (2)
FRACTURE, BONE	1 (<1)	1 (<1)	1 (<1)	1 (<1)	0	0
LACERATION, SKIN	0	1 (<1)	0	0	0	1 (2)
METABOLIC AND NUTRITIONAL DISORDERS	0	1 (<1)	0	1 (<1)	0	0
THIRST	0	1 (<1)	0	1 (<1)	0	0
MUSCULO-SKELETAL SYSTEM DISORDERS	6 (2)	8 (2)	6 (2)	7 (2)	0	1 (2)
ARTHRITIS AGGRAVATED	0	1 (<1)	0	1 (<1)	0	0
BACK PAIN	0	1 (<1)	0	1 (<1)	0	0
CRAMPS LEGS	1 (<1)	0	1 (<1)	0	0	0
HERNIA	1 (<1)	0	1 (<1)	0	0	0
MUSCULO-SKELETAL PAIN	1 (<1)	2 (1)	1 (<1)	2 (1)	0	0
MYALGIA	3 (1)	4 (1)	3 (1)	3 (1)	0	1 (2)
PSYCHIATRIC DISORDERS	0	1 (<1)	0	0	0	1 (2)
INSOMNIA	0	1 (<1)	0	0	0	1 (2)
RESPIRATORY SYSTEM DISORDERS	1 (<1)	1 (<1)	1 (<1)	0	0	1 (2)
ASTHMA AGGRAVATED	1 (<1)	0	1 (<1)	0	0	0
BRONCHITIS	0	1 (<1)	0	0	0	1 (2)
SURGICAL AND MEDICAL PROCEDURES	1 (<1)	2 (1)	1 (<1)	2 (1)	0	0
FOOT OPERATION NOS	0	1 (<1)	0	1 (<1)	0	0
PROCEDURE	1 (<1)	0	1 (<1)	0	0	0
PROCEDURE (NO ADVERSE EVENT)	0	1 (<1)	0	1 (<1)	0	0

EZ = ezetimibe 10 mg, Statins = all doses of atorvastatin or simvastatin; Atorva = all doses of atorvastatin, Simva = all doses of simvastatin; NOS = not otherwise specified.

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/s/

Bruce Stadel
9/17/02 02:30:40 PM
MEDICAL OFFICER

Mary Parks
9/18/02 04:32:23 PM
MEDICAL OFFICER

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NDA: 21,445
Drug: Zetia (Ezetimibe)
Sponsor: MSP Singapore Company, LLC
Date: October 4, 2002

ADDENDUM TO MEDICAL OFFICER'S REVIEW

This review addresses the following documents submitted by the sponsor:

Document Date:	Submission Type:
September 24, 2002	by study p-values to 4 decimal places for the lipid endpoints
September 25, 2002	diet and drug dosing compliance by race
September 26, 2002	additional p-values and financial disclosure information
October 1, 2002	Support Document: Zetia Labeling and Clinical Discussion Paper: Clinical Relevance of Zetia-Related TG Reduction and HDL-C Increase
October 2, 2002	additional information pertaining to diet and drug dosing compliance by race

This review will be organized as follows:
1. Issues related to TG lowering and HDL-C elevation
2. Diet and drug dosing compliance by race
3. Additional financial disclosure information
4. Errors noted in my September 18, 2002 review of efficacy

1. The effects of Zetia on TG and HDL-C when administered alone and in conjunction with an HMG-Co A reductase inhibitor:

Please also refer to my NDA review, dated September 18, 2002.

During our internal meeting on Thursday, September 19th, Dr. Choudhury, statistical reviewer, and Dr. Todd Sahlroot mentioned that while a p-value of ≤ 0.05 is statistically significant for a primary efficacy variable, for multiple comparisons of secondary efficacy endpoints, adjustments are needed.

Per Dr. Choudhury, if the adjustment for multiplicity is not pre-specified, the Bonferroni procedure is used. The p-value for statistical significance for TG, HDL-C, total-C and Apo B is <0.0125 (0.05/4, since, in this case, there are 4 secondary efficacy variables). The sponsor did not prospectively adjust for multiplicity. Post-hoc, they applied the Hochberg's procedure to the secondary variables, and this procedure is less conservative than Bonferroni.

TRIGLYCERIDES:

BASELINE MEAN/MEDIAN TG LEVELS AND SAMPLE SIZE FOR THE MONOTHERAPY STUDIES AND THE MONOTHERAPY ARMS OF THE FACTORIAL STUDIES:

Baseline Mean/Median TG levels in mg/dl and Sample Size in Parentheses														
	Monotherapy Studies						Monotherapy Arms of the Factorial Studies							
	P00474		P00475		P474+475		P00679		P00680		P00691		P00692	
	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]
Mean TG (n)	171 (n= 205)	163 (n= 622)	175 (n= 226)	169 (n= 666)	175 (n= 431)	168 (n= 1288)	168 (n= 64)	170 (n= 72)	171 (n= 70)	190 (n= 61)	163 (n= 65)	175 (n= 64)	157 (n= 60)	159 (n= 65)
Median TG	163	159	164	162	164	161	163	161	159	183	146	166	143	145

a= Pla= placebo;

b= Zet= Zetia

Comment on the above table:

Across all 6 studies, mean and median baseline TG levels were similar, ranging from 157-190 mg/dl for the mean and 143 to 183 mg/dl for the median values. However, the sponsor stated that for TG, medians, not means, should be used due to non-normality and skewness of these data. Dr. Choudhury verified this in the box plots of the TG data obtained in the Monotherapy, Factorial and Add-On studies.

For the purposes of this review, both mean and median TG data will be presented.

EFFECT OF ZETIA MONOTHERAPY ON MEAN AND MEDIAN TG:

Difference Between Zetia and Placebo in Mean and Median % Δ For TG From Baseline to Endpoint: [Zetia] – [Placebo]: Intent-to-Treat Data Set							
	Monotherapy Studies:			Monotherapy Arms of the Factorial Studies:			
	P00474	P00475	P474+ 475	P00679	P00680	P00691	P00692
Diff. in mean % Δ	-4.1% p= 0.0851[a]	-11.4% p< 0.0001[a]	-7.8% p< 0.0001[a]	-7.0% p= 0.10[a]	-10.7% p≤ 0.01[a]	-4.1% p= 0.45[a]	-7.9% p= 0.07[a]
Diff. in median % Δ	-6.1% p= 0.0315[b]	-11.4% p< 0.0001[b]	-8.8 p< 0.0001[b]	-10.4% p= 0.1395[b]	-13.0% p= 0.0085[b]	-4.5% p= 0.4992[b]	+1.3% p= 0.2130[b]

a= p-values based on ANOVA

b= p-values based on Wilcoxon non-parametric test

Comments on the above table:

In general, the difference between Zetia and placebo in the mean percent change in TG from baseline to endpoint was similar to the median percent change. The difference between Zetia and placebo in the median % change in TG ranged from +1.3% ***(i.e. the magnitude of the TG lowering effect was greater with placebo than with Zetia)*** *to –13% across these 6 studies. This comparison was statistically significant in only 2 of the 6 studies based on a post-hoc Bonferroni adjustment (applied by FDA) where p must be <0.0125 to meet statistical significance.*

On October 1, 2002, the sponsor submitted an analysis to FDA in which they pooled the factorial studies which yielded a 7.8% difference between Zetia and placebo in median % change in TG, with p= 0.0028. The validity and interpretation of this analysis with the resultant p-value is a statistical issue that will be deferred to the statistical review team.

BASELINE MEAN/MEDIAN TG LEVELS AND SAMPLE SIZE FOR THE ZETIA PLUS STATIN AND STATIN ARMS OF THE FACTORIAL COADMINISTRATION STUDIES AND THE ADD-ON STUDY:

Baseline Mean/Median TG levels in mg/dl and Sample Size in Parentheses										
	Factorial Coadministration Studies								Add-On Study	
	P00679: Lova		P00680: Simva		P00691: Prava		P00692:Atorva			
	Statin	Z+St[a]	Statin	Z+St[a]	Statin	Z+St[a]	Statin	Z+St[a]	Statin	Z+St[a]
Mean TG (n)	178 (n= 220)	172 (n= 192)	169 (n= 263)	179 (n= 274)	177 (n= 205)	177 (n= 204)	168 (n= 248)	175 (n= 255)	149 (n= 390)	152 (n= 379)
Median TG	167	164	157	168	180	173	155	165	137	136

a= Zetia plus statin

Comment on the above table:

Across all 5 studies, mean and median baseline TG levels were similar, ranging from 149-179 mg/dl for the mean and 136 to 180 mg/dl for the median values.

EFFECT OF ZETIA COADMINISTERED WITH STATIN, BY STATIN (ALL DOSES OF STATIN POOLED) ON MEAN AND MEDIAN TG:

Difference Between Zetia + All Doses of Statin Pooled and All Doses Pooled of Statin Alone: [Zetia + All Statin] – [All Statin] in Mean and Median % Δ For TG From Baseline to Endpoint (Intent-to-Treat):					
	Factorial Coadministration Studies				Add-On Study
	P00679: Lova	P00680: Simva	P00691: Prava	P00692:Atorva	
Diff. in mean % Δ	-10.5%, p< 0.0001	-7.4%, p= 0.0002	-10.0%, p= 0.0010	-8.0%, p< 0.0001	-11.4, p= 0.0001
Diff. in median % Δ	-13.1%, p<0.0001	-8.8%, p<0.0001	-6.6%, p<0.0001	-8.3%, p<0.0001	-11.1, p≤0.001

(note: p-values for the means were based on ANOVA and p-values for the medians were based on the Wilcoxon non-parametric test).

Comment on the above table:

In general, the difference between Zetia plus statin and statin alone in the mean % change in TG from baseline to endpoint was similar to the median percent change with these changes ranging from -7.4% to -11.4% for the mean and -6.6% to -13.1% for the median. This comparison was statistically significant in all 5 studies.

EFFECT OF ZETIA COADMINISTERED WITH STATIN, BY STATIN, BY DOSE ON MEAN AND MEDIAN TG (Intent-to-Treat Data Set):

	Statin 10 mg	Zetia + Statin 10 mg	Statin 20 mg	Zetia + Statin 20 mg	Statin 40 mg	Zetia + Statin 40 mg	Statin 80 mg	Zetia + Statin 80 mg
Lovastatin:	N= 73[a]	N= 65[a]	N= 74[a]	N= 62[a]	N= 73[a]	N= 65[a]	-	-
Mean % Δ Diff. in mean % Δ	-11.6%	-17.6% -6.0%, p=0.16[b]	-10.8%	-24.5% -13.7%, p≤0.01[b]	-11.1%	-22.9% -11.8%, p≤0.01		
Median % Δ Diff. in median % Δ	-10.9%	-18.8% -7.9%, p=0.08[b]	-11.9%	-27.1% -15.2%, p<0.01[b]	-15.3%	-27.3% -12.0%, p<0.01		
Simvastatin:	N= 70[a]	N= 67[a]	N= 61[a]	N= 69[a]	N= 65[a]	N= 73[a]	N= 67[a]	N= 65[a]
Mean % Δ Diff. in mean % Δ	-10.6%	-20.4% -9.8%, p=0.01[b]	-14.8%	-20.9% -6.1%, p=0.14[b]	-20.6%	-26.7% -6.1% p=0.13[b]	-20.5%	-28.3% -7.7%, p=0.06[b]
Median % Δ Diff. in median % Δ	-14.0%	-26.1% -12.1%, p<0.01[b]	-17.9%	-25.2% -7.3%, p=0.08[b]	-23.9%	-31.7% -7.8%, p=0.06[b]	-22.6%	-31.3%, -8.7%, p=0.02[b]
Pravastatin:	N= 66[a]	N= 71[a]	N= 69[a]	N= 66[a]	N= 70[a]	N= 67[a]		
Mean % Δ Diff. in mean % Δ	-7.4%	-20.0% -12.6%, p=0.02[b]	-2.8%	-14.9% -12.1%, p=0.02[b]	-12.5%	-17.9% -5.4%, p=0.30[b]		
Median % Δ Diff. in median % Δ	-14.2%	-22.9% -8.7%, p<0.01[b]	-8.1%	-20.6% -12.5%, p<0.01	-19.2%	-20.7% -1.5%, p=0.30[b]		
Atorvastatin:	N= 60[a]	N= 65[a]	N= 60[a]	N= 62[a]	N= 66[a]	N= 65[a]	N= 62[a]	N= 63[a]
Mean % Δ Diff. in mean % Δ	-16.3%	-25.8% -9.5%, p=0.03[b]	-19.3%	-27.0% -7.7%, p=0.08	-19.9%	-30.0% -10.2%, p=0.02[b]	-30.4%	-35.1% -4.7%, p=0.28[b]
Median % Δ Diff. in median % Δ	-20.8%	-31.1% -10.3%, p=0.01[b]	-22.7%	-30.0% -7.3%, p=0.08[b]	-24.4%	-33.8% -9.4%, p<0.01[b]	-30.6%	-40.0% -9.4%, p=0.07[b]

a= sample size at baseline

b= pairwise comparison of Zetia + statin to the same dose of statin

(note: p-values for the means were based on ANOVA and p-values for the medians were based on the Wilcoxon non-parametric test).

Comments on the above table:

For any given statin dose, the difference between Zetia + statin alone vs. the corresponding statin alone was of variable statistical significance (i.e. the statistical significance varied across the dosing range for any given statin) and ranged from:
Lovastatin: mean: -6.0% to –13.7%; median: -7.9% to –15.2%;
Simvastatin: mean: -6.1% to –9.8%; median: -7.3% to –12.1%;
Pravastatin: mean: -5.4% to –12.6%; median: -1.5% to –12.5%;
Atorvastatin: mean: -4.7% to –10.2%; median: -7.3% to –10.3%.

HDL-C:

BASELINE MEAN HDL-C LEVELS AND SAMPLE SIZE FOR THE MONOTHERAPY STUDIES AND THE MONOTHERAPY ARMS OF THE FACTORIAL STUDIES:

Baseline Mean HDL-C Levels in mg/dl and Sample Size in Parentheses														
	Monotherapy Studies						Monotherapy Arms of the Factorial Studies							
	P00474		P00475		P474+475		P00679		P00680		P00691		P00692	
	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]	Pla[a]	Zet[b]
Mean HDL-C (n)	51 (n= 205	52 (n= 622	52 (n= 226	52 (n= 666	52 (n= 431	52 (n= 1288	54 (n= 64)	51 (n= 72)	52 (n= 70)	51 (n= 61)	51 (n= 65)	51 (n= 64)	50 (n= 60)	51 (n= 65)

a= Pla= placebo

b= Zet= Zetia

Comment on the above table:

Mean baseline HDL-C levels were similar between the placebo and Zetia treatment arms.

EFFECT OF ZETIA MONOTHERAPY ON HDL-C:

Difference Between Zetia and Placebo in Mean % Δ For HDL-C From Baseline to Endpoint: [Zetia] – [Placebo]: Intent-to-Treat Data Set							
	Monotherapy Studies			Monotherapy Arms of the Factorial Studies			
	P00474	P00475	P474 +475	P00679	P00680	P00691	P00692
Diff. in mean % Δ	+2.3%, p= 0.0074[a,b]	+2.9%, p= 0.0002[b]	+2.6%, p< 0.0001[b]	+3.8%, p= 0.0378[b]	+4.3%, p= 0.0526[b]	+2.1%, p= 0.3065[b]	+0.5%, p= 0.8226[b]

a= p< 0.01, verified by Dr. Choudhury, for the mean % change in HDL-C, Zetia vs. placebo. In the NDA, the p-value was erroneously reported as p< 0.05.

b= p-values based on ANOVA

Comment on the above table:

The difference between Zetia and placebo in the mean % change in HDL-C ranged from +0.5% to +4.3% across these 6 studies. This comparison was statistically significant in only 2 of the 6 studies based on a post-hoc Bonferroni adjustment (applied by FDA) where p must be <0.0125 to meet statistical significance.

(Note: the sponsor was informed during our labeling teleconference on September 30th, that an [redacted] should have been deleted from FDA's version of the draft label sent to the sponsor on September 26th).

On October 1, 2002, the sponsor submitted an analysis to FDA in which they pooled the factorial studies that yielded a +2.7% difference between Zetia and placebo in mean % change in HDL-C, with a p-value of 0.0030. The validity and interpretation of this analysis with the resultant p-value is a statistical issue that will be deferred to the statistical review team.

BASELINE MEAN HDL-C LEVELS AND SAMPLE SIZE FOR THE ZETIA + STATIN AND STATIN ARMS OF THE FACTORIAL STUDIES & ADD-ON STUDY:

Baseline Mean HDL-C Levels in mg/dl and Sample Size in Parentheses										
	Factorial Coadministration Studies								Add-On Study	
	P00679: Lova		P00680: Simva		P00691: Prava		P00692:Atorva			
	Statin	Z + St	Statin	Z + St	Statin	Z + St	Statin	Z + St	Statin	Z + St
Mean HDL-C (n)	51 (n= 220)	50 (n= 192)	51 (n= 263)	50 (n= 274)	50 (n= 205)	52 (n= 204)	54 (n= 248)	51 (n= 255)	50 (n= 390)	49 (n= 379)

Comment on the above table:

Mean baseline HDL-C levels were similar between the statin and Zetia + statin treatment arms.

EFFECT OF ZETIA COADMINISTERED WITH STATIN, BY STATIN (ALL DOSES OF STATIN POOLED) ON HDL-C:

Difference Between Zetia + All Doses of Statin Pooled and All Doses Pooled of Statin Alone: [Zetia + All Statin] – [All Statin] in Mean % Δ From Baseline to Endpoint for HDL-C (Intent-to-Treat Data Set):					
	Factorial Coadministration Studies				Add-On Study
	P00679: Lova	P00680: Simva	P00691: Prava	P00692:Atorva	
Diff. in mean % Δ	+4.5%, p< 0.0001[a]	+2.4%, p= 0.0267[a]	+1.4%, p= 0.2150[a]	+3.1%, p= 0.0030[a]	+1.7%, p= 0.021[a]

a= p-values based on ANOVA

Comment on the above table:

The difference between Zetia plus statin and statin alone in the mean % change in HDL-C ranged from +1.4% to +4.5% across these 5 studies. This comparison was statistically significant in only 2 of the 5 studies based on a post-hoc Bonferroni adjustment (applied by FDA) where p must be <0.0125 to meet statistical significance.

EFFECT OF ZETIA COADMINISTERED WITH STATIN, BY STATIN, BY STATIN DOSE ON HDL-C (note: this is the relevant clinical comparison rather than the pooled analysis of all statin doses because this is how Zetia will be used in clinical practice):

	Statin 10 mg	Ez + Statin 10 mg	Statin 20 mg	Ez + Statin 20 mg	Statin 40 mg	Ez + Statin 40 mg	Statin 80 mg	Ez + Statin 80 mg
Lovastatin:	N= 73[a]	N= 65[a]	N= 74[a]	N= 62[a]	N= 73[a]	N= 65[a]	-	-
Mean % Δ Diff. in mean % Δ	+4.7	+7.9 +3.2, p=0.08[b]	+2.6	+8.7 +6.1, p<0.01[b]	+4.8	+9.1 +4.3, p=0.02[b]		
Simvastatin:	N= 70[a]	N= 67[a]	N= 61[a]	N= 69[a]	N= 65[a]	N= 73[a]	N= 67[a]	N= 65[a]
Mean % Δ Diff. in mean % Δ	+7.6	+8.6 +1.0, p=0.66[b]	+5.6	+9.2 +3.6, p=0.10[b]	+6.1	+11.0 +4.9, p=0.02[b]	+8.2	+8.4 +0.2, p=0.93[b]
Pravastatin:	N= 66[a]	N= 71[a]	N= 69[a]	N= 66[a]	N= 70[a]	N= 67[a]	-	-
Mean % Δ Diff. in mean % Δ	+5.6	+8.4 +2.8, p=0.16[b]	+8.2	+7.8 -0.5, p=0.81[b]	+6.1	+8.1 +2.0, p=0.32[b]		
Atorvastatin:	N= 60[a]	N= 65[a]	N= 60[a]	N= 62[a]	N= 66[a]	N= 65[a]	N= 62[a]	N= 63[a]
Mean % Δ Diff. in mean % Δ	+6.5	+9.0 +2.6, p=0.22[b]	+4.0	+9.2 +5.3, p=0.01[b]	+3.8	+4.6 +0.8, p=0.69[b]	+2.8	+6.6 +3.7, p=0.07[b]

a= sample size at baseline
b= pairwise comparison of Zetia + statin to the same dose of statin; p-values based on ANOVA
Comments on the above table:
For any given statin dose, the difference between Zetia + statin alone vs. the corresponding statin dose administered alone was of variable statistical significance and ranged from:
Lovastatin: +3.2% to +6.1%;
Simvastatin: +0.2% to +4.9%;
Pravastatin: -0.5% to +2.8% and
Atorvastatin: +0.8% to +5.3%.

2. **Diet and Drug Dosing Compliance By Race:**
   The distribution of RISCC diet ratings and score changes were provided for the racial subgroups enrolled in the Monotherapy and Factorial Coadministration Studies. The sample size for the Non-Caucasian subjects is small. Therefore, a variable number and % of Non-Caucasian subjects in each treatment group fell within the various RISCC diet rating categories.
   Dosing compliance was based not on tablet counts but on subjects reporting missed doses to the investigator who was, in turn, asked to enter these dates or the number of missed doses on the CRF. These data were collected for the Factorial Coadministration Studies only, not for either the Monotherapy Studies or the Add-On Study. In general, drug compliance was similar among the subgroups by race. Also, drug compliance was >80% in the subgroups by race. Numerically fewer subjects who discontinued from the studies tended to have compliance rates >80%.
   No conclusions can be drawn with regard to diet or drug dosing compliance on efficacy, either overall or by race. Due to the small number of Non-Caucasians enrolled in these studies, it is difficult to correlate dietary or treatment noncompliance with efficacy.

3. **Additional Financial Disclosure Information:**
   Additional financial disclosure information submitted on September 26, 2002 did not reveal any financial arrangements or significant payments of any sort between the sponsor and the investigators participating in the Phase II studies.

4. **Errors Noted in my September 18, 2002 Review of Efficacy:**
   Errors noted in my September 18, 2002 NDA review of efficacy:
   a. page 11. B.: plasma sitosterol levels were the primary efficacy variable in the homozygous sitosterolemia (not homozygous hypercholesterolemia) study
   b. pp. 63: footnote "f" pertaining to the p-value for the increase in HDL-C in study P00474 was erroneously reported in the NDA as $p \leq 0.05$. This was subsequently corrected by the sponsor in their September 24, 2002 submission to p= 0.0074.
   c. pp. 74, table comparing the least-square mean % change from baseline to endpoint in key 2^0 variables between ezetimibe and placebo: this difference was –10.7% in the simvastatin factorial study, not –12.0%.

d. pp.108: regarding the comment on the table: HDL-C should read "increasing", not "reducing".

CONCLUSIONS:
In general, Zetia when administered alone or with a statin, induced small changes in TG and HDL-C levels that were of variable statistical significance compared to placebo or to statin alone, respectively. The clinical relevance of these changes has not been defined.

The dietary and drug compliance data did not clarify the observed racial differences in LDL-C response.

The additional financial disclosure information submitted did not reveal any issues of concern.

Recommended Regulatory Action:

[redacted]. The sponsor was informed of this decision by the Division during the October 2, 2002 teleconference to discuss Zetia labeling.

Jean Temeck, M.D.

cc. HFD-510: Dr. Orloff, Dr. Parks, Dr. Stadel, Dr. Sahlroot, Dr. Choudhury and Mr. Koch

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/s/

Jean Temeck
10/4/02 03:22:32 PM
MEDICAL OFFICER

Mary Parks
10/4/02 03:38:43 PM
MEDICAL OFFICER

APPEARS THIS WAY ON ORIGINAL

MEDICAL OFFICER REVIEW

Division of Metabolic and Endocrine Drug Products (HFD-510)

Application #:	21-445	Application Type:	New Drug Application (NDA): new molecular entitiy
Sponsor:	MSP Singapore Company, LLC	Proprietary Name:	Zetia
Investigator:	Merck & Co., Inc. and Schering Corp.	USAN / Established Name:	Ezetimibe
Category:	Lipid-lowering	Route of Administration:	Oral
Medical Efficacy Reviewer:	Jean Temeck, M.D.	Review Date:	September 18, 2002
Medical Safety Reviewer:	Bruce Stadel, M.D.		

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
December 27, 2001	December 27, 2001	N 000	NDA
August 6, 2002	August 8, 2002	N 000 BM	Response to my requests for additional information/clarification
September 12, 2002		Fax and edr: N000 BM	Response to request for information

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:

REVIEW SUMMARY:

Zetia is a new molecular entity that inhibits the intestinal absorption of cholesterol. The sponsor is seeking approval of Zetia for lipid-lowering in patients with primary hypercholesterolemia, homozygous familial hypercholesterolemia and homozygous sitosterolemia.

The efficacy of Zetia in Primary Hypercholesterolemia is documented in 10 multicenter Phase II/III studies of 8-12 weeks duration that randomized 5,426 subjects. During the blinded studies, 1,983 subjects received ezetimibe as monotherapy and 1,304 subjects received ezetimibe coadministered with a statin (primarily lovastatin simvastatin, pravastatin or atorvastatin). Of those subjects who received ezetimibe alone, 1691 subjects were on 10 mg. 1,313 subjects have entered an open-label extension with 18-month data as of the cut-off date for data analysis (July 15, 2001) and are being treated with either ezetimibe as monotherapy, or

coadministered with lovastatin or simvastatin.

In the pooled monotherapy studies (P00474 + P00475) in patients with primary hypercholesterolemia, Zetia significantly lowered plasma concentrations of total cholesterol (TC), LDL-C and Apo B by 13%, 19% and 14%, respectively and increased HDL-C by 3%, relative to placebo ($p \leq 0.01$). The decrease in TG levels relative to placebo was significant in only one of the two studies (-11%, $p \leq 0.01$ in one; -4%, $p = 0.09$ in the other study).

Initial administration of Zetia plus all statin (i.e. all doses of all statins pooled) to patients with primary hypercholesterolemia produced an additional 14% lowering ($p < 0.01$) in LDL-C compared to all statin alone. This incremental LDL-C lowering effect was independent of statin type and dose. Also, coadministration of ezetimibe with the lowest dose of statin tested (10 mg) was as effective in reducing LDL-C as the highest dose of statin tested (40 mg for lovastatin and pravastatin and 80 mg for simvastatin and atorvastatin). Also, Zetia plus statin further reduced TC by 9-11% and TG by 7 to 11% (all p-values $\leq$ 0.01) and increased HDL-C by 1-5% (statistically significant for only 3 of the 4 statins) compared to statin alone.

Zetia was also administered to ongoing statin therapy in patients with primary hypercholesterolemia, CHD or multiple CV risk factors who had not achieved target LDL-C goal as defined by NCEP ATP II. In these patients, Zetia further reduced LDL-C, TC and TG by 21.5%, 15% and 11%, respectivly (all p-values <0.001) and increased HDL-C by 2% ($p < 0.05$).

Maximal or near-maximal reductions in plasma LDL-C concentrations with ezetimibe monotherapy or coadministration with statins occurred within 2 weeks and were maintained throughout 8-12 weeks of double-blind treatment as well as through 12 to 18 months of open-label treatment.

In a study of 50 subjects with homozygous familial hypercholesterolemia with calculated LDL-C levels $\geq$ 100 mg/dl on atorvastatin or simvastatin 40 mg, the addition of Zetia to a 40 or 80 mg dose of these statins was more effective in lowering LDL-C and TC compared to increasing the statin dose to 80 mg. Specifically, Zetia additionally decreased calculated-LDL-C by 15% and TC by 13% ($p < 0.01$) compared to statin 80 mg.

In a study of 37 subjects with homozygous sitosterolemia who had continued elevations of plasma sitosterol on their current therapeutic regimen, the addition of Zetia significantly reduced plasma sitosterol and campesterol levels by 25% and 27%, respectively, relative to placebo ($p < 0.001$).

With the exception of a race difference, reduction in LDL-C was consistent across all subgroups analyzed. In one of the Monotherapy Studies, P00475, the difference between Zetia and placebo in the mean percent change in LDL-C from baseline was –10.4% in Non-Caucasians compared to -17.8% in Caucasians. In the Factorial Studies and in the Add-On Study, the mean percent change from baseline with Zetia + statin relative to statin alone was less in Non-Caucasians than Caucasians. Additional subgroup analyses by race demonstrated that in study P00475, this diminished LDL-C response to ezetimibe compared to placebo was occurring over time predominately in Asian and Hispanic subjects. With coadministration, the decrease in LDL-response compared to statin alone was particularly evident in Black and Asian subjects. The small number of non-Caucasian subjects enrolled in these studies confounds interpretation of this finding.

In summary, the above data support the approval of Zetia administered alone or in conjunction with HMG-CoA reducatase inhibitors, as an adjunct to diet in patients with primary hypercholesterolemia. The data also support the approval of Zetia administered with simvastatin or atorvastatin, as an adjunct to other lipid-lowering therapy in patients with homozygous familial hypercholesterolemia. Finally, the data support the approval of Zetia as adjunctive therapy for the reduction of elevated plasma sitosterol and campesterol levels in patients with homozygous sitosterolemia.

OUTSTANDING ISSUES:
A study is recommended to further evaluate the racial/ethnic variation in efficacy of Zetia as monotherapy and when coadministered with statin. The timing of this study in relation to approval of Zetia requires discussion at the Division and Office levels.
Additional financial disclosure information has been requested.

RECOMMENDED REGULATORY ACTION:

New Clinical Studies: _____Clinical Hold _____Study May Proceed

NDA, Efficacy/ Label Supplement: _____X_Approvable _____ Not Approvable

SIGNATURES: Medical Efficacy Reviewer: Jean Temeck, M.D. Date: 9/18/02

Medical Team Leader: _____ Date: _____

APPEARS THIS WAY
ON ORIGINAL

Clinical Review for NDA 21-445

Executive Summary

I. Recommendations

A. Recommendation on Approvability

The efficacy data obtained from the Phase II /III clinical studies support the approval of ezetimibe for the reduction of the following lipid variables in the following patient groups:

Primary Hypercholesterolemia:
Ezetimibe as monotherapy in these patients for the reduction of LDL-C, total cholesterol (TC) and Apo B. (Note: compared to placebo, ezetimibe significantly reduced LDL-C, TC and Apo B in each of the two monotherapy studies and in each of the monotherapy arms of the four factorial studies. However, ezetimibe monotherapy did not statistically differ from placebo in lowering TG in study P00474 or in the monotherapy arms of the lovastatin, pravastatin and atorvastatin factorial studies. Also, ezetimibe monotherapy did not statistically differ from placebo in increasing HDL-C in the ezetimibe monotherapy arms of the pravastatin and atorvastatin factorial studies);

Ezetimibe as adjunctive therapy to diet and statins for the reduction of LDL-C, TC, TG and Apo B (Note: compared to statin alone, ezetimibe coadministered with statin significantly reduced LDL-C, TC, TG and Apo B in each of the 4 factorial studies and in the Add-On Study. However, coadministration did not significantly increase HDL-C compared to statin alone in the pravastatin factorial study).

Homozygous Familial Hypercholesterolemia (HoFH):
Ezetimibe as adjunctive therapy to statins approved for HoFH (currently, simvastatin and atorvastatin) to reduce LDL-C and TC.

Homozygous Sitosterolemia:
Ezetimibe as adjunctive therapy for the reduction of elevated sitosterol and campesterol levels.

B. Recommendation on Phase 4 Studies and/or Risk Management Steps

A study is recommended to further evaluate the racial/ethnic variation in efficacy of Zetia as monotherapy and when coadministered with statin. The timing of this study in relation to approval of Zetia requires discussion at the Division and Office levels.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

The Phase II/III clinical program was comprised of 12 completed double-blind, placebo- or active-controlled studies of 8 to 12 weeks duration and an ongoing, open-label, 24-month extension study to support approval of ezetimibe therapy for the following indications:

Primary (heterozygous familial and non-familial) hypercholesterlemia: use of ezetimibe alone or in conjunction with a statin as an adjunct to diet for reduction of elevated LDL-C, TC, Apo B

Homozygous Familial Hypercholesterolemia (HoFH): use of ezetimibe with a statin approved for HoFH for the reduction of elevated LDL-C and TC, as an adjunct to other lipid-lowering treatments (e.g. LDL apheresis) or if such treatments are unavailable;

Homozygous Familial Sitosterolemia: use of ezetimibe as adjunctive therapy for the reduction of elevated sitosterol and campesterol levels.

The specific Phase II/III clinical studies performed to support these indications and the total numbers of patients by treatment by study is displayed in the following table:

Phase II Ezetimibe Clinical Studies in Patients With Primary Hypercholesterolemia				
Protocol No.	Type of study	Total Sample Size	# Patients Exposed to Ezetimibe Only	# Patients Exposed to Ezetimibe + Statin
C96-411/C96-345	Double-blind, pilot dose-ranging study: ez (10, mg) compared to placebo and to lovastatin (40 mg)	124	89 (18 at 10 mg)	0
C98-010	Double-blind, dose-response study of 4 doses of ez 10 mg) compared to placebo	243	191 (46 at 10 mg)	0

C98-258	Double-blind study of morning versus evening dosing of ez — 10 mg) compared to placebo	189	153 (77 at 10 mg0	0

Phase III Ezetimibe Monotherapy Studies in Patients With Primary Hypercholesterolemia				
Protocol No.	Type of study	Total Sample Size	# Patients Exposed to Ezetimibe Only	# Patients Exposed to Ezetimibe + Statin
P00474	Double-blind study comparing ez 10 mg to placebo	827	622	0
P00475	Double-blind study comparing ez 10 mg to placebo	892	666	0

Phase III Ezetimibe/Statin Coadministration- Factorial Studies in Patients With Primary Hypercholesterolemia				
Protocol No.	Type of study	Total Sample Size	# Patients Exposed to Ezetimibe Only	# Patients Exposed to Ezetimibe + Statin
P00679	Double-blind study of ez 10 mg in addition to lovastatin compared to placebo	548	72	192
P00680	Double-blind study of ez 10 mg in addition to simvastatin compared to placebo	668	61	274
P00691	Double-blind study of ez 10 mg in addition to pravastatin compared to placebo	538	64	204
P00692	Double-blind study of ez 10 mg in addition to atorvastatin compared to placebo	628	65	255

Phase III Ezetimibe/Statin Coadministration- Add-On Study in Patients With Primary Hypercholesterolemia, Known Coronary Heart Disease, or Multiple Cardiovascular Risk Factors				
Protocol No.	Type of study	Total Sample Size	# Patients Exposed to Ezetimibe Only	# Patients Exposed to Ezetimibe + Statin
P02173/P02246	Double-blind, placebo-controlled study of ez 10 mg added to ongoing statin therapy	769	0	379

Phase III Ezetimibe Clinical Study in Patients With Homozygous Hypercholesterolemia				
Protocol No.	Type of study	Total Sample Size	# Patients Exposed to Ezetimibe Only	# Patients Exposed to Ezetimibe + Statin

P01030	A Phase III study of Ez in addition to Atorvastatin or Simvastatin	50	0	33

Phase III Ezetimibe Clinical Study in Patients With Homozygous Sitosterolemia				
Protocol No.	Type of study	Total Sample Size	# Patients Exposed to Ezetimibe Only	# Patients Exposed to Ezetimibe + Statin
P02243/P02257	Multicenter, randomized, double-blind, placebo-controlled study of ez when added to current therapy	37	30[d]	0
d: in 8 of these patients, ezetimibe was added to ongoing therapy with bile-acid-binding resins				

A total of 5,513 patients were enrolled in these 12 Phase II/III clinical trials. Of these, 2,013 were exposed to ezetimibe (1,721 to 10 mg) and 1,337 to ezetimibe + statin.

Ongoing, Uncontrolled, Open-Label, Long-Term Extension Study in Patients With Primary Hypercholesterolemia				
Protocol No.	Type of study	Total Sample Size	# Patients Exposed to Ezetimibe Only	# Patients Exposed to Ezetimibe + Statin
P00476 (extension to P00474/P00475)	24-month safety and tolerability study of ez 10 mg	1313	783	530

The above 3 Phase II studies with treatment phases of 8-12 weeks were performed to support the selected therapeutic dose (10 mg), the dose interval (once daily), and the timing of dose administration (AM or PM) for the Phase III studies.

7 Phase III studies with treatment phases of 8-12 weeks were performed to support the use of ezetimibe in the treatment of primary hypercholesterolemia. Studies P00474 and P00475 (Monotherapy Studies) were performed to support the use of ezetimibe administered alone; the 4 Factorial Studies to support simulataneous administration of ezetimibe and statins; and the Add-On Study to support the addition of ezetimibe to ongoing statin therapy.

In the Monotherapy Studies, P00474 and P00475, subjects with primary hypercholesterolemia (LDL-C 130-250 mg/dl) received randomized treatment with ezetimibe 10 mg or placebo for 12 weeks.

In the 4 Factorial Coadministration Studies, subjects with primary hypercholesterolemia received randomized treatment with ezetimibe 10 mg alone, various doses of statin alone (lovastatin, simvastatin, pravastatin or atorvastatin) alone, ezetimibe with various doses of statin, or placebo.

In the Add-On Study, randomized treatment with either ezetimibe or matching placebo was added to ongoing statin therapy in patients with primary hypercholesterolemia, known CHD, or multiple CV risk factors and who required further LDL-C lowering.

The homozygous familial hypercholesterolemia trial evaluated the efficacy of coadministering ezetimibe 10 mg with simvastatin or atorvastatin (40 or 80 mg) as well as with LDL apheresis in subjects already stabilized on such treatments.

The homozygous sitosterolemia study evaluated the efficacy of ezetimibe as an adjunct to current therapeutic regimens, which generally consisted of a low-plant-sterol-diet and, in some subjects, the use of bile-acid binding resins.

Among these core Phase II/III studies, a total of 2,995 subjects with primary hypercholesterolemia were exposed to ezetimibe 10 mg/day for at least 8 weeks; 2,598 of these were exposed to ezetimibe 10 mg/day for 12 weeks. 33 patients with HoFH and 30 patients with homozygous sitosterolemia were exposed to ezetimibe 10 mg/day for 12 weeks and 8 weeks, respectively. Of the exposed subjects, 2013 were treated with ezetimibe monotherapy and an additional 1334 were treated with ezetimibe/statin coadministration.

In addition to the results of these pivotal studies, results from an ongoing, open-label, long-term extension study, P00476, were included to support the long-term durability of ezetimibe-induced reductions in LDL-C concentrations. In this study, subjects who completed P00474 or P00475 are continuing on ezetimibe for up to 24 months. Investigators have the option of adding lovastatin or simvastatin to ongoing ezetimibe therapy to achieve LDL-C targets established by NCEP ATP II. Thus far in this study, 1313 subjects have been exposed to ezetimibe for up to 18 months; 530 (40%) of these are also currently on statins.

B. Efficacy

All efficacy analyses reported in this review are for the Intent-to-Treat Population unless otherwise stated.

Among the Phase III clinical studies, the change in plasma concentrations of direct LDL-C (measured by a standard ultracentrifugation procedure) was the primary efficacy variable in all but 2 studies, with values expressed as the percent change from baseline to endpoint (the last point at which postbaseline measurements were available). Exceptions included the Add-On Study, in which change in plasma concentrations of calculated LDL-C (based on the Friedewald equation) was the primary efficacy variable, and the study in homozygous hypercholesterolemia subjects in which change in plasma concentrations of sitosterol was the primary efficacy variable.

Key secondary efficacy variables included change from baseline to endpoint in plasma concentrations of direct LDL-C, calculated LDL-C, total cholesterol (TC), TG, Apo B and HDL-C. The percentage of subjects reaching target LDL-C levels established by the NCEP ATP II was a key secondary variable in the Add-On Study. Change from baseline to endpoint in plasma concentrations of campesterol

was a key secondary efficacy variable in the homozygous sitosterolemia study. Other secondary variables included HDL_2-C, HDL_3-C, Apo A-1, Lp(a), non-HDL-C, direct LDL-C/HDL-C and TC/HDL-C.

Ezetimibe Monotherapy:
In the pooled Phase III Monotherapy Studies, treatment with ezetimibe 10 mg reduced plasma concentrations of the following lipid variables relative to baseline: direct LDL-C, 17.4%; calculated LDL-C, 18.2%; TC, 12.7%, TG, 4.2% (this was mean; median was –8.0%) and Apo B, 15.7% and increased HDL-C by 1.0%. The corresponding mean changes in the ezetimibe group relative to the placebo group were-17.7% for direct LDL-C, -19.1% for calculated LDL-C, -13.1% for TC, -7.8% for TG, -14.1% for Apo B and +2.6% for HDL-C (all p values were ≤ 0.01).

In each study, the difference between ezetimibe and placebo was statistically significant ($p \leq 0.05$) for direct and calculated LDL-C, TC, HDL-C and Apo B. TG lowering was statisticlly significant in study P00475 only (P00475: -11.4%, $p \leq 0.01$; P00474: -4.1%, 0.09).

The changes in LDL-C occurred as early as week 2 and were maintained for the 12-week study duration.

In one of these Monotherapy Studies, P00475, the difference between ezetimibe and placebo in the mean percent LDL-C reduction from baseline was –17.8% in Caucasians and –10.4% in Non-Caucasians. Additional post-hoc subgroup analyses by race/ethnic origin demonstrated diminished LDL-response to ezetimibe compared to placebo over time in Asian and Hispanic subjects. Given the small sample size of non-Caucasians enrolled in these studies, these results should be interpreted with caution but this issue requires further study. (Please refer to section IX.B. for detailed information).

Results were generally consistent between the Monotherapy Studies and the ezetimibe monotherapy arms of the Factorial Studies. In the Factorial Studies, ezetimibe reduced direct LDL-C by 18.1 to 18.7% and calculated LDL-C by 18.7 to 20.0% relative to baseline. Compared to placebo, additional reductions in LDL-C attributable to ezetimibe ranged from 17 to 24% for direct LDL-C and from 18 to 24% for calculated LDL-C ($p \leq 0.01$). The difference between ezetimibe and placebo was also statistically significantly ($p < 0.05$) for TC and Apo B in each of the Factorial Studies but not for TG (significant difference in simvastatin factorial study only) or HDL-C (significant difference in simvastatin and lovastatin factorial studies only).

Ezetimibe Coadministered With Statins: Factorial Studies:
(Note: the results obtained for direct LDL-C were very similar to those obtained for calculated LDL-C).

In 3 of the 4 Factorial Studies, there was no statistically significant treatment-by-dose interaction. A significant interaction was noted in the simvastatin factorial study (p= 0.04). This finding was attributed to anomalous values at endpoint for the low-to-mid dose range, irregularities which were not apparent at earlier time points, and even at endpoint did not result in a significant interaction in the protocol-evaluable analysis. Thus, the average effect across all doses was still considered the best estimate of overall ezetimibe effect when coadministered with different doses of simvastatin.

Pooling the mean percent LDL-C reduction observed with coadministration across all 4 Factorial Studies (ezetimibe + all statin), the extent of LDL-C reduction attributable to ezetimibe was –13.3% for direct LDL-C and –13.8% for calculated LDL-C relative to all statin alone ($p < 0.01$). The additional LDL-C lowering with coadministration compared to statin alone was consistent across the 4 statins. For calculated LDL-C, the additional lowering with coadministration by statin was: lovastatin, -15.0%; simvastatin, -14.8%; pravastatin, -13.4% and atorvastatin, -12.1% (all p-values ≤ 0.01). Across all 4 statins, the incremental mean percent change in LDL-C gained by the coadministration of ezetimibe and each dose of statin ranged from –7 to –18% and it was independent of a given statin dose. In pairwise comparisons, coadministration of ezetimibe with the lowest dose of each statin, 10 mg, resulted in LDL-C concentrations similar to that seen with the highest dose tested of statin alone (40 mg of lovastatin or pravastatin and 80 mg of simvastatin or atorvastatin). The reductions in LDL-C occurred as early as week 2 and were maintained for the study duration. The pooled Factorial Studies suggested a race difference in the LDL-C response to coadministration therapy between Caucasians and Non-Caucasians. In the pooled Factorial Studies, ezetimibe resulted in an additional 14.6% reduction in mean LDL-C when coadministered with statin compared to statin alone (all doses of all statins pooled). The corresponding additional reduction in Non-Caucasians was 6.6%. Additional subgroup analyses by race indicated that this finding was due to diminished LDL-C lowering efficacy of coadministration therapy over time in Black and Asian subjects. Given the small sample size of non-Caucasians enrolled in these studies, these results should be interpreted with caution but this issue requires further study. (Please refer to section IX.B. for detailed information).

With the exception of HDL-C, statistically significant differences ($p < 0.01$) were observed between coadministration and statin alone, pooled across statin doses in each of the Factorial Studies for the key secondary variables, TC, TG and Apo B. An additional 9.1 to 10.8% lowering was observed for TC with coadministration; 7.4 to 10.5% for TG and 9.3 to 12.3% for Apo B. The additional increases in HDL-C were small, 1.4 to 4.5%; and were statistically significant ($p < 0.05$) in only 3 of the 4 Factorial Studies (lovastatin, simvastatin and atorvastatin).

Ezetimibe Coadministered With Statins: Add-On Study:

Addition of ezetimibe to ongoing statin therapy further reduced calculated LDL-C by 21.5% ($p< 0.001$). This additional decrease was observed as early as week 2 and was maintained for the study duration. A race difference was observed in the response to LDL-C to coadministration therapy. The mean percent change in LDL-C between ezetimibe plus statin versus statin alone was –22% for Caucasians and –15% for Non-Caucasians. Additional post-hoc analyses suggested diminished LDL-C response over time in Black, Asian and Hispanic subjects. Given the small sample size of non-Caucasians enrolled in this study, these results should be interpreted with caution but this issue requires further study.

Among subjects not at their NCEP II LDL-C targets at baseline, 72% on ezetimibe + statin versus 19% on statin alone reached their LDL-C targets at endpoint.

Also, the addition of ezetimibe further reduced TC and TG by 14.7% and 11.1%, respectively ($p < 0.001$) and increased HDL-C by 1.7% ($p < 0.05$) relative to statin alone.

Ezetimibe Therapy for the Treatment of Homozygous Hypercholesterolemia:
50 patients, aged 11-74 years, with a clinical or genotypic diagnosis of HoFH, with or without concomitant LDL apheresis, already receiving simvastatin or atorvastatin, 40 mg, and with LDL-C $\geq$ 100 mg/dl, were enrolled in this study. Due to decreased bioavailability of ezetimibe in patients concomitantly receiving cholestyramine, ezetimibe was dosed at least 4 hours before or after administration of resins.

After 12-weeks of double-blind treatment, coadministration of ezetimibe with statins (simvastatin or atorvastatin 40/80 mg) resulted in significantly greater mean percent changes in plasma LDL-C concentrations from baseline to endpoint than did statins titrated to their maximal dose of 80 mg. The difference between ezetimibe +statin 40/80 mg and statin 80 mg in mean percent changes from baseline in direct and calculated LDL-C concentrations were –14.1% and -14.8%, respectively, $p= 0.007$. A greater difference (-20.5%, $p= 0.0001$) was observed for ezetimibe + statin 80 mg versus statin 80 mg alone. Significant ($p< 0.01$) beneficial treatment effects were also noted for TC. TC was reduced by an additional 13.3% with ezetimibe + statin 40/80 mg compared to statin 80 mg and by an additional 18.1% with ezetimibe + statin 80 mg compared to statin 80 mg alone. These results support the use of ezetimibe as an adjunct to simvastatin or atorvastatin and also, to LDL apheresis, to reduce elevated LDL-C and TC levels in patients with HoFH.

It should be noted that there were no significant differences between ezetimibe + statin 40/80 mg and statin 80 mg nor between ezetimibe + statin 80 mg versus statin 80 mg in the mean percent changes from baseline in the plasma

concentrations of TG, Apo B and HDL-C. It should also be noted that ezetimibe exerted a 2-3% lowering effect on HDL-C in this patient population compared to an ~4% increase with placebo.

Ezetimibe Therapy for the Treatment of Homozygous Sitosterolemia:
37 patients, aged 9-72 years, with elevated sitosterol levels on their current therapeutic regimen were enrolled in this study. Due to *in vitro* and *in vivo* data demonstrating a drug interaction between ezetimibe and bile salt binding resins (BSBR), the protocol was amended to either reduce or discontinue BSBR therapy, if clinically appropriate. If this change was not deemed appropriate, ezetimibe was dosed at least 2 hours before or 4 hours after resins were administered.

After 8 weeks of daily treatment with ezetimibe 10 mg, plasma concentrations of sitosterol and campesterol were significantly ($p< 0.001$) reduced relative to baseline and to placebo. The mean percent reduction in sitosterol and campesterol from baseline to endpoint with ezetimibe therapy was 21% and ~24%, respectively. On placebo, these mean values increased by 4% and ~3%, respectively. These results support the use of ezetimibe as adjunctive therapy (to diet restricted in plant and shellfish sterols, [redacted]) for patients with homozygous sitosterolemia.

Subgroup analyses showed that in subjects receiving ezetimibe, the reduction in sitosterol concentrations was similar between those who received concomitant bile-acid-binding resins and those who did not.

It should be noted that ezetimibe did not significantly differ from placebo in effects on LDL-C, TC, TG and HDL-C.

Efficacy in the Long-term, Open-Label Extension Study, P00476:
P00476 was the long-term, open-label extension study of the Monotherapy Studies, P00474 and P00475.

Among the 1313 subjects who continued into the open-label extension and received treatment, 569 remained on ezetimibe monotherapy for a cumulative duration of 12 months or longer. The observed mean percent change in LDL-C in this group, as of the last measurement in the 12- to <18-month period, was –21.5% in conjunction with a decrease in TC of –14.5% and TG of –4.4% and an increase in HDL-C of +1.9%. These results suggest that the treatment effects are persistent over the long-term. Also, although these changes are consistent with those observed after 3-months of double-blind ezetimibe monotherapy, caution is recommended in comparing the long-term study to the 12- week studies due to different study designs (open-label vs. placebo-control) and different objectives (titration of therapy to LDL-C goal vs. double-blind treatment with a fixed dose).

C. Safety

Dr. Bruce Stadel is the Medical Officer assigned to review the safety data submitted in this NDA. Please refer to his review for safety.

D. Dosing

The dosing regimen for ezetimibe was identified in the Phase II studies as 10 mg administered orally once daily. Food did not affect the oral bioavailability of ezetimibe.

Administration of ezetimibe to patients with moderate or severe hepatic insufficiency is not recommended. In a 14-day, multiple-dose study (10 mg daily) in patients with moderate hepatic insufficiency, the mean AUC for total ezetimibe was increased ~4-fold on day 1 and day 14 compared to healthy subjects.

A single 10 mg dose of ezetimibe in 8 patients with severe renal disease (CrCl $\leq$ 30 ml/min) increased the mean AUC for total ezetimibe by ~1.5-fold compared to healthy subjects. The result was not considered clinically significant. Therefore, no dosing adjustments are recommended for renally impaired patients. An additional patient in this study, post-renal transplant and receiving multiple medications including cyclosporine, had a 12-fold greater exposure to total ezetimibe. Per Dr. Wei Qiu, the biopharmaceutics reviewer, the sponsor will be conducting a drug interaction study with cyclosporine. In the meantime, I would recommend that this case be cited in the PRECAUTIONS section of the package insert for both products.

E. Special Populations

See above under "Dosing" for dosing of ezetimibe in patients with hepatic or renal impairment.

Pediatric Patients:

[

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Geriatric Patients:

[

]

Gender:
Plasma concentrations of total ezetimibe – slightly higher (<20%) in women than in men.

Race:

[

]

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

Established name: Ezetimibe;

Trade name: Zetia;

Drug class: lipid-lowering;

Sponsor's proposed indications:

Primary Hypercholesterolemia:

ZETIA, administered alone or with an HMG-CoA reductase inhibitor, is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, [redacted] in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

Homozygous Familial Hypercholesterolemia (HoFH):

ZETIA, administered with an HMG-CoA reductase inhibitor approved for HoFH, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

Homozygous Sitosterolemia:

ZETIA is indicated as adjunctive therapy for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia;

Dose and Regimens:

The recommended dose of Zetia is 10 mg once daily, which can be taken with or without an HMG-CoA reductase inhibitor. Zetia may be taken with or without food.

Age Groups:

Treatment experience with Zetia in the pediatric population is limited to 5 patients, ages [redacted]-17 years in the homozygous familial hypercholesterolemia study and 4 patients, ages 9-17 years, in the sitosterolemia study. The sponsor does not recommend treatment with Zetia in children below 10 years of age.

B. State of Armamentarium for Indication(s)

HMG-CoA reductase inhibitors, bile acid sequestrants, nicotinic acid and fibric acid derivatives are the major classes of drugs that have been approved for the treatment of primary hypercholesterolemia. The reader is referred to the National Cholesterol Education Program (NCEP) Treatment Guidelines, Adult Treatment Panel (ATP) II (JAMA 269(23):3015-3023, 1993) and ATP III (JAMA 285(19):2486-2497, 2001) for further information.

Current therapeutic options for patients with homozygous hypercholesterolemia include HMG-CoA reductase inhibitors, LDL apheresis, portacaval shunting, and ultimately liver transplantation.

Current treatment of homozygous sitosterolemia consists of dietary restriction of plant and shellfish sterols, as well as the useof bile salt binding resins. Ileal bypass surgery, to induce bile salt malabsorption, is another treatment option, particularly in patients who do not tolerate resin therapy.

C. Important Milestones in Product Development

April 25, 2001: pre-NDA meeting and first Proposed Pediatric Study Request (PPSR). The Agency concluded that based upon a preliminary review, the efficacy data are adequate to file and NDA and that ezetimibe-statin coadministration exposure for safety is reasonable. FDA agreed to grant a deferral in pediatric patients ≥10 years of age and a waiver for those <10 years of age;

August 30, 2001: internal meeting to discuss the clinical development program for ezetimibe and issuance of a letter to the sposor stating that a Written Request cannot be issued before completion of the review of the NDA;

September 6, 2001: teleconference with the sponsor to provide guidance on the format and content of the ISE and ISS;

September 26, 2001: sponsor submitted a revised PPSR;

November 1, 2001: FDA issues a letter to the sponsor stating that a Written Request cannot be issued before completion of the review of the NDA

D. Other Relevant Information

The Division of Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Zetia" to determine the potential for confusion with approved proprietary and established names as well as pending names. Their recommendation was that the proprietary name "Zetia" not be used. See their review dated April 8, 2002.

The Division of Metabolic and Endocrine Drug Products (DMEDP) concurred with the DMETS recommendation and sent a letter dated July 8, 2002 to the sponsor.

There was a subsequent teleconference between Dr. Orloff and Dr. Parks of DMEDP with the sponsor to discuss the proprietary name "Zetia".

A draft copy of this review was given to Dr. Parks on July 31, 2002. The draft review contained a detailed review of the 12 pivotal Phase II/III clinical trials as well as the ongoing long-term, open-label study, P00476, and the efficacy conclusions from these studies.

Mechanism of Action:

Ezetimibe inhibits the intestinal absorption of cholesterol while statins act by inhibiting endogenous production of cholesterol. Therefore, ezetimibe's effect on lipids should be complementary to that of the statins. The clinical studies demonstrate that coadministration of ezetimibe with statin has an additive effect on LDL-C reduction.

E. Important Issues with Pharmacologically Related Agents

Ezetimibe is an NME, therefore, this section is not applicable.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

See chemistry, biopharmaceutics, pharmacology and statistical reviews.

In the animal toxicolgy studies, heart and lymph node toxicity was the major concern with monotherapy in 1-month and 6-month toxicity studies in dogs and rats, at 7 to 18x the human exposures. However, heart toxicity was not observed in the 12-month study in dogs.

The main target organs of toxicity with combination therapy in rats were liver, stomach and skeletal muscles (and sometimes the spleen, heart and prostate in individual studies). In dogs, it was mainly the liver (and sometimes testes, heart and lungs in individual studies). In general, NOAELs could not be established for the combination studies in rats/dogs.

III. Human Pharmacokinetics and Pharmacodynamics

A. Pharmacokinetics

After oral administration, ezetimibe is rapidly absorbed. It is metabolized primarily in the small intestine and the liver via glucuronide conjugation. Ezetimibe and ezetimibe-glucuronide constitute approximately 10-20% and 80-90% of the total drug in plasma, respectively. After glucuronidation, ezetimibe and ezetimibe-glucuronide are slowly eliminated from the plasma via biliary excretion. Their half-lives are ~22 hours.

After administration of a single 10 mg dose of ezetimibe to fasted adults, mean ezetimibe peak plasma concentrations (C_{max}) of 3.4 to 5.5 ng/ml are attained within 4 to 12 hours and mean ezetimibe-glucuronide C_{max} values of 45 to 71 ng/ml are achieved between 1 and 2 hours. There is no substantial deviation from dose proportionality between 5 and 20 mg.

Both ezetimibe and the glucuronide are highly protein bound.

Food did not affect bioavailability when ezetimibe was administered as 10 mg tablets.

There is no clinically important drug interaction between ezetimibe and statins.

Pharmacokinetic data in the pediatric population less than 10 years of age are not available.

B. Pharmacodynamics

Drug Dose, Drug Concentration and Relationships to Response:

Phase II Studies:

C96-411/C96-345:
The trough concentrations of total and unconjugated ezetimibe were determined to evaluate the relationship between dose and systemic exposure in subjects with primary hypercholesterolemia. The sponsor did not attempt to correlate these concentrations with response.

In brief, the mean trough plasma concentration (C_{min}) of total and unconjugated ezetimibe increased in a dose-related manner. Mean dose-adjusted C_{min} values were similar among the groups of subjects who received [redacted] mg qd. Mean C_{min} among subjects who received [redacted] mg qd was less than the dose-adjusted C_{min} values in the other four groups, but little can be inferred because almost all subjects (15/17) had values that were less than the lower limit of quantification (LOQ) of each assay. The results are summarized below:

Mean (coefficient of variation) Trough Plasma Concentrations of Unconjugated and Total Ezetimibe in Samples Collected at Week 8 of the Randomized Phase (C96-411/C96-345)

Daily Dose of Ezetimibe	N	Ezetimibe	
		Unconjugated	Total
[redacted] mg	17	6.12 (46%)	74.9 (54%)
[redacted] mg	16	4.31 (70%)	53.4 (75%)
10 mg	16	1.75 (98%)	30.7 (112%)
[redacted] mg	20	0.86 (104%)	11.0 (79%)
[redacted] mg	17	0[a] (NA)	0.73[b] (283%)

a= all values <LOQ; b= 15/17 values <LOQ; LOQ= lower limit of quantification; NA= not applicable

C98-010:
The trough concentrations of total and unconjugated ezetimibe were determined to evaluate the relationship between dose and systemic exposure in subjects with primary hypercholesterolemia. The sponsor did not attempt to correlate these concentrations with response.

In brief, the mean trough plasma concentration (C_{min}) of total and unconjugated ezetimibe increased in a dose-related manner and mean dose-adjusted C_{min} values were similar among the dose groups. The results are summarized below:

Mean (coefficient of variation) Trough Plasma Concentrations of Unconjugated and Total Ezetimibe in Samples Collected at Week 12 of the Randomized/Active Treatment Phase (C98-010)

Daily Dose of Ezetimibe	N[a]	Ezetimibe	
		Unconjugated	Total
10 mg	43	2.61 (75%)	33.0 (72%)
[redacted] mg	49	1.10 (68%)	16.1 (93%)

- mg	46	0.27 (66%)	3.0 (65%)
— mg	45	0.08[b] (62%)	0.9 (91%)

a= number of subjects from whom a sample was collected at week 12; b= n=44 for this determination

C98-258:

The concentrations of total and unconjugated ezetimibe approximately 12 hours (PM dosing groups) and 24 hours (AM dosing groups [trough]) after the previous dose were determined to make an evaluation of the relationship between dose and systemic exposure in subjects with primary hypercholesterolemia. The sponsor did not attempt to correlate these concentrations with response.

Mean plasma concentration of total and unconjugated ezetimibe increased in a dose-related fashion as demonstrated in the table below:

Mean (coefficient of variation) Plasma Concentrations of Unconjugated and Total Ezetimibe in Samples Collected at Week 12 of the Randomization/Active Treatment Phase, ~12 hours (PM dosing) and24 hours (AM dosing [trough] After the Previous Dose

Daily Dose of Ezetimibe	N[a]	Ezetimibe	
		Unconjugated	Total
- mg AM	34	1.32 (92%)	15.0 (121%)
- mg PM	39	1.57 (63%	16.1 (52%)
10 mg AM	35	2.64 (87%)	28.0 (84%)
10 mg PM	36	4.31 (69%)	42.6 (60%)

a= number of subjects from whom a sample was collected at week 12

Mean plasma concentrations associated with AM dosing were less than those associated with PM dosing. The sponsor stated that this difference was most likely due to the difference in the interval between time of dosing and time of the blood sample. Ezetimibe has an accumulation half-life of ~24 hours, which suggests that concentrations 24 hours after a dose should be ~70% of those observed 12 hours after a dose. Median plasma concentrations associated with AM dosing were 54% to 73% of the values associated with PM dosing; thus, plasma concentrations are expected to be similar for AM and PM dosing (adjusting for differences in sampling times).

Drug Interaction Studies:

See Dr. Wei Qiu's biopharmaceutics review for a complete and detailed review of the drug interaction studies. Only the results of the potential interactions between ezetimibe and cholestyramine, ezetimibe and fibrates and ezetimibe and statins will be presented here.

Protocol P00776:

In this 14-day, placebo-controlled, parallel-group study, 40 healthy hypercholesterolemic subjects were randomized to one of 5 treatment group (8/group): placebo, cholestyramine 4g