

Report on the Deliberation Results

March 6, 2007

Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name] Zetia Tablets 10 mg
[Non-proprietary name] Ezetimibe (JAN*)
[Applicant] Schering-Plough K.K.
[Date of application] October 31, 2003

[Results of deliberation]

In the meeting held on January 31, 2007, the First Committee on New Drugs concluded that the product may be approved and that this result is to be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product, its re-examination period is 8 years, and either the drug substance or the drug product is not classified as a poisonous drug or a powerful drug.

The wording “severe hypercholesterolemia” in the package insert (CLINICAL STUDIES) should be replaced appropriately, and the proposed Japanese Brand name for the product should be modified with a view to the prevention of medication errors.

**Japanese Accepted Name (modified INN)*

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

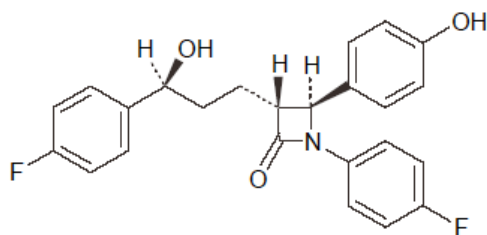
Review Report

January 19, 2007

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name] Zetia Tablets 10 mg
[Non-proprietary name] Ezetimibe
[Applicant] Schering-Plough K.K.
[Date of application] October 31, 2003
[Dosage form/Strength] Tablets: Each tablet contains 10 mg as Ezetimibe
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure]



Molecular formula: C₂₄H₂₁F₂NO₃

Molecular weight: 409.43

Chemical name: (3R,4S)-1-(4-Fluorophenyl)-3-[(3S)-3-(4-fluorophenyl)-3-hydroxypropyl]-4-(4-hydroxyphenyl)azetidin-2-one

[Items warranting special mention] None

[Reviewing office] Office of New Drug II

This English version of the Japanese review report is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail. The PMDA shall not be responsible for any consequence resulting from use of this English version.

Review Results

January 19, 2007

[Brand name] Zetia Tablets 10 mg
[Non-proprietary name] Ezetimibe
[Name of applicant] Schering-Plough K.K.
[Date of application] October 31, 2003 (application for marketing approval for imported drugs)

[Results of review]

Ezetimibe has a novel mechanism of action: it selectively inhibits the absorption of dietary cholesterol and plant sterols by targeting a protein that is involved in the absorption of cholesterol in enterocytes of the small intestine (Niemann-Pick C1 Like 1). A phase III double-blind comparative study in Japanese patients with hypercholesterolemia confirmed the non-inferiority of Ezetimibe over colestimide, a comparator, for the percent change in LDL-cholesterol after 12 weeks of treatment. With regard to the safety, in the Japanese phase III, double-blind comparative study, the incidence of adverse events was 58.5% in the Ezetimibe group and 69.0% in the comparator group and the adverse events reported in the Ezetimibe group were all mild or moderate in severity. Although rhabdomyolysis, hepatic dysfunction, and increased fasting blood glucose levels in diabetic patients, etc. have also been reported with Ezetimibe, appropriate caution statements are included in the package insert and as long as the product is used properly, there should be no serious concerns affecting approval.

Ezetimibe has a mechanism of action that differs from those of other classes of cholesterol-reducing drugs. Incremental effects of Ezetimibe in combination with a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (a statin) can be expected in patients with hypercholesterolemia or familial hypercholesterolemia who require more aggressive treatment. Moreover, Ezetimibe also has significance in terms of offering more therapeutic options to hypercholesterolemic patients who can not tolerate the statins, etc. Homozygous sitosterolemia is an extremely rare disease and Ezetimibe has never been administered to Japanese patients. However, the indication of homozygous sitosterolemia can be approvable based on the mechanism of action of Ezetimibe and foreign clinical study data etc., while post-marketing information collection is required.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that it is appropriate for the application to be discussed at the First Committee on New Drugs, considering that the product may be approved for the following indications and dosage and administration.

[Indications]

Hypercholesterolemia, familial hypercholesterolemia, homozygous sitosterolemia

[Dosage and administration]

The usual adult dosage for oral use is 10 mg of Ezetimibe once daily after a meal. The dosage may be reduced according to the patient's age and symptoms.

Review Report (1)

December 15, 2006

I. Product Submitted for Registration

[Brand name] Zetia Tablets 10 mg

[Non-proprietary name] Ezetimibe

[Name of applicant] Schering-Plough K.K.

[Date of application] October 31, 2003 (application for marketing approval for imported drugs)

[Dosage form/Strength] Tablets: Each tablet contains 10 mg as Ezetimibe

[Proposed indications]

Hypercholesterolemia, familial hypercholesterolemia, homozygous sitosterolemia

[Proposed dosage and administration]

The usual adult dosage for oral use is 10 mg of Ezetimibe once daily. The dosage may be increased or decreased according to the patient's age and symptoms.

II. Summary of the Submitted Data and the Outline of Review by the Pharmaceuticals and Medical Devices Agency

As of April 1, 2004, Pharmaceuticals and Medical Devices Agency (PMDA) was established, consolidating the services of the Pharmaceuticals and Medical Devices Evaluation Center of the National Institute of Health Sciences (PMDEC) and the Organization for Pharmaceutical Safety and Research, etc. Accordingly, questions asked and judgments made by the PMDEC before April 1, 2004 are also deemed as those by the PMDA for writing this review report. Summaries of the data submitted by the applicant and the applicant's responses to the questions from the PMDA are as follows.

1. Origin or background of discovery and usage conditions in foreign countries etc.

Ezetimibe is an antihypercholesterolemic drug discovered by Schering-Plough Corporation (in the U.S.), which inhibits the absorption of dietary and biliary cholesterol by the small intestine. In 2002, the product was approved for the indications of primary hypercholesterolemia, homozygous familial hypercholesterolemia, and homozygous sitosterolemia in Germany, and as of September 2006, regulatory approval has been granted in over 89 countries and regions including the U.S. In Japan, the product was developed and its approval application was filed by Schering-Plough K.K.

2. Physicochemical properties and specifications

<Summary of the submitted data>

Ezetimibe is a compound with an azetidine ring. The empirical formula is $C_{24}H_{21}F_2NO_3$ and its molecular weight is 409.43. It has three asymmetric carbons and is levorotatory. An elliptical tablet was used in phase I studies and a capsule-shaped tablet was used in phase II and phase III studies. The proposed commercial formulation is a white capsule-shaped tablet with a scored line on one side.

(1) Drug substance

The drug substance was manufactured in the following 4 stages.

In Stage 1, [REDACTED] (Compound I) was dissolved in [REDACTED] and [REDACTED] and then cooled (Step 1), and [REDACTED] (Compound II) was added gradually (Step 2) to obtain [REDACTED] (Compound III). Compound III was added with [REDACTED] (Compound IV), [REDACTED], and [REDACTED] and heated at reflux (Step 3). The Step 3 solution was cooled and added with [REDACTED], and the organic layer was washed with [REDACTED] solution and then concentrated, and added with [REDACTED] and concentrated under vacuum (Step 4). The reaction solution was filtered and the solid was washed with cooled [REDACTED], and dried under vacuum to obtain [REDACTED] (Compound V) (Step 5).

In Stage 2, Compound V was dissolved in [REDACTED] containing [REDACTED] and water was removed by azeotropic distillation (Step 1), [REDACTED] solution of a chiral catalyst ([REDACTED]) was added, and 1 mol/L of [REDACTED] was added during reaction (Step 2). After the end of reaction, the reaction mixture was added with [REDACTED] and cooled, concentrated under vacuum, and added with [REDACTED] and [REDACTED], and the aqueous layer was acidified to $\leq \text{pH}$ [REDACTED] (Step 3). After the aqueous layer was removed from the Step 3 solution, the organic layer was washed with [REDACTED] (until the pH of the washings was \geq [REDACTED]) and concentrated under vacuum, and [REDACTED] (Compound VI) solution was added with [REDACTED] and distilled azeotropically, concentrated under vacuum, and then diluted with [REDACTED] (Step 4).

In Stage 3, [REDACTED] (Compound VII) was added with the Compound VI solution, diluted with [REDACTED] and then cooled (Step 1). [REDACTED] and [REDACTED] were added for silylation (Step 2), which was added with [REDACTED] and stirred (Step 3), added with [REDACTED] and allowed to stand, added to cooled [REDACTED] solution and [REDACTED] solution and allowed to stand, and the liquid layer was separated (Step 4). The aqueous layer was fractionated with [REDACTED], and the organic layer was washed with [REDACTED], separated for azeotropic drying (Step 5). The organic layer was added with [REDACTED] and heated under reflux, and the reaction solution was concentrated and added with [REDACTED]. [REDACTED] solution of [REDACTED] (Compound VIII)

was diluted with [REDACTED] and gradually cooled to crystallize Compound VIII (Step 6). Compound VIII was allowed to stand and then filtered, washed with cooled [REDACTED]/[REDACTED] mixed solution, refluxed with [REDACTED] and suspended, and then diluted with [REDACTED] and gradually cooled (Step 7). Compound VIII was filtered, washed with cooled [REDACTED]/[REDACTED] mixed solution and dried (Step 8).

In Stage 4, Compound VIII was added with [REDACTED] and suspended (Step 1), added with [REDACTED] and [REDACTED] as a catalyst and stirred (Step 2), added with [REDACTED], concentrated under vacuum, added with [REDACTED] and [REDACTED], and heated (Step 3). Ezetimibe was crystallized (Step 4), slurries of Ezetimibe were allowed to stand and then filtered, and washed with cooled [REDACTED] until the pH of the washings was \geq [REDACTED] (Step 5). Ezetimibe was dried (Step 6) and then finely-ground by [REDACTED] mill (Step 7). Step 1 and Step 4 of Stage 2 and Step 2 and Step 3 of Stage 4 were defined as critical process steps, and Compounds V, VI, and VIII were defined as key intermediates and control values were established.

The structure of the drug substance was elucidated by elementary analysis, various spectral analyses (hydrogen nuclear magnetic resonance spectrum, carbon nuclear magnetic resonance spectrum, infrared absorption spectrum (IR), and mass spectrum), and X ray crystallography. Chiral impurities of Ezetimibe are controlled by optical rotation and chiral liquid chromatography (chiral HPLC).

The proposed specifications for the drug substance include description (appearance), identification (IR and chiral HPLC), optical rotation, purity (heavy metals, related substances (achiral and chiral), total related substances, and residual solvents), water content, residue on ignition, particle size, and assay.

The following stability studies were conducted: long-term testing (25°C, 60%RH, 36 months), accelerated testing (40°C, 75%RH, 6 months), intermediate testing (30°C, 60%RH, 12 months), and stress testing at elevated temperatures (50°C, 3 months) for the drug substance placed in double low-density polyethylene bags/a metal can, and stress testing under humidity conditions for the drug substance placed in a petri dish (open) (25°C, 75%RH, 3 months), and stress testing under light conditions for the drug substance placed in a petri dish (closed) (cool white fluorescent lamp: 1.2 million lx·hr, near ultraviolet fluorescent lamp: 215 W·hr/m²). Description (appearance), identification (IR), optical rotation, related substances (achiral, chiral, and total), water content, particle size, x-ray powder diffraction, and assay were measured. In the long-term testing, the water content increased after [REDACTED] months and the particle size increased over time. In the accelerated testing, the water content and the particle size increased. In the intermediate testing, the particle size increased. In the stress testing at elevated temperatures, the particle size increased. In the stress testing under humidity conditions, an increase in water content accompanied by conversion from the anhydride form to the [REDACTED] hydrate form of Ezetimibe and increased particle size were noted. In the stress testing under light conditions, the water content increased for both the sample and the control. Based on the results of stability studies (the long-term testing and the accelerated testing) and statistical analysis, a re-test period of [REDACTED] months was proposed for the drug substance.

(2) Drug product

The drug product was manufactured in the following process steps. In Process Step 1 (mixing, granulation, and drying), Ezetimibe, [REDACTED], [REDACTED], and [REDACTED] corresponding to [REDACTED]% of the batch size were [REDACTED] by [REDACTED] granulator, and then [REDACTED] with [REDACTED] aqueous solution and subsequently with [REDACTED], granulated and then dried. In Process Step 2 (size reduction), the granules were reduced in size with [REDACTED] (screen size Φ [REDACTED] mm). In Process Step 3 (blending of granules), the size-reduced granules, [REDACTED], and [REDACTED] corresponding to [REDACTED]% of the batch size were blended using [REDACTED] blender, and then mixed with [REDACTED] sieved through [REDACTED] mesh. In Process Step 4 (tableting), the mixture of granules was pressed into tablets. In Process Step 5 (packaging), polyvinyl chloride (PVC)/Aclar (polychlorotrifluoroethylene) films were molded at high temperature and then the tablets were filled into there and heat sealed with aluminum foil, or the tablets were filled into high density polyethylene (HDPE) bottles and absorbent cotton was additionally put into the bottles before the opening was sealed, and then the bottles were closed with polypropylene (PP) screw caps. Process Steps 1, 3, and 4 were defined as critical process steps, control values for the key intermediates produced in those steps were established, and the quality was assured.

The proposed specifications for the drug product include description (appearance), identification (HPLC and thin layer chromatography), purity (degradation products), water content, content uniformity, dissolution, and assay.

The following stability studies were conducted: long-term testing (25°C, 60%RH, 36 months), accelerated testing (40°C, 75%RH, 6 months), and intermediate testing (30°C, 60%RH, 15 months) for the drug product packaged in a Push Through Pack (PTP) sheet (PVC/Aclar and aluminum) and a plastic bottle (HDPE bottle/PP cap (with an aluminum seal): 500 tablets (well-sealed)), and photostability testing for the drug product placed in a petri dish (open) (cool white fluorescent lamp: 1.2 million lx·hr, near ultraviolet fluorescent lamp: 200 W·hr/m²). Description (appearance), purity (degradation products), water content, dissolution, assay, hardness, and abrasion were measured at all timepoints in the long-term testing, the accelerated testing, the intermediate testing, and the stress testing. Microbial limit testing was performed at 12, 24, and 36 months of the long-term testing. In the long-term testing, the water content increased by up to [REDACTED]% for the drug product packaged in a PTP sheet while there were no changes over time for the drug product packaged in a HDPE bottle. In the accelerated testing, changes in the appearance (a slightly [REDACTED] discoloration) and up to [REDACTED]% increases in water content for the drug product packaged in a PTP sheet, and changes in the appearance (a slightly [REDACTED] discoloration) for the drug product packaged in a HDPE bottle were observed. In the intermediate testing, the water content increased by up to [REDACTED]% for the drug product packaged in a PTP sheet. In the photostability testing, the water content decreased by [REDACTED]% for the drug product placed in a petri dish (open). Based on the results of stability studies and statistical analysis, a shelf life of 34 months was proposed for the drug product packaged in a PTP sheet or a HDPE bottle.

<Outline of the review by the PMDA>

The PMDA asked the applicant whether there is any necessity to establish specific control values for Step 3 of Stage 4 in the drug substance manufacturing process, which was positioned as a critical process step.

The applicant responded as follows:

We consider that there is no need to establish specific control values because the formation of impurities including [REDACTED] can be controlled by maintaining the temperature at [REDACTED]°C or less during vacuum concentration, and their quantities can be controlled during drug substance testing.

The PMDA asked the applicant to reconsider the water content specification, taking account of the effects of the [REDACTED] hydrate form on the efficacy, safety, manufacturing process, etc. of Ezetimibe.

The applicant responded as follows:

The measured water content in the drug substance is likely to be derived from the [REDACTED] hydrate form, and the upper limit of the water content specification of [REDACTED]% corresponds to approximately [REDACTED]% [REDACTED] hydrate form in the drug substance. As the [REDACTED] hydrate form has similar physicochemical properties as the anhydride form, the presence of the [REDACTED] hydrate form in the drug substance does not affect the manufacturing process, and since the tablets manufactured using the [REDACTED] hydrate form have similar dissolution and stability characteristics as the product (tablets containing the anhydride form), the presence of the [REDACTED] hydrate form neither affect the efficacy nor safety of Ezetimibe. Therefore, the water content specification established based on actual values and the results of stability studies is considered appropriate.

The PMDA asked the applicant to provide a justification for inclusion of the acceptance criteria of the United States Pharmacopeia (USP) in the content uniformity and dissolution specifications for Ezetimibe by referring to the Japanese Pharmacopoeia (JP).

The applicant responded as follows:

Although the USP acceptance criteria were included in the content uniformity specification for Ezetimibe, as the acceptance criteria of the JP will be more stringent than those of the USP if a difference between the lot mean content and the labeled amount is large, we will change it to the JP acceptance criteria. In addition, although the acceptance criteria of the USP were included in the dissolution specification for Ezetimibe, as the specification limit for individual dissolution rates in Stage [REDACTED] seems too low in view of the results of the long term testing, the acceptance criterion for Stage [REDACTED]: “None of the individual dissolution rates is less than [REDACTED]%” will be deleted.

The PMDA accepted the above response and judged that there are no particular problems with the quality of Ezetimibe.

3. Non-clinical data

(i) Summary of pharmacology studies

<Summary of the submitted data>

(1) Primary pharmacodynamics

1) Lipid-lowering effect in hyperlipidemic animals

(a) Cholesterol-fed mice (Documents 4.2.1.1.1)

Male CF-1 mice (n=5) were fed Ezetimibe 0, 0.1, 0.3, 1, 3, and 10 mg/kg once daily for 7 days in a diet containing 1% cholesterol and 0.5% cholic acid. The serum total cholesterol was 176 mg/dL in the non-cholesterol fed/untreated control group while the serum total cholesterol level in the vehicle-fed (corn oil) group increased by 74 mg/dL at the end of treatment. Ezetimibe reduced serum total cholesterol (lowest-observed-effect level (LOEL): 1 mg/kg/day) and hepatic cholesteryl ester (ED₅₀ value: 0.7 mg/kg/day).

(b) ApoE knockout mice (Documents 4.2.1.1.2)

Male apoE knockout mice (n=8-12) were fed a high-fat diet (40 kcal% butter/0.15% cholesterol), a low-fat diet (10 kcal% corn oil/0.15% cholesterol) or a cholesterol-free diet (10 kcal% corn oil) containing Ezetimibe for 6 months (Ezetimibe doses: 5.31, 5.93, and 4.65 mg/kg/day, respectively). In all groups, Ezetimibe reduced plasma total cholesterol levels primarily through the reduction in chylomicron/very low-density lipoprotein cholesterol (chylomicron/VLDL-C). Ezetimibe decreased plasma intermediate-density lipoprotein/low-density lipoprotein cholesterol (IDL/LDL-C) levels and increased plasma high-density lipoprotein cholesterol (HDL-C) levels. Ezetimibe also reduced hepatic cholesteryl ester and hepatic free cholesterol levels.

(c) LDL receptor and apoE knockout mice (Documents 4.2.1.1.3)

Male LDL receptor and apoE knockout mice (n=3-4) were fed a cholesterol-free diet (10 kcal% corn oil) containing Ezetimibe 5 mg/kg/day for 6 months. Ezetimibe significantly reduced plasma total cholesterol, chylomicron/VLDL-C, and IDL/LDL-C levels (1,205±46→934±84, 781±54→462±71, and 542±26→386±19 mg/dL, respectively (Mean±SEM)).

(d) Cholesterol-fed rats (Documents 4.2.1.1.1)

Female SD rats (n=4-6) were fed Ezetimibe 0, 0.1, 0.3, 1, and 3 mg/kg once daily for 7 days in a diet containing 1% cholesterol and 0.5% cholic acid. At the end of treatment, plasma total cholesterol (ED₅₀ value: 0.03 mg/kg/day) and hepatic cholesteryl ester (ED₅₀ value: Not calculable) levels were reduced in the Ezetimibe group compared to the untreated control group.

(e) Cholesterol-fed hamsters (Documents 4.2.1.1.1)

Male golden syrian hamsters were fed Ezetimibe 0, 0.03, 0.1, 0.3, and 1 mg/kg once daily for 7 days in a 0.5% cholesterol-containing diet. Ezetimibe reduced plasma total cholesterol and hepatic cholesteryl ester levels (ED₅₀ values: 0.12 and 0.04 mg/kg/day, respectively, n=4-12), but had no effect on hepatic free cholesterol or plasma triglycerides (n=4-6).

(f) High-fat diet fed rabbits (Documents 4.2.1.1.1, 4.2.1.1.4)

Among male New Zealand white rabbits fed a diet containing 1% cholesterol/6% peanut oil for 1 week, those with a level of plasma total cholesterol within the range of Mean \pm 2S.D. (standard deviation) were fed the same diet containing Ezetimibe 0.6 mg/kg/day for 4 weeks. The high-fat diet fed before administration of Ezetimibe in the diet caused an increase in plasma total cholesterol from 50 to 609 mg/dL, and a further increase was observed in the non-Ezetimibe group (n=8), while the Ezetimibe group (n=8) showed a reduction at Week 1 and thereafter and the effect persisted throughout the treatment period. Plasma cholesterol at the end of study was mostly distributed in the VLDL/IDL fractions and Ezetimibe reduced VLDL/IDL-C, chylomicron-cholesterol, low-density lipoprotein cholesterol (LDL-C), and HDL-C levels.

Female New Zealand white rabbits (n=4-5) fed a diet containing 0.5% cholesterol/6% peanut oil were orally administered Ezetimibe 0, 0.003, 0.01, 0.03, 0.1, 0.3, and 1 mg/kg once daily for 2 weeks. Ezetimibe reduced the elevated level of serum total cholesterol (64.6 \pm 8.6 \rightarrow 477 \pm 45.4 mg/dL) due to a high-fat diet (ED₅₀ value: 0.055 mg/kg/day).

(g) High-fat diet fed dogs (Documents 4.2.1.1.5)

Male beagle dogs (n=5) fed a diet containing 5.5% lard, 0.2% cholic acid, and 1% cholesterol were given Ezetimibe 0, 0.003, 0.01, and 0.03 mg/kg/day for 7 days. Ezetimibe reduced the elevated level of fasting plasma total cholesterol (119 \pm 13 \rightarrow 165 \pm 20 mg/dL) due to a high-fat diet (ED₅₀ value: 0.007 mg/kg/day).

(h) High-fat diet fed monkeys (Documents 4.2.1.1.6)

(h)-1. Plasma cholesterol

Male and female rhesus monkeys fed a diet containing 15% reduced coconut oil, 7.5% olive oil, and 0.25% cholesterol (150 g/day) for 35 days were given Ezetimibe 0.1 mg/kg/day (Group A: for 15 days from Day 21 of a high-fat diet (treatment administration), Group B: for 20 days from the start of a high-fat diet (prophylactic administration), n=5). In Group A, the plasma total cholesterol increased from 148 to 294 mg/dL following a 20-day high-fat diet, which was reduced to the baseline level (a level before the start of a high-fat diet) on the 9th day of Ezetimibe administration. In Group B, an increase in plasma total cholesterol was completely inhibited and the effect of Ezetimibe persisted up to 3 days after the discontinuation of Ezetimibe, but the plasma total cholesterol level was elevated thereafter, indicating that the effect of Ezetimibe is reversible. The time course of plasma LDL-C was also similar to those of plasma total cholesterol in Group A and Group B, respectively.

Male and female rhesus monkeys fed the same high-fat diet were given Ezetimibe 0, 0.0003, 0.001, 0.003, and 0.01 mg/kg/day for 3 weeks (n=5-10). Ezetimibe inhibited an increase in plasma total cholesterol caused by a high-fat diet (ED₅₀ value: 0.0005 mg/kg/day). Ezetimibe also reduced the elevated level of plasma LDL-C due to a high-fat diet, whereas plasma HDL-C was unaffected by a high-fat diet and Ezetimibe administration. Ezetimibe did not decrease plasma total cholesterol or LDL-C to below baseline levels in either study.

(h)-2. Lipids in the plasma chylomicron fraction after feeding

Cynomolgus monkeys fasted for 20 hours were fed a single dose of 0 or 10 mg/kg of SCH48461 (a compound with a similar structure and action as Ezetimibe) in a diet containing 15% reduced coconut oil, 7.5% olive oil, and 0.25% cholesterol (150 g) (n=3). SCH48461 decreased cholesteryl ester and free cholesterol in the plasma chylomicron fraction at 5 hours post-dose by 69% and 64%, respectively, but had no effect on triglycerides.

(h)-3. ApoB₄₈ and apoB₁₀₀ content in the plasma lipoprotein fractions after feeding

Rhesus monkeys were fed 0 or 10 mg/kg/day of SCH48461 in a diet containing 15% reduced coconut oil, 7.5% olive oil, and 0.25% cholesterol (150 g/day) for 19 days (n=4). SCH48461 did not affect the apoB₄₈ content in the plasma chylomicron fraction 4 hours after the last dose, but reduced the apoB₁₀₀ content in the plasma LDL fraction. These results suggested that Ezetimibe does not affect the number of plasma chylomicron particles, reduces cholesterol content per chylomicron particle, and decreases plasma LDL-C and LDL particles.

(i) Lipid lowering effect in animals with normal lipid levels (Documents 4.2.1.1.1)

Following repeated oral doses of 0 or 100 mg/kg of Ezetimibe once daily for 7 days to female SD rats (n=4-5), Ezetimibe reduced plasma triglycerides levels, but had no effect on plasma total cholesterol or hepatic lipids. In male golden syrian hamsters (n=4-6) administered 0 or 1 mg/kg of Ezetimibe in the same manner, Ezetimibe had no significant effect on plasma and hepatic lipids.

(j) Atherosclerosis model

(j)-1. ApoE knockout mice (Documents 4.2.1.1.2)

Male apoE knockout mice (n=8-12) were fed a high-fat diet (40 kcal% butter/0.15% cholesterol), a low-fat diet (10 kcal% corn oil/0.15% cholesterol), or a cholesterol-free diet (10 kcal% corn oil) containing Ezetimibe for 6 months (Ezetimibe doses: 5.31, 5.93, and 4.65 mg/kg/day, respectively). After the 6-month treatment, atherosclerotic lesions in the aorta and right carotid artery were noted in the untreated control group for all three diets, whereas the development of lesions was inhibited at all sites in the Ezetimibe-treated group.

(j)-2. LDL receptor and apoE knockout mice (Documents 4.2.1.1.3)

Male LDL receptor and apoE knockout mice (n=3-4) were fed Ezetimibe 5 mg/kg/day in a cholesterol-free diet (10 kcal% corn oil) for 6 months. After the 6-month treatment, in the Ezetimibe-treated group, the intimal lesion cross-sectional area of the aortic arch and the ratio of intimal/medial cross-sectional areas were reduced and the development of atherosclerotic lesions was inhibited.

(j)-3. High-fat diet fed rabbits (Documents 4.2.1.1.1)

Among male New Zealand white rabbits fed a diet containing 1% cholesterol/6% peanut oil for 1 week, those with a level of plasma total cholesterol within the range of Mean \pm 2S.D. were fed a diet containing Ezetimibe 0.6 mg/kg/day for 4 weeks (n=8). At the end of treatment, fatty streak lesions consisting of foam

cells in aortic tissue were noted in the untreated control group while the fatty streak lesion development was completely inhibited in the Ezetimibe-treated group. Ezetimibe reduced cholesteryl ester and free cholesterol in the aortic arch by 68% and 55%, respectively.

2) Investigation of mechanism of action

(a) Cholesterol absorption inhibitory activity

(a)-1. Single dose administration (Documents 4.2.1.1.1)

Ezetimibe doses of 0.03, 0.1, and 1 mg/kg or vehicle were orally administered to male CF-1 mice (n=4), male SD rats (n=5), and male golden syrian hamsters (n=4) 30 minutes (mice) or 1 hour (rats and hamsters) prior to the oral administration of ¹⁴C-labeled (¹⁴C-) cholesterol. Two hours after the administration of ¹⁴C-cholesterol, Ezetimibe reduced plasma radioactivity in mice, rats, and hamsters by 67%, 84%, and 76%, respectively.

Ezetimibe doses of 0 or 0.0001-0.03 mg/kg with 1 mL of rat bile were intraduodenally administered to anesthetized fasted male SD rats (n=5-10) 1 hour prior to the intraduodenal administration of an emulsion containing ¹⁴C-cholesterol (19 mM sodium taurocholate/PBS containing triolein 35.4 mg, L- α -phosphatidylcholine 6.69 mg, and ¹⁴C-cholesterol (3 mL, pH6.4)). One and a half hours after the administration of the emulsion, Ezetimibe reduced plasma radioactivity in a dose-dependent manner (ED₅₀ value: 0.0016 mg/kg).

(a)-2. Repeated-dose administration (Documents 4.2.1.1.2)

Ezetimibe doses of 0.3-10 mg/kg were orally administered to male C57BL mice 30 minutes prior to the administration of ¹⁴C-cholesterol and ³H-labeled (³H-) sitosterol (n=4-5). From the following day, the same doses of Ezetimibe were orally administered once daily for 3 days, and the ¹⁴C- and ³H-radioactivity in feces was determined. As sitosterol is very poorly absorbed in the small intestine, the absorption rate of cholesterol calculated using the following formula was 51.2%. The lack of apoE protein did not alter the cholesterol absorption inhibitory activity of Ezetimibe.

$$\text{Cholesterol absorption (\%)} = \left(1 - \frac{\text{fecal cholesterol radioactivity}}{\text{administered cholesterol radioactivity}} \times \frac{\text{administered sitosterol radioactivity}}{\text{fecal sitosterol radioactivity}}\right) \times 100$$

(a)-3. Effects on cholesterol transport through the small intestinal wall (Documents 4.2.1.1.1)

Ezetimibe doses of 1.0 mg/kg with the emulsion (19 mM sodium taurocholate/PBS containing triolein 35.4 mg and L- α -phosphatidylcholine 6.69 mg (3 mL, pH6.4)) mentioned in 2) a)-1 above were intraduodenally administered to anesthetized fasted male SD rats (n=5) 1 hour prior to the intraduodenal administration of 3 mL of an emulsion containing ¹⁴C-free cholesterol and ³H-cholesterol oleate. One and a half hours after the administration of the latter emulsion, ¹⁴C- and ³H-radioactivity in different tissues was determined. In addition, free cholesterol and cholesteryl ester were extracted from the rat small intestinal wall at the end of the study and separated by thin-layer chromatography, and ¹⁴C- and ³H-radioactivity in each band from the thin layer chromatography plate was determined. Since Ezetimibe decreased ¹⁴C- and ³H-radioactivity in plasma or small intestinal wall and more ¹⁴C- and ³H-radioactivity remained in the small intestinal lumen,

Ezetimibe was considered to inhibit cholesterol absorption at the intestinal wall of small intestine. Ezetimibe also reduced ¹⁴C-free cholesterol in the small intestinal wall by 41%, ¹⁴C-cholesteryl ester produced via esterification by 86%, and ³H-free cholesterol by 42% and ³H-cholesteryl ester produced via reesterification by 76% in the small intestinal wall.

(b) Investigation of Niemann-Pick C1 Like 1 (NPC1L1)

It was predicted that a cholesterol transporter in the small intestine would be expressed on the cellular membrane of enterocytes of the small intestine and have transmembrane domains, extracellular characteristic N-linked glycosylation sites, a signal peptide of a secreted protein, and sterol sensing domains, etc. in the molecule, and NPC1L1 was identified as the relevant protein from the gene database.

(b)-1. NPC1L1 expression site (Documents 4.2.1.1.12)

mRNAs were prepared from tissues of SD rats, C57BL/6 mice, and humans, and the level of mRNA expression of NPC1L1 was determined. As a result, the level of expression was highest in the small intestine in all species studied and there were species differences for other tissues. In humans, the level of expression was high in the liver, second only to the small intestine, and weak expression was detected also in the stomach, ovaries, heart, lungs, etc. When rat small intestinal mucosal epithelial cells from the pyloric valve to the ileocecal valve were divided into 10 portions (about 10 cm long each), mRNA of NPC1L1 was expressed most abundantly in the jejunum portions (n=4).

(b)-2. Study in NPC1L1 knockout mice (Documents 4.2.1.1.12)

Absorption rate of cholesterol (n=4-5): ¹⁴C-cholesterol and ³H-sitostanol were orally administered to male and female NPC1L1 homo-knockout mice (-/-) mice), hetero -knockout mice (+/-) mice), and wild-type C57BL/6 mice (+/+) mice). The fecal ¹⁴C- and ³H-radioactivity recovered over 3 days was determined. In addition, another (-/-) and (+/+) mice were orally administered Ezetimibe 10 mg/kg prior to the administration of radiolabeled sterol and the same dose of Ezetimibe was administered once daily for 2 days from the following day. As sitostanol is very poorly absorbed in the small intestine, the absorption rate of cholesterol was corrected using the following formula.

$$\text{Cholesterol absorption (\%)} = \left(1 - \frac{\text{fecal cholesterol radioactivity}}{\text{administered cholesterol radioactivity}} \times \frac{\text{administered sitostanol radioactivity}}{\text{fecal sitostanol radioactivity}} \right) \times 100$$

The absorption rate of cholesterol in (+/-) mice was similar to that in (+/+) mice. The absorption rate of cholesterol in (-/-) mice was 69% lower compared to that in (+/+) mice, and Ezetimibe reduced the absorption rate of cholesterol in (+/+) mice to a level similar to that in (-/-) mice.

Cholesterol transport through the small intestinal wall (n=5): ¹⁴C-cholesterol 0.1 mg was orally administered to female (-/-) mice and (+/+) mice. Two hours later, ¹⁴C-radioactivity in plasma+liver and small intestinal wall in (-/-) mice was decreased by 86 and 72%, respectively, compared to those in (+/+) mice, and more ¹⁴C-radioactivity remained in the small intestinal lumen.

The above results suggested that NPC1L1 is involved in cholesterol absorption at the small intestinal wall and is associated with the cholesterol absorption inhibitory activity of Ezetimibe.

(b)-3. Study on binding to NPC1L1 (Documents 4.2.1.1.13)

Brush border membranes were prepared from the small intestines of (-/-) mice and (+/+) mice, added with ³H-SCH60663 (active metabolite), and incubated until equilibrium was reached. Then, ³H-radioactivity bound to the brush border membranes was determined. As a result, unlike the case of (+/+) mice, SCH60663 showed no affinity for the brush border membranes of (-/-) mice. A similar study was performed using the brush border membranes of the small intestines of C57BL/6N mice, SD rats, and rhesus monkeys, and the dissociation constants (K_D values) were calculated. As a result, SCH60663 showed an affinity for the brush border membranes of the small intestines of mice, rats, and rhesus monkeys (K_D values: 12,000, 542, and 41 nM, respectively). Scatchard analysis indicated the presence of one type of binding site for SCH60663 at the brush border membrane of small intestine of the rat and rhesus monkey. The above results suggested that the molecular target of Ezetimibe is NPC1L1 and the affinity for NPC1L1 varies among the animal species.

(b)-4. Plasma and hepatic lipids and the absorption of triglyceride in NPC1L1 knockout mice (Documents 4.2.1.1.12)

¹⁴C-triolein was orally administered to male (-/-) mice and (+/+) mice (n=4-5) 2 hours before ¹⁴C-radioactivity in plasma and liver was determined. As a result, there were no differences in the absorption of the triglyceride between (-/-) and (+/+) mice. Although hepatic cholesteryl ester was reduced in (-/-) mice compared to (+/+) mice, there were no differences in plasma lipids or free cholesterol and triglycerides in the liver. The reduction in hepatic cholesteryl ester observed in (-/-) mice was considered attributable to the inhibition of cholesterol absorption through the small intestinal wall, resulting in a decrease in cholesterol delivery to the liver.

(b)-5. Expression of cholesterol metabolism-related proteins in the small intestine and liver of NPC1L1 knockout mice (Documents 4.2.1.1.12)

In an investigation of RNA prepared from the small intestines and livers of (-/-) mice and (+/+) mice (n=4), the lack of NPC1L1 gene resulted in the induction of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) synthase expression in the small intestine and liver, but did not affect the expression of the ATP-binding cassette (ABC) transporters, ABCG5 and ABCG8, which efflux plant sterols and cholesterol extracellularly and whose mutations cause homozygous sitosterolemia (Science 290:1771-1775, 2000). Although cholesterol absorption is inhibited in the small intestinal wall of (-/-) mice and the cholesteryl ester content in the liver is also reduced, it seems that normal levels of plasma total cholesterol are maintained by compensatory induction of the expression of HMG-CoA synthase in the small intestine and liver.

(c) Other investigations of the mechanism of action

In a study using rat liver microsome fraction and HMG-CoA reductase-induced HepG2 cells, 50 and 10

μM of Ezetimibe had no significant effect on cholesterol biosynthesis. Also in a study using anesthetized fasted male SD rats (intraduodenal administration of Ezetimibe with 1 mL of rat bile), 10 mg/kg of Ezetimibe had no significant effect on cholesterol biosynthesis (Documents 4.2.1.1.1).

In liver microsomes of rats ($n=2$), where the activity of cholesterol 7 α -hydroxylase (the rate-limiting enzyme in bile acid synthesis pathway) was induced by administering cholestyramine (2.5%), which binds bile acids, in a diet for 10 days, the synthesis of 7 α -hydroxy cholesterol was not inhibited by 50 μM of Ezetimibe and there seemed no effect on the biosynthesis of bile acids (Documents 4.2.1.1.1).

Ezetimibe 2 mg/kg with rat bile was intraduodenally administered to anesthetized fasted male SD rats 1 hour prior to the infusion of ^3H -sodium taurocholate into the duodenum. As a result, the absorption of taurocholic acid was not inhibited and a single intraduodenal dose of Ezetimibe 2 mg/kg had no effect on the absorption of bile acid (Documents 4.2.1.1.1).

In a study using rat liver microsomes, the 50% inhibitory concentration of Ezetimibe (IC_{50} value) against acyl CoA:cholesterol acyl transferase (ACAT) was estimated to be 18 μM . Meanwhile, in a study using HepG2 cells, Ezetimibe exhibited a weak inhibitory effect (IC_{50} value: 30 μM). In a study using male golden syrian hamsters ($n=5$), Ezetimibe 10 mg/kg/day orally administered once daily for 7 days had no effect on hepatic ACAT activity (Documents 4.2.1.1.1).

In a cell-free system using 0.25 units of purified bovine pancreatic cholesteryl esterase, Ezetimibe 10 μM tended to enhance the pancreatic cholesteryl esterase activity. Meanwhile, a study where Ezetimibe 3 mg/kg was intraduodenally administered to pancreatic duct-ligated (inhibit the influx of pancreatic juice into the intestinal tract while maintaining bile secretion into the intestinal tract) male SD rats ($n=5-6$), showed that pancreatic cholesteryl esterase is not involved in the action of Ezetimibe (Documents 4.2.1.1.1).

Ezetimibe showed a weak inhibitory effect on the transfer of ^3H -cholesteryl ester from HDL to LDL by cholesteryl ester transfer protein (CETP) with an inhibition rate of 29% at 50 μM . Thus, it seemed that Ezetimibe does not have much effect on the transfer of cholesteryl ester between lipoproteins via CETP (Documents 4.2.1.1.1).

Brush border membranes were prepared from the rabbit small intestine, and added with Ezetimibe or SCH60663 (20 μM) and liposome containing ^{14}C -cholesterol, and the uptake of cholesterol from liposome into the brush border membrane was assessed. Ezetimibe and SCH60663 had no effect on the uptake of cholesterol into the intestinal brush border membrane (Documents 4.2.1.1.1).

Using multidrug resistance transporter (MDR1) overexpressed murine macrophage cell line J7.v1.1, the effects of Ezetimibe on the excretion of vinblastine by MDR1 were evaluated. As a result, there were no effects up to 40 μM of Ezetimibe added, showing that Ezetimibe does not affect the drug excretion

capacity by MDR1 (Documents 4.2.1.1.1).

Ezetimibe was confirmed to bind to scavenger receptor class B type I (SR-BI: transports cholesterol from HDL to hepatocytes), which is a protein in the small intestinal wall as the site of action of Ezetimibe, and which has been suggested to be related to cholesterol absorption. In a study assessing the effects of Ezetimibe on the uptake of cholesterol by SR-BI expressed CHO cells (*in vitro*) (n=4), Ezetimibe inhibited increases in the uptake of cholesterol by SR-BI expression (Ki value 1 minute after the start of incubation: 1.6 μ M (0.66 μ g/mL)). Meanwhile, in a study assessing the effects of Ezetimibe on cholesterol transport through the small intestinal wall in SR-BI knockout mice (n=4-5) (*in vivo*), SR-BI was not involved in either cholesterol absorption or the inhibition of cholesterol absorption by Ezetimibe, suggesting that SR-BI is not a site of action for Ezetimibe (Documents 4.2.1.1.7).

In female 129/Sv mice fed a cholesterol-containing diet for an average of 23 days (n=3), mRNA expression of ABC transporters, ABCA1, ABCG5, and ABCG8, which supposedly efflux free cholesterol from the small intestinal wall back into the intestinal lumen, was enhanced, whereas SCH58053 with a similar structure and action to those of Ezetimibe did not increase their levels of expression. Thus, the possibility that Ezetimibe induces cholesterol efflux by ABC-transporters and inhibits cholesterol absorption was ruled out (Documents 4.2.1.1.8).

3) Effects on the absorption of other lipids

(a) Effects on the absorption of fatty acids (Documents 4.2.1.1.1)

In a study using male golden syrian hamsters (n=4-5), Ezetimibe had no effect on the metabolism of triglycerides and cholesteryl ester (pancreatic lipase and pancreatic cholesteryl esterase activities) or the absorption of free fatty acids.

(b) Effects on the absorption of sterols

(b)-1. Study using NPC1L1 knockout mice (Documents 4.2.1.1.15)

Absorption of lipids: Following the oral administration of 14 C-cholesterol, 3 H-sitosterol, or 14 C-triolein to NPC1L1 knockout mice, 14 C-cholesterol-derived radioactivity in plasma+liver and small intestinal wall of (-/-) mice was reduced by 86% and 64%, respectively, compared to (+/+) mice and 3 H-sitosterol-derived radioactivity was decreased by 64% and 52%, respectively, whereas there were no differences for 14 C-triolein-derived radioactivity. When Ezetimibe 10 mg/kg was orally administered to female (+/+) mice 30 minutes prior to the oral administration of 3 H-sitosterol, Ezetimibe lowered the radioactivity in plasma+liver and small intestinal wall of (+/+) mice to a level similar to those of (-/-) mice (67% and 55%, respectively).

Plasma cholesterol and plant sterols: Although there were no differences in plasma cholesterol between male NPC1L1 (-/-) and (+/+) mice (n=4-5), plasma sitosterol and campesterol levels in (-/-) mice were reduced by $\geq 90\%$ compared to those in (+/+) mice.

The above results suggested that NPC1L1 in the small intestinal wall is involved in the absorption of plant sterols as well as cholesterol and is associated with the sitosterol absorption inhibitory activity of Ezetimibe.

(b)-2. Study in rats (Documents 4.2.1.1.1)

Male SD rats were orally administered Ezetimibe 0.3 mg/kg followed by ¹⁴C-cholesterol, ³H-progesterone, ³H-ethinyl estradiol, or ³H-sitosterol. Ezetimibe decreased ³H-sitosterol-derived radioactivity in the liver by 37% and ¹⁴C-cholesterol-derived radioactivity in plasma, liver, and small intestinal wall by 67%, 67%, and 57%, respectively. Meanwhile, Ezetimibe had no effect on ³H-progesterone or ³H-ethinyl estradiol-derived radioactivity. Based on the above, Ezetimibe was considered to selectively inhibit the absorption of cholesterol and sitosterol (n=5).

(c) Effects on the absorption of vitamin A and vitamin D (Documents 4.2.1.1.1)

In anesthetized fasted male SD rats, intraduodenal Ezetimibe 10 mg/kg had no effect on the absorption of ³H-vitamin A or ³H-vitamin D in the small intestine (n=5).

4) Activity of a metabolite of Ezetimibe (the glucuronide: SCH60663)

It is inferred that Ezetimibe is quickly absorbed in the small intestine and glucuronidated to SCH60663 in the tissue of small intestine, goes into the portal vein and through the liver into the bile, deglucuronidated and reabsorbed, and undergoes enterohepatic circulation.

(a) Comparison of the cholesterol absorption inhibitory activity between Ezetimibe and SCH60663 (Documents 4.2.1.1.1)

Ezetimibe or SCH60663 0.003 and 0.01 mg/kg with 1 mL of rat bile were intraduodenally administered to anesthetized fasted male SD rats (n=5) 5 minutes prior to the intraduodenal administration of an emulsion containing ¹⁴C-cholesterol (19 mM sodium taurocholate/PBS containing triolein 35.4 mg, L- α -phosphatidylcholine 6.69 mg, and ¹⁴C-cholesterol (3 mL, pH6.4)). As a result, SCH60663 was more potent than Ezetimibe in inhibiting the absorption of cholesterol.

(b) Absorption of SCH60663 and the inhibition of cholesterol absorption in the presence of a glucuronidase inhibitor (Documents 4.2.1.1.10)

It is inferred that SCH60663 is gradually deglucuronidated by β -glucuronidase from intestinal bacterial flora or small intestinal tissue in the small intestine back to Ezetimibe, which is reabsorbed and undergoes enterohepatic circulation.

Inhibition of the deglucuronidation and absorption of ¹²⁵I-SCH60663 by glucarolactone (GL: β -glucuronidase inhibitor): GL 250 mg/kg was intraduodenally administered to anesthetized fasted male SD rats (n=6) at 30-minute intervals. ¹²⁵I-SCH60663 was intraduodenally administered 1.5 hours prior to the intraduodenal administration of an emulsion (19 mM sodium taurocholate/PBS containing triolein 35.4 mg, L- α -phosphatidylcholine 6.69 mg, and cholesterol (3 mL, pH6.4)), and 1.5 hours later, the

radioactivity in plasma and liver was determined. The deglucuronidation rates of ¹²⁵I-SCH60663 in the small intestinal lumen and the small intestinal mucosal tissue in the GL-untreated control group were approximately 14% and 21%, respectively, whereas GL administration decreased the deglucuronidation rates to approximately 3% and 4%, respectively. GL administration reduced the amounts of the labeled drug in plasma and liver by 76% and 83%, respectively and a reduction of 33% was observed in the small intestinal mucosal tissue. On the other hand, an increase of 12% was seen in the small intestinal lumen.

Cholesterol absorption inhibition by SCH60663: As described in the above, GL or vehicle was intraduodenally administered to rats and then 1-10 µg/kg of SCH60663 was intraduodenally administered 30 minutes prior to the intraduodenal administration of ¹⁴C-cholesterol. One and a half hours after the administration of ¹⁴C-cholesterol, plasma and hepatic radioactivity was determined (n=4-5). The cholesterol absorption inhibition by SCH60663 was unaffected by GL administration.

In summary, it was shown that as a result of inhibiting β-glucuronidase from intestinal bacterial flora or small intestinal tissue by GL, most of SCH60663 was not deglucuronidated and its absorption in the small intestine was markedly reduced. Even though the deglucuronidation of SCH60663 was inhibited, the cholesterol absorption inhibition was unaffected, which suggested that SCH60663 also has an activity as a cholesterol absorption inhibitor.

5) Comparison with other agents (Documents 4.2.1.1.1, 11)

The test compound was orally administered once daily for 7 days to male golden syrian hamsters fed a 0.5% cholesterol-containing diet (n=4-20). The ED₅₀ values for the reduction of plasma total cholesterol and hepatic cholesteryl ester at the end of treatment were 0.12 and 0.04 mg/kg/day, respectively, for Ezetimibe, and were both 2 mg/kg/day for SCH48461 (a compound with a similar structure and action as Ezetimibe). Although comparison was not made in the same study, it seemed that the effect of Ezetimibe is seen from a lower dose even when compared to cholestyramine (a bile acid binder) and PD128042 (ACAT inhibitor).

6) Coadministration with 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) (Documents 4.2.1.1.5)

(a) Plasma cholesterol lowering effect

Male beagle dogs were fed Ezetimibe 0.007 mg/kg/day and statins (lovastatin 5 mg/kg/day, pravastatin 2.5 mg/kg/day, fluvastatin 5 mg/kg/day, simvastatin 1 mg/kg/day, and atorvastatin 1 mg/kg/day) as monotherapy or combination therapy in a cholesterol-free diet for 14 days (n=5). On the 15th day after the start of treatment, the same doses of statins were administered and plasma statin concentrations were measured. Coadministration of Ezetimibe and a statin reduced plasma total cholesterol levels compared with each drug alone. The therapeutic dose of Ezetimibe had no significant effect on the area under the plasma concentration-time curve (AUC) of statins (lovastatin and its metabolite, pravastatin, and fluvastatin were measured).

(b) Effects on HMG-CoA reductase

SCH48461 300 mg/kg was orally administered once daily for 7 days to male beagle dogs fed a non high-fat diet or a diet containing 5.5% lard, 0.2% cholic acid, and 1% cholesterol. SCH48461 had little effect on plasma and hepatic cholesterol levels in dogs with normal lipid levels, but reduced plasma and hepatic cholesterol levels in dogs fed a high-fat diet. A high-fat diet reduced the activity of hepatic HMG-CoA reductase while SCH48461 induced the hepatic HMG-CoA reductase activity, regardless of whether the dogs were fed a high-fat diet. Enhanced effect of Ezetimibe in combination with a statin in lowering plasma cholesterol was considered to be due to the statin inhibition of the hepatic HMG-CoA reductase activity induced by Ezetimibe.

(2) Secondary pharmacodynamics (Documents 4.2.1.1.1)

Ezetimibe's affinity for or inhibition of 129 different receptors, transporters and enzymes were investigated. As a result, Ezetimibe and SCH60663 had no significant effect on various receptors, transporters, or enzymes.

(3) Safety pharmacology

1) Effects on the central nervous system (general symptoms) (Documents 4.2.1.1.1, 4.2.1.3.2)

Irwin's multidimensional observation: Ezetimibe (3-30 mg/kg) was orally administered to male SD rats (n=6). At 10 or 30 mg/kg, increased passivity, staggering gait, crouching position, abnormal limb position, and an increase in the excretion of feces were noted at 1 hour post-dose. At 30 mg/kg, increased passivity and an increase in the excretion of feces persisted up to 4 hours post-dose. No death occurred up to 24 hours post-dose.

Functional observational battery (FOB): Ezetimibe (30-1,000 mg/kg) was orally administered to male and female SD rats (n=6). Ezetimibe did not affect general symptoms at 1 hour post-dose or spontaneous locomotor activity after FOB test.

2) Effects on the cardiovascular system (Documents 4.2.1.1.1, 4.2.1.3.3, 4.2.1.3.4)

Following the oral administration of Ezetimibe 25 mg/kg to unanesthetized restrained male SD rats (n=4), there were no effects on blood pressure or heart rates at 1-4 hours post-dose. Following the oral administration of Ezetimibe 300 and 1,000 mg/kg to unanesthetized, unrestrained male beagle dogs, there were no effects on blood pressure, heart rates or ECG (RR, QT, PR, and QRS intervals) up to 8 hours post-dose. In L-929 cells transfected with hERG, Ezetimibe (0.1 μ M) or SCH60663 (1 μ M) had no effect on hERG currents.

3) Effects on other organ systems (Documents 4.2.1.1.1, 4.2.1.3.5)

Following the oral administration of Ezetimibe (30-1,000 mg/kg) to unanesthetized restrained male and female SD rats, there were no effects on respiration rate, tidal volume, or minute ventilation up to 5 hours post-dose (n=6).

In fasted male SD rats given saline (15 mL/kg) (n=8), oral administration of Ezetimibe 25 mg/kg had no effect on urine volume or urinary sodium excretion up to 5 hours post-dose.

In fasted male SD rats, oral administration of Ezetimibe 25 mg/kg did not produce gastric lesions (n=8) and did not affect charcoal transit in the small intestine (n=6).

(4) Pharmacodynamic drug interactions

No data submitted.

<Outline of the review by the PMDA>

The PMDA asked the applicant to discuss whether any clinical problems associated with the inhibition of NPC1L1 by Ezetimibe are anticipated, taking also account of safety information from Japanese and foreign clinical studies and overseas post-marketing reports obtained to date, since in humans, mRNA of NPC1L1 is expressed in the stomach, ovaries, heart, lungs, and muscles as well as the small intestine and liver.

The applicant responded as follows:

The level of mRNA expression is not necessarily correlated with the level of protein expression. The expression of NPC1L1 protein in human tissues has not been studied. However, based on gastric, ovarian, cardiac, pulmonary, and muscular adverse events reported from Japanese and foreign clinical studies, there is no trend towards increased risk with Ezetimibe compared to placebo, and in view of the overall adverse event profile, there should be no possibility that any particular clinical problems arise associated with the inhibition of NPC1L1 by Ezetimibe.

On the basis of the applicant's explanation that one of the reasons for the persistence of the effect of Ezetimibe is its enterohepatic circulation, the PMDA asked the applicant to discuss the possibility that species differences in the action of Ezetimibe are attributable to differences in the function, morphology, intestinal bacterial flora, etc. of the small intestine among different animals, and the potential effects of intestinal diseases etc. on the efficacy and safety of Ezetimibe in a clinical setting.

The applicant responded as follows:

The rank order of the potency of the affinity of the unchanged drug and glucuronide for NPC1L1 was as follows: Monkeys > Dogs > Hamsters, Rats >> Mice, which was correlated with *in vivo* activity, suggesting that small variations in NPC1L1 amino acid sequence can profoundly influence the binding of Ezetimibe to NPC1L1 and *in vivo* activity. The ability of Ezetimibe present at the jejunal site of action to bind to NPC1L1 is the most important determinant of *in vivo* responsiveness, and differences in the metabolism of Ezetimibe and the intestinal function among different animal species are less likely involved. No clinical study in patients with intestinal disease has been conducted and the effects of such disease on the efficacy and safety of Ezetimibe are unknown.

Although some aspects of the mechanism of action of Ezetimibe are unclear, its cholesterol absorption

inhibitory activity has been confirmed and no events that are of special clinical concern have been identified in safety pharmacology studies etc. Therefore, the PMDA has judged that the pharmacological usefulness of Ezetimibe can be inferred from the submitted data.

(ii) Summary of pharmacokinetic studies

<Summary of the submitted data>

Plasma Ezetimibe concentrations and plasma total Ezetimibe concentrations were measured by high performance liquid chromatography/tandem mass spectrometry (LC-MS/MS), using untreated plasma and plasma treated with β -glucuronidase for deglucuronidation, respectively. As the glucuronide conjugates of Ezetimibe, SCH60663 (phenolic glucuronide) and SCH488128 (benzylic glucuronide) were identified. However, *in vivo* pharmacokinetic study showed that SCH488128 concentrations in various biological samples were trace (≤ 2 to < 3 times the background cpm) or below the detection limit (< 2 times the background cpm) in all animal species including humans, the difference between the plasma total Ezetimibe level and the plasma Ezetimibe level was considered as the plasma SCH60663 level. Plasma SCH60663 concentrations and derived pharmacokinetic parameters were expressed in Ezetimibe equivalents (ng•Eq/mL).

(1) Absorption

1) Studies with unlabeled drug

(a) Single intravenous administration

Following a single intravenous dose of Ezetimibe 1 mg/kg to male and female rats, the plasma Ezetimibe concentrations at 5 minutes post-dose (the initial sampling point) were 196 ng/mL in males and 190 ng/mL in females, the half lives ($t_{1/2}$) were 0.95 and 0.86 hr, respectively, and the AUC values up to the last measurable concentration (AUC_{0-t}) were 173 and 214 ng•hr/mL, respectively. The plasma SCH60663 concentrations reached maximum values (C_{max}) of 92.2 and 102 ng Eq/mL, respectively, at the initial sampling point, then fell in both males and females, and went up again at 4 and 8 hours post-dose in males and at 2 and 6 hours post-dose in females. The AUC_{0-t} values were 201 and 236 ng Eq•hr/mL, respectively, and the ratio of Ezetimibe to SCH60663 in plasma, which was calculated based on AUC_{0-t} , was roughly 1:1.

Following a single intravenous dose of Ezetimibe 5 mg/kg to male and female dogs, the plasma Ezetimibe concentrations were 7,193 ng/mL in males and 8,253 ng/mL in females at 5 minutes post-dose (the initial sampling point), and declined biphasically (the elimination phase $t_{1/2}$: 4.70 and 3.93 hr, respectively). The AUC_{0-t} values were 3,223 and 4,152 ng•hr/mL, respectively. The C_{max} values of SCH60663 were 3,552 ng Eq/mL (time to the maximum plasma concentration (t_{max}): 0.303 hr) and 4,058 ng Eq/mL (0.332 hr), respectively, and the AUC_{0-t} values were 3,005 and 3,601 ng Eq•hr/mL, respectively, which declined almost in parallel with those of Ezetimibe.

(b) Single oral administration

Following a single oral dose of Ezetimibe 10 and 30 mg/kg to male and female rats, the plasma Ezetimibe

concentration reached C_{max} at 3-8 hours post-dose, and the C_{max} value in female rats was approximately 2-fold that in male rats. As the Ezetimibe concentration was below the lower limit of quantification (1 ng/mL) at most of the sampling points, AUC could not be calculated. Following the administration of Ezetimibe 10 and 30 mg/kg, SCH60663 concentration reached C_{max} at 1-6 hours post-dose and the AUC_{0-t} values were 2,037 and 2,467 ng Eq•hr/mL, respectively, in males and 1,243 and 1,819 ng Eq•hr/mL, respectively, in females. The rates of increases in C_{max} and AUC between the doses were less than the ratio of the doses (3-fold). After oral administration, SCH60663 accounted for 99.7-99.9% of AUC.

Following a single oral dose of Ezetimibe 5 mg/kg to male and female dogs, the plasma Ezetimibe concentrations reached C_{max} at 2-5 hours post-dose, and the AUC_{0-t} value in females was approximately 3-fold higher than that in males. SCH60663 concentrations reached C_{max} at 0.5 hour post-dose in both males and females, the AUC_{0-t} values were 178 ng Eq•hr/mL in males and 363 ng Eq•hr/mL in females, and the ratio of Ezetimibe to SCH60663 in plasma was 1:7 to 1:9. The absolute bioavailability (BA) of Ezetimibe was 0.578% in males and 1.10% in females.

(c) Multiple oral administration

Ezetimibe doses of 0, 100, 500, and 2,000 mg/kg were orally administered in a diet for 3 months to male and female mice. The AUC values of plasma Ezetimibe in Week 4 increased dose-proportionally at 100-500 mg/kg, but were almost constant at 500-2,000 mg/kg. Males had higher values than females. The plasma total Ezetimibe concentrations increased in a dose-dependent manner, and were higher in females than in males.

Ezetimibe doses of 0, 20, 100, 500, and 1,500 mg/kg were orally administered in a diet for 3 months to male and female rats. The AUC values of plasma Ezetimibe in Week 14 increased in a dose-dependent manner at 20-1,500 mg/kg in males while there were no further increases at ≥ 500 mg/kg in females. The total Ezetimibe concentration was higher in males than in females at Ezetimibe 20 mg/kg and higher in females than in males at 100-1,500 mg/kg.

Male and female dogs were gavaged with Ezetimibe 0, 3, 30, 100, and 300 mg/kg filled in gelatin capsules for 3 months. The AUC values of Ezetimibe and total Ezetimibe in plasma increased in a dose-dependent manner, showed no gender differences, and were higher in Week 13 compared with Day 1.

2) Studies with labeled drug

Following a single intravenous dose of ^{14}C -Ezetimibe 1 mg/kg to male and female rats, the radioactivity levels were 416 (males) and 388 ng Eq/mL (females) at 5 minutes post-dose (the initial sampling point) and then declined biphasically, and the AUC_{0-t} values were 507 and 381 ng Eq•hr/mL, respectively. Following the oral administration of ^{14}C -Ezetimibe 10 mg/kg, C_{max} was attained at 3-4 hours post-dose and the AUC_{0-t} values were 879 and 671 ng Eq•hr/mL, respectively. The percentage of the drug entering the systemic circulation was 17.3% in males and 17.6% in females.

Following single intravenous or oral administration of ^{14}C -Ezetimibe 5 mg/kg to male and female dogs, the whole blood to plasma ratios of the radioactivity AUC were 0.47 (males) and 0.48 (females), indicating limited distribution into blood cells. Following the oral administration, the C_{\max} values in males and females were 45.7 and 55.2 ng Eq/mL, respectively (at 8.00 and 2.01 hours post-dose, respectively), and the AUC_{0-t} values were 267 and 361 ng Eq•hr/mL, respectively. The rate of the drug entering the systemic circulation was 6.6% in males and 11.0% in females.

After the intraduodenal administration of ^3H -Ezetimibe 0.01 mg/kg with bile to rats, the radioactivity in portal plasma peaked at 1 minute post-dose and then declined. Although no radioactivity was detected in bile until 1 minute post-dose, 8% of the administered radioactivity and 23% of the administered radioactivity were detected at 1-7 minutes post-dose and at 7-15 minutes post-dose, respectively, and the detected radioactivity increased over time. Based on the above, it seemed that Ezetimibe is quickly absorbed in the small intestine and delivered to the liver via the portal vein, and then the radioactivity is promptly excreted via bile. Since $\geq 95\%$ of the radioactivity in portal plasma and $\geq 99\%$ of the radioactivity in bile exist as SCH60663, the major site of metabolism of orally administered Ezetimibe in rats appeared to be the small intestine.

(2) Distribution

1) Tissue distribution of radioactivity

Following a single oral dose of ^{14}C -Ezetimibe 1 mg/kg to male rats, most of the radioactivity was distributed in the gastrointestinal tract and its contents, and the radioactivity in the stomach, small and large intestinal contents at 8 hours post-dose was approximately 80% of the administered radioactivity. In the small intestine, which is considered to be the site of action of Ezetimibe, the radioactivity levels peaked at 4 hours post-dose (about 148 times the maximum plasma radioactivity level) and then declined steadily up to 72 hours post-dose, and were below the lower limit of quantification after 168 hours post-dose. The radioactivity levels in the liver and mesenteric lymph nodes were as high as approximately 13 times and 5.4 times the plasma radioactivity level, respectively. The radioactivity levels in other organs were lower than the plasma radioactivity level, and especially in the central nervous system, little radioactivity was observed. The distribution pattern of radioactivity in female rats was similar to that in male rats, and the maximum radioactivity levels in the small intestine, liver, and mesenteric lymph nodes were about 238, 38, and 9.3 times the maximum plasma radioactivity level. Little radioactivity was seen in the central nervous system and ovaries/uterus.

Following repeated oral administration of ^{14}C -Ezetimibe 10 mg/kg once daily for 21 days to male and female rats, the distribution of radioactivity in males was similar to what was observed after a single oral dose and no marked accumulation was noted. In females, the distribution of radioactivity was similar to that seen in males except for the reproductive organs, and repeated dosing resulted in clear accumulation of radioactivity in the ovaries. However, a repeated-dose toxicity study showed no effects on rat ovaries (See 3. (iii) <Summary of the submitted data> “(2) Repeated-dose toxicity”).

2) Plasma protein binding

The plasma protein binding of ³H-Ezetimibe (5-200 ng/mL) was 98.1-99.6% in mice, rats, rabbits, and monkeys, and the plasma protein binding of ³H-SCH60663 (2-2,000 ng/mL) was 81.0-98.1%.

3) Feto-placental transfer

Following a single oral dose of ¹⁴C-Ezetimibe 10 mg/kg to female rats on gestation day 18 under non-fasted conditions, the radioactivity levels in the mammary gland, uterus, placenta, amniotic fluid, and amnions were below the lower limit of quantification up to 48 hours post-dose, whereas the level of radioactivity detected in the ovaries at 4 hours after dosing was about one-third of the maternal plasma radioactivity. The radioactivity levels in the fetal blood and the major fetal organs (liver, kidneys, lungs, heart, and brain) were below the lower limit of quantification.

(3) Metabolism

1) Metabolic pathway

The major metabolic pathway of Ezetimibe is glucuronidation of the hydroxyphenol group (metabolite: SCH60663). Other metabolic pathways include ketonization of the benzylic hydroxyl group (SCH57871) and glucuronidation of its hydroxyphenol group (SCH57871-glucuronide), and glucuronidation of the benzylic hydroxyl group (SCH488128). Furthermore, as a chemical degradation product, a tetrahydropyran derivative (SCH59566) has been identified, which is formed as a result of cleavage of the azetidinone ring of Ezetimibe followed by re-linkage to the benzylic hydroxyl group.

2) *In vitro* metabolism

When liver tissue slices, kidney tissue slices, and liver microsomes from rats and dogs were added with ³H-Ezetimibe or ¹⁴C-Ezetimibe and incubated, the major metabolite formed was SCH60663.

Using rat and dog liver microsomes, Ezetimibe and testosterone were simultaneously incubated for 10 minutes in the presence of NADPH. As a result, Ezetimibe inhibited the activity of testosterone 6 β -hydroxylation (IC₅₀ values: 4.9 μ M and 53 μ M, respectively). When rat and dog liver microsomes were preincubated with Ezetimibe for 30 minutes, the inhibitory effect was enhanced to 3- and 19-fold, respectively. This phenomenon was also observed in a study using human biomaterial, and the inactivation by binding of Ezetimibe's metabolite to CYP3A, in addition to competitive inhibition, were suggested as the mode of inhibition (See 4. (ii) <Summary of the submitted data>" (1) *In vitro* studies using human biomaterials").

3) Induction of liver drug metabolizing enzymes

Following multiple oral administration of Ezetimibe 510 mg/kg once daily for 8 days to female rats, there were no changes suggesting the induction of liver drug metabolizing enzymes.

(4) Excretion

1) Urinary and fecal excretion

Following the intravenous administration of ^{14}C -Ezetimibe 1 mg/kg to male and female rats, 98.1% and 92.2% of the administered radioactivity were excreted in feces over 0-168 hours in males and females, respectively, and Ezetimibe accounted for $\geq 90\%$ of the fecal radioactivity. The percent urinary excretion of the administered radioactivity was 0.616% and 3.87%, respectively, and SCH60663 accounted for 70-80% of the urinary radioactivity. Following the oral administration of ^{14}C -Ezetimibe 1 mg/kg, 97.0% and 85.2%, respectively, of the administered radioactivity were excreted in feces over 0-168 hours and Ezetimibe accounted for 97-98% of the fecal radioactivity while SCH60663 accounted for about 97% of the biliary radioactivity. The percent urinary excretion of the administered radioactivity was 0.052% and 1.48%, respectively, and SCH60663 accounted for about 80% of the urinary radioactivity and Ezetimibe accounted for the remaining percent. In rats, there were no gender differences in fecal excretion while higher excretion was observed in urine of females.

Following the intravenous administration of ^{14}C -Ezetimibe 5 mg/kg to male and female dogs, as with that in rats, the drug was mainly excreted in feces via biliary excretion and the percent fecal excretion of the administered radioactivity over 0-336 hours after dosing was 78.2% in males and 85.5% in females, and Ezetimibe accounted for $\geq 90\%$ of the fecal radioactivity. The percent urinary excretion of the administered radioactivity was 1.65% and 1.70%, respectively, and SCH60663 accounted for 70-80% of the urinary radioactivity, and SCH59566 and unidentified metabolites accounted for about 10%. Following the oral administration of ^{14}C -Ezetimibe 5 mg/kg, the percent fecal excretion of the administered radioactivity was 87.6% and 85.5%, respectively, and the percent urinary excretion was 0.618% and 0.682%, respectively, and the profile of the metabolites etc. was similar to that after intravenous administration. In dogs, there were no gender differences in excretion of the drug.

2) Biliary excretion

Following a single oral dose of ^{14}C -Ezetimibe 1 mg/kg to bile duct cannulated rats, the percent biliary excretion of the administered radioactivity up to 48 hours after dosing was 40.1% in males and 62.7% in females, the percent urinary excretion was 0.0534% and 3.03%, respectively, and the percent fecal excretion was 32.0% and 20.9%, respectively. When bile collected from donor rats up to 24 hours post-dose was intraduodenally administered to recipient rats, 34.1% and 15.3%, respectively, of radioactivity were in feces. The percent biliary excretion of the administered radioactivity up to 48 hours post-dose was 53.8% and 81.2%, respectively, and the percent urinary excretion was 0.0385% and 0.996%, respectively, demonstrating the enterohepatic circulation of Ezetimibe.

Following single intravenous administration of ^{14}C -Ezetimibe 5 mg/kg to dogs, the percent biliary excretion of the administered radioactivity up to 144 hours post-dose was 99.0% in males and 88.6% in females, and the percent urinary and fecal excretion were 1.83% and 1.17%, respectively, in males and 7.36% and 1.94%, respectively, in females. The excretion profile after oral administration was different from that after intravenous administration. The percent biliary excretion of the administered radioactivity

up to 96 hours post-dose was 7.74% in males and 10.3% in females, the percent fecal excretion was 84.6% and 46.1%, respectively, and the percent urinary excretion was 0.749% and 1.23%, respectively. The differences between the rats and the dogs were considered attributable to decreased intestinal absorption of Ezetimibe in the dogs compared to the rats.

3) Excretion in milk

Following a single oral dose of ¹⁴C-Ezetimibe 5 mg/kg to female rats on day 12 post-partum, no radioactivity was excreted into milk.

(5) Pharmacokinetic drug interactions

Examination was made on the effects of Ezetimibe on the metabolism of lovastatin in the NADPH reconstituted system using rat and dog liver microsomes. In the rat liver microsomes, Ezetimibe inhibited the metabolism of lovastatin to various hydroxylated metabolites at its concentrations $\geq 100 \mu\text{M}$. In the dog liver microsomes, Ezetimibe competitively inhibited the metabolism of lovastatin to 6 β -hydroxylated metabolite (inhibition constant (K_i): 21 μM).

An *in vitro* study using cell line enriched in hamster MDR1 (CR1R12) confirmed that Ezetimibe serves as a substrate for P-glycoprotein (V_{max}: 270%, K_m: 21 μM) and also inhibits the extracellular efflux of other drugs that serve as a substrate for P-glycoprotein (daunorubicin and rhodamine) (IC₅₀ values: 24 and 184 μM , respectively).

<Outline of the review by the PMDA>

With regard to the absorption section, the PMDA asked for the applicant's view on species differences and gender differences in the time course of plasma concentrations of Ezetimibe and its active metabolite, SCH60663.

The applicant responded as follows:

Following a single oral dose of Ezetimibe 10 and 30 mg/kg to rats, the plasma Ezetimibe concentration was below the lower limit of quantification (<1 ng/mL) at most of the sampling points in both male and female rats. Although the AUC_{0-t} value of SCH60663 was higher in male rats than in female rats, the inter-animal variability was high, and the presence or absence of a gender difference was unclear. Following a single oral dose of Ezetimibe 5 mg/kg to dogs, the Ezetimibe AUC_{0-t} value was about 3-fold higher in female dogs than in male dogs and the SCH60663 AUC_{0-t} value was about 2-fold higher in female dogs than in male dogs, showing clear gender differences. Although the major metabolic pathway of Ezetimibe in dogs is glucuronidation at the hydroxyphenol group, as with that in other animal species including humans, there have been few reports on gender differences in the glucuronidation ability in dogs. On the other hand, in the single low-dose pharmacokinetic study showing gender differences in systemic exposure, one female dog had high plasma Ezetimibe concentrations, which could be outliers, and the other 5 dogs excluding this one (3 males, 2 females) showed a similar range of concentrations over time, suggesting the possibility that such big gender differences as observed for the mean AUC did not actually

occur. Also for plasma SCH60663 concentrations, based on the visual inspection of individual plots, it does not appear that such clear gender differences as observed for the mean AUC occurred. Therefore, the gender differences in systemic exposure observed after single low-dose administration may have been attributable to the occurrence of outliers in one animal in an experiment with a relatively small number of animals. Also, there were clear species differences in the plasma pharmacokinetics after the oral administration of Ezetimibe and SCH60663 between rats and dogs, and it was suggested that rats have higher glucuronidation ability as a first pass effect compared to dogs.

The PMDA considers that gender differences in pharmacokinetics in humans should be determined carefully since gender differences in rats and dogs were both observed after oral administration (See 4. (ii) <Outline of the review by the PMDA> “(3) Effects of age and gender”).

(iii) Summary of toxicology studies

<Summary of the submitted data>

Ezetimibe toxicity studies conducted include single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, and antigenicity studies. Repeated-dose toxicity and genotoxicity studies on impurities present in the drug substance were performed. Single-dose toxicity, repeated-dose toxicity, genotoxicity, and reproductive and developmental toxicity studies with combination therapy with typical statins were also conducted. Furthermore, the effects of Ezetimibe on bile composition, typical findings observed with the coadministration of Ezetimibe and statins, and the effects on mevalonic acid and serum cholesterol were assessed.

(1) Single-dose toxicity

Following the oral administration of Ezetimibe 5,000 mg/kg to mice and rats and following the oral administration of Ezetimibe 3,000 mg/kg to dogs, there were no deaths or noteworthy findings.

Following the intraperitoneal administration of Ezetimibe to mice and rats, deaths occurred in male and female mice and female rats at 2,000 mg/kg. In both mice and rats, hypoactivity, reductions in body weight gains, residual compound like material in abdomen cavity, pyrogranulomas, and adhesions were mainly observed. The approximate lethal doses were determined to be 1,000-2,000 mg/kg in mice, and 2,000 mg/kg in rats.

(2) Repeated-dose toxicity

In a 3-month oral dietary toxicity study in mice (Ezetimibe 0, 100, 500, and 2,000 mg/kg/day), there were no noteworthy findings, except for reductions in body weight gains at 2,000 mg/kg/day. The AUC values in Week 4 increased in a dose-dependent manner at 100-500 mg/kg/day, but remained almost constant at 500-2,000 mg/kg/day.

In a 3-month oral dietary toxicity study in rats (Ezetimibe 0, 20, 100, 500, and 1,500 mg/kg/day), decreases in serum cholesterol were noted in males in all Ezetimibe-treated groups and decreases in triglycerides

were observed in males at 1,500 mg/kg/day, which were both related to the pharmacological action of Ezetimibe and were not considered as toxic findings. One female rat in the 1,500 mg/kg/day group died in Week 5 of withdrawal, but there were no noteworthy findings other than hematoma associated with bleeding after jugular venipuncture, and the cause of death was considered to be errors in blood sampling. The no observed adverse effect level (NOAEL) was determined to be 1,500 mg/kg for both male and female rats.

In a 6-month oral dietary toxicity study in rats (males: Ezetimibe 0, 150, 750, and 1,500 mg/kg/day, females: Ezetimibe 0, 50, 250, and 500 mg/kg/day), increases in serum glutamic oxaloacetic transaminase (aspartate aminotransferase (AST)) were observed in females at 500 mg/kg/day. Thus, the NOAEL was determined to be 1,500 mg/kg/day for male rats and 250 mg/kg/day for female rats.

In a 3-month oral administration study in dogs (Ezetimibe 0, 3, 30, 100, and 300 mg/kg/day, gelatin capsules), loose stools and decreases in serum cholesterol and triglycerides were noted from 3 mg/kg/day. However, loose stools were not considered as toxicity because histopathological examination revealed no histological abnormalities and the symptoms resolved during the withdrawal period. Consequently, the NOAEL was determined to be 300 mg/kg/day for both male and female dogs.

In a 3-month oral administration study in dogs, Ezetimibe (0, 300, 600, and 1,000 mg/kg/day) suspended in 0.4% methylcellulose solution was administered. In the Ezetimibe groups, discolored stools (white), loose stools, and decreased serum cholesterol were observed, but there were no other noteworthy findings. The NOAEL was determined to be 1,000 mg/kg/day for both male and female dogs.

In a 6-month oral administration study in dogs, Ezetimibe (0, 30, 100, and 300 mg/kg/day) suspended in 0.4% methylcellulose solution was administered. Since white stools due to unabsorbed drug were observed in the 3-month study, 300 mg/kg/day was chosen as the highest dose. Decreased serum cholesterol levels were noted in females at ≥ 30 mg/kg/day and in males at ≥ 100 mg/kg/day, but there were no other noteworthy findings, and the NOAEL was determined to be 300 mg/kg/day for both male and female dogs.

A 12-month oral administration study in dogs was conducted at the same doses as in the 6-month study. Decreased serum cholesterol only was observed at ≥ 30 mg/kg/day, but there were no other noteworthy findings, and the NOAEL was determined to be 300 mg/kg/day.

(3) Genotoxicity

The genotoxicity of Ezetimibe was studied by a reverse mutation test with *Salmonella typhimurium* (TA100, TA1535, TA98, TA102, TA97a) and *Escherichia coli* (WP2uvrA) (the highest dose of Ezetimibe: 5,000 $\mu\text{g}/\text{plate}$) and a chromosomal aberration test in human peripheral blood lymphocytes (Ezetimibe 0.985-125 $\mu\text{g}/\text{mL}$) with and without metabolic activation system, and a mouse micronucleus test at 200, 400, and 800 mg/kg of Ezetimibe administered intraperitoneally once daily for 2 days for both male and female mice. All genotoxicity studies produced negative results.

(4) Carcinogenicity

A mouse carcinogenicity study (Ezetimibe 25, 100, and 500 mg/kg) was conducted using ICR mice, where 500 mg/kg was chosen as the highest dose because in the 3-month oral toxicity study in mice, plasma concentrations of Ezetimibe did not increase at ≥ 500 mg/kg and the plasma total Ezetimibe concentration was ≥ 25 -fold the human plasma concentration. No findings suggestive of carcinogenicity were noted and there were no changes in survival rate, general condition, body weight, or food consumption.

A rat carcinogenicity study (males: 150, 750, and 1,500 mg/kg, females: 50, 250, and 500 mg/kg) was conducted using 1,500 mg/kg for males and 500 mg/kg for females as the highest doses, at which saturation of absorption occurred in a 3-month oral toxicity study and a 2-week dietary or oral gavage TK study in rats. No findings suggestive of carcinogenicity were noted and although mild decreases in body weight gains were only observed in males at the high dose, there were no noteworthy findings in the survival rate, general condition, food consumption, etc.

(5) Reproductive and developmental toxicity

1) Rat study of fertility and early embryonic development to implantation

SD rats were gavaged with Ezetimibe 0, 250, 500, and 1,000 mg/kg/day (males: from 4 weeks prior to, and throughout mating, females: from 2 weeks prior to mating, throughout mating, and until gestation day 7). At 500 mg/kg, one female was found dead 7 days after dosing, which was considered to be due to drug-administration errors based on the necropsy findings. There were no other noteworthy findings and the NOAELs were determined to be 1,000 mg/kg/day for general and reproductive toxicity in adult animals and for early embryonic development.

2) Rat/rabbit studies for effects on embryo-fetal development

Pregnant SD rats and New Zealand white rabbits were gavaged with Ezetimibe 0, 250, 500, and 1,000 mg/kg/day from gestation day 6 through day 15 and from gestation day 7 through gestation day 19, respectively. In either study, there were no noteworthy findings and the NOAELs for maternal general and reproductive toxicity and for fetuses (the next generation) were determined to be 1,000 mg/kg/day for both rats and rabbits.

3) Rat study for effects on pre-and postnatal development, including maternal function

Pregnant SD rats were gavaged with Ezetimibe 0, 100, 300, and 1,000 mg/kg from gestation day 6 through lactation day 21. After all animals had natural delivery, the maternal animals were sacrificed on lactation day 21. Behavioral function, morphological appearance, and reproductive capacity of F₁ offspring were assessed. All F₁ maternal animals were allowed to deliver naturally, and F₁ maternal animals and F₂ offspring were necropsied on postnatal day 4. No drug-related findings were observed in any animal and the NOAELs in this study were determined to be 1,000 mg/kg/day for F₀ maternal general and reproductive toxicity and for F₁ and F₂.

(6) Local tolerance study

No local tolerance study has been performed.

(7) Other toxicity studies

1) Antigenicity study

An active systemic anaphylaxis (ASA) test and a homologous passive cutaneous anaphylaxis (PCA) test in guinea pigs were performed, both of which produced negative results.

2) Dependence

No study investigating the dependence potential of Ezetimibe has been performed.

3) Toxicity studies on impurities

Toxicity studies of Ezetimibe with added impurities (█% Impurity A (█), █% Impurity B (█), █% Impurity C (█), █% Impurity D (█), █% Impurity E (█), █% Impurity F (█), and █% Impurity G (█)) were conducted. In 1-month and 3-month repeated-dose toxicity studies in rats (males: 0, 150, 750, and 1,500 mg/kg/day, females: 0, 50, 250, and 500 mg/kg/day), there were no noteworthy findings. In 1-month and 3-month repeated-dose toxicity studies in dogs (males and females: 0, 30, 100, and 300 mg/kg/day), only decreases in serum cholesterol levels related to the pharmacological action of Ezetimibe were noted from the low dose. Therefore, no new toxicities emerged due to the impurities added, and the NOAELs in the 1-month and 3-month repeated-dose toxicity studies in rats were determined to be 1,500 mg/kg/day for males and 500 mg/kg/day for females, and those in the 1-month and 3-month repeated-dose toxicity studies in dogs were determined to be 300 mg/kg/day for both males and females. The genotoxicity of Ezetimibe with impurities was studied by a bacterial reverse mutation test and a mouse micronucleus test, which both produced negative results. Based on the above results, it was concluded that no new toxicities emerge due to the addition of impurities.

4) Combination therapy studies

As Ezetimibe is expected to be administered in combination with statins, single-dose toxicity, repeated-dose toxicity, genotoxicity, and reproductive and developmental toxicity studies with combination therapy were conducted using simvastatin, pravastatin, atorvastatin (these three drugs have been approved in Japan) and lovastatin (unapproved in Japan), in order to determine whether any new toxicities emerge due to coadministration. The doses in combination therapy studies are expressed as “Ezetimibe+statin” mg/kg, as a rule.

(a) Toxicity studies with combination therapy

(a)-1. Single-dose toxicity

Following the administration of 1,000+1,000 mg/kg of Ezetimibe + simvastatin or Ezetimibe+lovastatin in male and female mice and rats, neither mortality nor noteworthy findings were observed. Following the

intraperitoneal administration of Ezetimibe+lovastatin, mortality was seen starting at 500+500 mg/kg in male mice, at 750+750 mg/kg in female mice, at 750+750 mg/kg in male rats, and at 500+500 mg/kg in female rats. Following the intraperitoneal administration of Ezetimibe + simvastatin, mortality was observed from 100+100 mg/kg in male mice, from 250+250 mg/kg in female mice, and from 500+500 mg/kg in male and female rats. The main findings common to different combinations were soiled perineal fur, decreased locomotor activity, scant feces, hypothermia, dehydration, moribundity, and decreases in body weight gains, and those observed in rats included nasal discharge, rough fur, labored breathing, and loose stools.

(a)-2. Repeated-dose toxicity

Repeated oral doses of Ezetimibe+simvastatin (males: 50+10 to 250+50 mg/kg/day, females: 12+10 to 50+50 mg/kg/day), Ezetimibe+pravastatin (males: 15+25 to 750+250 mg/kg/day, females: 15+25 to 150+250 mg/kg/day), Ezetimibe+atorvastatin (males: 15+10 to 250+100 mg/kg/day, females: 15+10 to 50+100 mg/kg/day), or Ezetimibe+lovastatin (males: 50+10 to 750+100 mg/kg/day, females: 12+10 to 250+100 mg/kg/day) were administered for 3 months in male and female rats. The main findings common to different combinations were decreases in body weight gains, decreases in serum cholesterol and triglycerides, and increases in glutamic pyruvic transaminase (alanine aminotransferase (ALT)), AST, alkaline phosphatase (ALP) and liver weight. Histopathological examination revealed hepatocellular hypertrophy, vacuolation, single cell necrosis or while mitotic figures, bile duct hyperplasia, Kupffer cell hypertrophy or pigmentation (all Ezetimibe+statin combination therapies), degeneration or regeneration of skeletal muscle, cellular infiltration, interstitial edema or fibrosis (Ezetimibe+pravastatin (males: 250+250 mg/kg/day) and Ezetimibe+lovastatin (males: \geq 250+100 mg/kg/day, females: \geq 50+100 mg/kg/day)), hyperkeratosis of the forestomach mucosa, acanthosis, and cellular infiltration or edema (Ezetimibe+simvastatin (males: 250+50 mg/kg/day, females: 50+50 mg/kg/day), Ezetimibe+pravastatin (males: 750+250 mg/kg/day) and Ezetimibe+lovastatin (males: \geq 250+100 mg/kg/day, females: \geq 50+100 mg/kg/day)). One rat in the Ezetimibe+pravastatin 250+250 mg/kg/day group and 4 rats in the Ezetimibe+lovastatin 50+100 mg/kg/day or higher groups died or were killed in extremis due to aggravated general condition, and the cause of death was considered to be degeneration of skeletal muscle or non-specific focal necrosis of hepatocytes (Ezetimibe+lovastatin, one rat). Increases in plasma SCH60663 concentrations were noted with Ezetimibe+simvastatin, Ezetimibe+pravastatin, and Ezetimibe+lovastatin. Increases in plasma statin or its active metabolite levels were observed with Ezetimibe+simvastatin, Ezetimibe+pravastatin, and Ezetimibe+lovastatin, which were considered to be due to pharmacokinetic interactions.

Repeated oral doses of Ezetimibe+simvastatin (0.3+1 to 30+10 mg/kg/day), Ezetimibe+pravastatin (3+1 to 30+10 mg/kg/day), Ezetimibe+atorvastatin (0.3+1 to 30+10 mg/kg/day), or Ezetimibe+lovastatin (0.03+2 to 30+60 mg/kg/day) were administered for 3 months in dogs. The main findings in these combination therapy studies were decreases in serum cholesterol, triglycerides, or total protein, and increases in ALT, AST, or ALP. Histopathological examination revealed cytoplasmic eosinophilia of hepatocytes, hepatocellular hypertrophy, bile duct hyperplasia, and Kupffer cell hypertrophy or pigmentation. In dogs

treated with Ezetimibe+lovastatin, cholestasis (30+60 mg/kg/day) and degeneration or agglutination of sperm ($\geq 30+20$ mg/kg/day) were also observed. In the high dose combination therapy groups, marked increases in serum ALT (15- to 74-fold the mean level in the control group) were seen, but there were no findings, such as necrosis, in tissues of the liver or other organs. Increases in plasma statin or its active metabolite concentrations were noted with Ezetimibe+simvastatin and Ezetimibe+lovastatin, which were considered to be due to pharmacokinetic interactions.

Six-month and 14-month repeated oral dose toxicity studies with Ezetimibe+simvastatin (0.3+2, 1+2, 3+2 mg/kg/day) in dogs were conducted. As a result, laboratory changes similar to those in the 3-month combination therapy study were observed and histopathological examination showed changes in the liver only. From the low dose, decreases in serum cholesterol, triglycerides, and total protein, increases in ALT, AST, and ALP, slight increases in prothrombin time (≤ 1 sec), and decreased liver weights were mainly observed. From the low and middle doses, bile duct hyperplasia, cellular infiltration, pigmentation (lipofuscin) in Kupffer cell, macrophage, or hepatocytes, glycogen accumulation or small hepatocytes were observed. The changes other than glycogen accumulation were reversible after a 3-month withdrawal period. In both studies, from the low dose, increases in plasma simvastatin and its active metabolite concentrations were observed, which were considered to be due to the pharmacokinetic interactions.

(b) Genotoxicity with combination therapy

The genotoxicity of Ezetimibe+simvastatin, Ezetimibe+pravastatin, Ezetimibe+atorvastatin, and Ezetimibe+lovastatin was studied by a bacterial reverse mutation test, a chromosomal aberration test in human peripheral blood lymphocytes, and a mouse micronucleus test, which all produced negative results.

(c) Reproductive and developmental toxicity with combination therapy

Rat embryo-fetal developmental toxicity studies with combination therapy were conducted using Ezetimibe+simvastatin (1,000+5 to 25 mg/kg/day), Ezetimibe+pravastatin (1,000+131 to 526 mg/kg/day), Ezetimibe+atorvastatin (1,000+27.1 to 108.6 mg/kg/day), and Ezetimibe+lovastatin (1,000+10 to 50 mg/kg/day). In maternal animals, salivation, decreased body weight gain, or decreased food consumption (Ezetimibe+pravastatin, Ezetimibe+atorvastatin, or Ezetimibe+lovastatin) were noted. Decreased fetal body weight (Ezetimibe+simvastatin and Ezetimibe+atorvastatin), skeletal variations (delayed ossification (Ezetimibe+simvastatin, Ezetimibe+atorvastatin or Ezetimibe+lovastatin)), the thoracic vertebral centra asymmetrical (Ezetimibe+lovastatin)) or visceral variations (dilation of ureter (Ezetimibe+pravastatin)) were observed, but no malformations occurred. Similar changes were also seen in the statin monotherapy groups. Increases in plasma Ezetimibe concentrations with Ezetimibe+atorvastatin, increases in plasma SCH60663 concentrations with Ezetimibe+simvastatin, Ezetimibe+pravastatin, Ezetimibe+atorvastatin, and Ezetimibe+lovastatin, and increases in plasma statin or its active metabolite concentrations with Ezetimibe+simvastatin and Ezetimibe+lovastatin, were observed, which were considered to be due to pharmacokinetic interactions.

Rabbit embryo-fetal developmental toxicity studies with combination therapy were conducted using

Ezetimibe+simvastatin (1,000+1 to 10 mg/kg/day), Ezetimibe+pravastatin (1,000+5.2 to 52.5 mg/kg/day), Ezetimibe+atorvastatin (1,000+ 5.5 to 54.5 mg/kg/day), and Ezetimibe+lovastatin (1,000+2.5 to 25 mg/kg/day). In maternal animals, scant feces, loose stools, soiled perineal region, decreased body weight gain, or decreased food consumption (Ezetimibe+all statins), abortion (Ezetimibe+lovastatin), and increased embryonic resorptions (Ezetimibe+lovastatin) were observed. In addition, there were increased external and skeletal malformations of tail (brachyury, kinked tail, fused caudal vertebra, reduced number of caudal vertebrae or sternebra fused (Ezetimibe+simvastatin, Ezetimibe+pravastatin, or Ezetimibe+atorvastatin)), but their incidences were low (0.6-4%), and there were no clear dose-dependency. Increased skeletal variations (sternebra asymmetrical (Ezetimibe+atorvastatin)) were also observed.

Increases in plasma statin or its active metabolite concentrations were seen with Ezetimibe+atorvastatin, which were considered to be due to pharmacokinetic interactions.

Maternal (general toxicity/reproductive toxicity) and fetal NOAELs were determined to be 1,000+<1/1,000+10 mg/kg/day and 1,000+1 mg/kg/day, respectively, for Ezetimibe+simvastatin, 1,000+<5.2/1,000+52.5 mg/kg/day and 1,000+5.2 mg/kg/day, respectively, for Ezetimibe+pravastatin, 1,000+<5.5/1,000+54.5 mg/kg/day and 1,000+<5.5 mg/kg/day, respectively, for Ezetimibe+atorvastatin, 1,000+2.5/1,000+10 mg/kg/day and 1,000+2.5 mg/kg/day, respectively, for Ezetimibe+lovastatin.

<Outline of the review by the PMDA>

The PMDA asked the applicant to explain concerns about human safety in view of the findings observed with Ezetimibe alone or in combination with statins.

The applicant responded as follows:

(1) Assessment in terms of exposure

The ratios of the NOAELs in the Ezetimibe monotherapy studies to the clinical dose are 1,250-7,500, and the systemic exposure ratios ($AUC_{\text{animal}}/AUC_{\text{human}}$) are 23-30 for rats and 15 for dogs in chronic repeated-dose toxicity studies, 273-375 for mice and 21-29 for rats in carcinogenicity studies, and 12 for pregnant rats and 273 for pregnant rabbits in reproductive toxicity studies. Therefore, the clinical safety of Ezetimibe is assured on the basis of the dose ratios and systemic exposure ratios.

Following the coadministration of Ezetimibe with statins, increases in plasma drug concentrations, which were considered to be due to pharmacokinetic interactions, were observed (especially in the high dose combination groups). The presence/absence and extent of such interactions depend on animal species and the type and dose of a statin combined. Under the conditions of these combination therapy studies, increases in plasma SCH60663 concentrations were seen in rats only and increases in statin and its pharmacologically active hydroxylated metabolite concentrations were noted in rats, dogs, and rabbits. However, in healthy non-Japanese male adults, no pharmacokinetic interactions occurred even when the clinical dose of Ezetimibe (10 mg/day) was coadministered with a statin.

(2) Effects on the liver

Also in a rat repeated-dose toxicity study with statin monotherapy, changes in the liver have been reported. The mechanism for responding to hepatic cholesterol reductions by statins differs between rodents and non-rodents. In non-rodents, mainly, hepatocellular LDL receptors are increased and blood cholesterol is taken up. On the other hand, in rodents, HMG-CoA reductase is compensatorily induced, trying to maintain hepatic cholesterol. Consequently, in rodents, the serum cholesterol concentration remains unchanged, and there are increases in smooth-surfaced endoplasmic reticulum, hepatocellular hypertrophy, changes in the staining property of hepatocytes (eosinophilic or basophilic change) or hepatocellular atypia characterized by increased multinucleated hepatocytes, and increased liver weight, associated with the induction of HMG-CoA reductase. In severe cases, bile duct hyperplasia or single cell necrosis may also occur. These changes associated with statins occur primarily in the periportal region where HMG-CoA reductase is abundantly distributed, and are inhibited by coadministration of mevalonic acid, the product of HMG-CoA reductase. Therefore, these are an adaptive response to the pharmacological activity of statins and do not suggest a risk in humans. The changes in the liver observed in rats in the combination therapy groups are similar to those reported with statins as described above, and are considered to be an adaptive response. The reasons for severer changes with combination therapy compared to statin monotherapy are inferred as follows: Plasma concentrations of statin and its hydroxylated metabolite were increased (approximately 2- to 15-fold) and as serum cholesterol levels were decreased due to combination therapy (up to approximately 40-50% reductions in each combination therapy study), HMG-CoA reductase was induced more strongly in the coadministration group compared to the statin monotherapy group (the control group) where the serum cholesterol level remained unchanged, resulting in severer changes in the liver.

Meanwhile, the findings observed with combination therapy in the dog 3-month studies, such as changes in bile duct, hepatocytes, and Kupffer cell, and cholestasis were similar to those reported in the statin monotherapy groups or statin repeated-dose studies. However, as there were no effects on the liver in the Ezetimibe repeated-dose toxicity studies in dogs, the findings in the combination therapy groups should be attributable to statins. The reasons for severer changes in the combination therapy groups compared to the monotherapy groups are considered as follows: Since plasma concentrations of statin and its hydroxylated metabolite were increased (approximately 2- to 4-fold) and the percent reduction in the serum cholesterol level was greater in the combination therapy groups compared to the corresponding statin monotherapy groups (up to 90% reductions (individual values of animals)), the effects on the liver were enhanced. In all cases with bile duct hyperplasia, the serum cholesterol levels were approximately 40 mg/dL or less and the percent reduction from baseline was approximately 70% or more, suggesting its relationship with decreased serum cholesterol levels. In the dog 6-month and 14-month studies with combination therapy with simvastatin, there were bile duct hyperplasia, cellular infiltration, pigmentation (lipofuscin) in Kupffer cell, macrophage, or hepatocytes, glycogen accumulation or small hepatocytes from the middle and low doses, but the changes other than glycogen accumulation were reversible upon drug withdrawal. Similar findings have also been reported in an atorvastatin chronic administration study, which were inferred to be

an adaptive response associated with changes in lipid metabolism. Although changes occurred from a lower dose with combination therapy compared to statin monotherapy, these changes in the liver are adequately predictable from reports on statins.

(3) Effects on liver enzymes

In the dog 3-month studies with combination therapy, marked increases in ALT (up to 15- to 74-fold increases compared to the controls) and increases in AST (2- to 5-fold increases compared to the controls) were observed. Histopathological examination revealed no findings associated with increased ALT, such as necrosis, in the liver, intestine, or skeletal muscles at various sites. No interference with serum ALT test was found. Although serum ALT protein was increased, there were no increases in ALT activity or ALT protein content in the liver, muscle, or small intestinal tissue, and the source of increased serum ALT protein was unknown. Increased ALT was not observed in the Ezetimibe repeated-dose studies in dogs, and was markedly reduced by the coadministration of mevalonic acid, the product of HMG-CoA reductase. Therefore, it is considered attributable to the pharmacological action of statins and is reversible upon drug withdrawal. These results are consistent with a report that increases in serum ALT without hepatic dysfunction, which is inhibited by the administration of mevalonic acid, are observed after repeated administration of simvastatin or lovastatin to dogs.

(4) Effects on skeletal muscle

In the rat studies with combination therapy, degeneration and regeneration of muscle fiber, cellular infiltration, and interstitial edema or fibrosis were observed in dead rats treated with Ezetimibe in combination with lovastatin or pravastatin, which were considered related to the cause of death. Degeneration or regeneration of muscle fiber with increased creatine kinase (CK) was observed in a 2-week preliminary study of Ezetimibe+simvastatin coadministration, whereas there were no effects on skeletal muscle even at the same dose in the 3-month administration study. The effects on skeletal muscle seem to be common changes observed in statin treatment and it has been reported that such changes are induced by repeated administration of high-dose statins in rats and dogs, and rhabdomyolysis is known also in clinical experience. In the repeated-dose studies with Ezetimibe monotherapy in rats and dogs, there were no effects on skeletal muscle. Thus, the effects on skeletal muscle observed in the studies with combination therapy in rats should be attributable to statins. The effects on skeletal muscle were seen only at the high dose where plasma concentrations of statin and its hydroxylated metabolite were elevated (about 2- to 18-fold) due to pharmacokinetic interactions. In the studies of Ezetimibe administration in combination with simvastatin, pravastatin, and atorvastatin, which have been approved in Japan, the ratios of the NOAELs for skeletal muscle to the clinical dose for statins were 100, 125, and 500, respectively, and the systemic exposure ratios for statin or its hydroxylated metabolite were 14, 5.8, and 77, respectively. Furthermore, in the dog studies with combination therapy, no effects on skeletal muscle were seen. Therefore, in humans where no pharmacokinetic interactions occur due to coadministration, Ezetimibe is unlikely to increase the skeletal muscle risk associated with statins.

(5) Effects on the gastrointestinal tract

In the rat studies with combination therapy, hyperkeratosis of the forestomach, acanthosis, cellular infiltration, or submucosal edema were noted and ulcer was also observed with Ezetimibe in combination with lovastatin. Hyperkeratosis, acanthosis, and submucosal edema were observed in the statin monotherapy groups as well. The effects on the forestomach have been reported in rat repeated dose studies with different statins, which are considered to be induced by the local inhibition of HMG-CoA reductase. Since humans and dogs have no forestomach and there were no effects on the esophagus or stomach in the dog studies with combination therapy, combination therapy is unlikely to cause effects on the gastrointestinal tract in humans.

(6) Effects on the testes

There were effects on the testes of dogs at $\geq 30+20$ mg/kg in the Ezetimibe+lovastatin coadministration study while no effects on the testes of dogs were observed in other chronic coadministration studies. Since it has been reported that poorly reproducible degeneration of the testes occurs following repeated administration of statins to dogs, and Ezetimibe alone had no effects on the testes, this finding should be attributable to lovastatin. It is inferred that there were effects on the testes only in the Ezetimibe+lovastatin coadministration group because plasma concentrations of lovastatin and hydroxy-lovastatin in the combination therapy group were increased to approximately 2-4 times due to pharmacokinetic interactions. However, in the 3-month studies with Ezetimibe in combination with simvastatin, pravastatin, and atorvastatin, which have been approved in Japan, there were no effects on the testes, and the ratios of the NOAELs for the testes in the combination therapy studies to the clinical dose for statins were $\geq 50-100$, and the systemic exposure ratios for statin and its hydroxylated metabolite were $\geq 16-165$. Furthermore, there were no effects on the testes in the rat studies with combination therapy and the ratios of the NOAELs for the testes in the combination therapy studies to the clinical dose for statins were $\geq 500-1,250$ and the systemic exposure ratios for statin and its active metabolite were $\geq 68-1,179$. In humans, there are no increases in plasma drug concentrations due to pharmacokinetic interactions even when Ezetimibe is coadministered with statins and it has been reported that there were no effects on the testicular function after lovastatin administration in humans. Thus, there should be no possibility that coadministration in clinical practice increases the risk of testicular function impairment in humans.

(7) Carcinogenic potential

Genotoxicity studies were negative for both monotherapy and combination therapy and Ezetimibe has been determined to be non-genotoxic. Statins have been reported to be nonmutagenic rodent carcinogens, and tumors were found in the target organs in a repeated dose study, such as the liver and forestomach. Meanwhile, an epidemiological study has reported that there was no increased risk for carcinogenicity in humans. Although no carcinogenicity study with combination therapy has been conducted, similar results as statin monotherapy are likely to be obtained.

(8) Effects on reproduction and development

In the rat embryo-fetal developmental toxicity study, decreased fetal body weight, skeletal variations

(delayed ossification), and visceral variations were mainly observed at doses affecting maternal animals, but there was no evidence of teratogenicity. In rabbits, fetal skeletal abnormalities (mainly, fused caudal vertebra and reduced number of caudal vertebrae, sternebra fused) were observed at doses affecting maternal animals, which were not dose-dependent and were infrequent. Although there was no evidence of teratogenicity with Ezetimibe alone, the package inserts for statins state that the drug is contraindicated in pregnant women or women of child bearing potential because malformations in rat and human fetuses have been reported. Thus, it is inappropriate to coadminister Ezetimibe and a statin to these patients.

The PMDA accepted the above response. It was judged that any new toxicities other than known findings are unlikely to emerge with Ezetimibe alone or in combination with statins that have been approved in Japan.

4. Clinical Data

(i) Summary of human pharmacokinetics and pharmacodynamics

<Summary of the submitted data>

(1) Bioequivalence between different drug products

Two types of drug products, i.e. the elliptical tablet and the capsule-shaped tablet, which had the same formulation, were used in Japanese clinical studies. The elliptical tablets of 0.25 mg, 1 mg, and 10 mg were used in phase I studies, the capsule-shaped tablets of 5 mg and 10 mg were used in phase II studies, and the capsule-shaped tablets of 10 mg were used in phase III studies.

1) BE study of the elliptical tablet and the capsule-shaped tablet (the proposed commercial formulation)

A dissolution test of the elliptical tablets manufactured by **Manufacturing Method A**, and the capsule-shaped tablets with the same formulation, manufactured by **Manufacturing Method B**, was performed. As a result, the f_2 values were ■■■ and ■■■%, respectively and it was concluded that the two drug products are considered bioequivalent.

2) BE study of the 5 mg tablet and the 10 mg tablet of Ezetimibe

In accordance with “Guideline for Bioequivalence studies for different solid oral dosage strengths” (PMSB/ELD Notification No. 64 dated February 14, 2000), the level of changes in formulation for Ezetimibe 5 mg tablet and 10 mg tablet, is Level B (only a ■■■% difference in the content of the excipient lactose) and Ezetimibe was expected to be insoluble. Thus, a dissolution test was performed using various dissolution media. As a result, the equivalence criteria for dissolution profile were met, and it was concluded that the 5 mg tablet×2 and the 10 mg tablet are considered bioequivalent.

(ii) Summary of clinical pharmacology

<Summary of the submitted data>

(1) *In vitro* studies using human biomaterials

1) Plasma protein binding

The *in vitro* Ezetimibe plasma protein binding in human was 99.5-99.8% at Ezetimibe concentrations of 5-200 ng/mL. The range of *in vitro* binding of SCH60663, the major metabolite, to human plasma proteins at concentrations of 2-2,000 ng/mL was 87.8-92.0%. It was suggested that human serum albumin (HSA) is a major binding protein for Ezetimibe in humans.

2) Study using tissue slices

Liver and kidney tissue slices from human (non-Japanese) were incubated with ³H-Ezetimibe added in extratissue fluid and the composition of radioactivity in extratissue fluid was analyzed. As a result, the major metabolic pathway was a pathway forming SCH60663.

3) Study using liver microsomes

After the incubation of ¹⁴C-Ezetimibe with human liver microsomes, the major metabolite was SCH60663,

whereas in human jejunum microsomes, the formation of the benzylic glucuronide (SCH488128) in addition to SCH60663 was detected. In an *in vivo* setting, the urinary excretion of SCH488128 was 0.91% of the administered dose. Thus, glucuronidation at the benzylic hydroxyl group was considered a secondary metabolic pathway to phenolic glucuronidation.

4) Identification of the isoform(s) of UDP-glucuronosyltransferase (UGT)

After the incubation of ¹⁴C-Ezetimibe with cDNA-expressed human UGT in an UDP-glucuronic acid reconstituted system, UGT1A1 and 1A3 exhibited the most activity for the formation of SCH60663 followed by UGT2B15. Michaelis constant (K_m) of UGT1A1 and 1A3 was 64.3 and 41.7 μM, respectively, the maximum velocity (V_{max}) was 0.71 and 0.48 nmol/mg protein/min, respectively, and the intrinsic clearance (V_{max}/K_m) was 0.011 mL/mg protein/min for both. UGT2B7 formed SCH 488128. (K_m: 20.9 μM, V_{max}: 0.05 nmol/mg protein/min, V_{max}/K_m: 0.002 mL/mg protein/min).

5) *In vitro* drug interactions

(a) Effects on liver drug metabolizing enzymes

Ezetimibe inhibited testosterone 6β-hydroxylation activity in human liver microsomes (IC₅₀ value: 7 μM), and the inhibitory effect of Ezetimibe on testosterone 6β-hydroxylation activity was increased by about 28 times (IC₅₀ value: 0.25 μM) when Ezetimibe was reacted before the addition of testosterone, suggesting the inactivation by binding to CYP3A4 of a metabolic intermediate formed by the metabolism of Ezetimibe as well as competitive inhibition of CYP3A4, as the mode of inhibition. However, as the above-mentioned *in vitro* study was performed under non-physiological conditions without UDP-glucuronic acid added, and Ezetimibe is preferentially glucuronidated *in vivo*, oxidative metabolic intermediate will scarcely be formed.

(b) Effects on the P-glycoprotein transport system

In an *in vitro* study using human MDR1-transfected cell line (NIH-3T3), Ezetimibe inhibited the extracellular efflux of other drugs that are substrates for P-glycoprotein (daunorubicin and rhodamine). (IC₅₀ values: 25.3 and 42.3 μM, respectively)

(2) Pharmacokinetics in healthy adults

Five Japanese pharmacokinetic studies and one Japanese clinical pharmacology study were submitted as Evaluation Data and foreign pharmacokinetic studies were submitted as Reference Data.

1) Single dose study (Japanese Study JPC-98-335-12)

Following a single oral dose of Ezetimibe (elliptical tablets) 10, 20, and 40 mg (6 subjects per group) and placebo (9 subjects) administered at 30 minutes after consuming breakfast in 27 healthy Japanese adult male subjects (including 1 subject with hyperlipidemia), the plasma Ezetimibe concentration reached C_{max} (6.79±2.12 (Mean±SD), 11.5±6.69, and 22.9±5.26 ng/mL, respectively) at 1.08-2.5 hours post-dose and the AUC_{0-t} value was 64.9±20.4, 130±46.0, and 279±54.5 ng•hr/mL, respectively. In many subjects, the concentration-time profile showed a biphasic pattern, suggesting enterohepatic circulation. Ezetimibe C_{max}

and AUC_{0-t} were correlated with the dose within a dose range of 10-40 mg. The plasma total Ezetimibe (unconjugated + conjugated) concentration reached C_{max} (66.0 ± 22.5 , 127 ± 28.7 , and 414 ± 339 ng Eq/mL, respectively) at 1.2-1.8 hours post-dose, and the AUC_{0-t} value was 335 ± 179 , 787 ± 390 , and $2,711 \pm 2,004$ ng Eq·hr/mL, respectively. In a few subjects, the concentration-time profile showed a biphasic pattern, suggesting enterohepatic circulation. Total Ezetimibe C_{max} and AUC_{0-t} were also correlated with the dose within a dose range of 10-40 mg. Ezetimibe constituted 7.43-11.3% of total Ezetimibe based on C_{max} and 14.2-22.5% based on AUC_{0-t} . The cumulative urinary excretion rate of total Ezetimibe up to 72 hours post-dose was 8.68-11.2% while the cumulative urinary excretion rate of Ezetimibe was 0.02-0.04%.

2) Multiple dose study (Japanese Study JPC-98-335-13)

Following multiple oral doses of Ezetimibe 20 mg (the 10 mg elliptical tablet $\times 2$, 9 subjects) and placebo (3 subjects) administered once daily immediately before breakfast (within 5 minutes prior to consuming breakfast) for 14 days in 12 healthy Japanese adult male subjects (including 1 subject with hyperlipidemia), the plasma Ezetimibe concentration reached C_{max} at 1 hour after the first dose, increased again at 4 hours post-dose and then decreased. At 0.5 hours after the last dose, C_{max} was attained and then the mean concentration decreased over time. The plasma Ezetimibe and total Ezetimibe concentrations reached a steady-state by Day 3.

Ezetimibe C_{max} values after the first and last doses were 8.62 ± 4.08 and 14.9 ± 7.8 ng/mL, respectively, the AUC_{0-24hr} values were 78.9 ± 33.0 and 114 ± 30 ng·hr/mL, respectively, and the accumulation ratio was 1.87 ± 0.67 for C_{max} and 1.54 ± 0.27 for AUC_{0-24hr} . Total Ezetimibe C_{max} values after the first and last doses were 116 ± 32 and 130 ± 31 ng Eq/mL, respectively, the AUC_{0-24hr} values were 581 ± 186 and 725 ± 204 ng Eq·hr/mL, respectively, and the accumulation ratio was 1.18 ± 0.34 for C_{max} and 1.43 ± 0.45 for AUC_{0-24hr} .

After the first and last doses, Ezetimibe constituted 7.52 ± 2.97 and $11.8 \pm 5.7\%$, respectively, of total Ezetimibe based on C_{max} and 12.4 ± 6.1 and $19.4 \pm 8.8\%$, respectively, based on AUC_{0-t} , showing that multiple dose administration resulted in increased proportion of Ezetimibe.

(3) Human pharmacokinetics in special populations

1) Pharmacokinetics in elderly subjects (Japanese Study JPC-02-335-17)

Multiple oral doses of Ezetimibe (capsule-shaped tablets) 10 mg were administered once daily within 30 minutes after breakfast (in the fasted state on Day 10 only) for 10 days in 12 Japanese elderly subjects (≥ 65 years) and 12 non-elderly subjects (20-40 years). As one non-elderly subject was withdrawn from the study due to the subject's own convenience, 23 subjects were included in the pharmacokinetic analysis. Ezetimibe C_{max} was 4.60 ng/mL in the elderly subjects and 5.77 ng/mL in the non-elderly subjects (point estimate for the ratio of elderly/non-elderly: 75.2% (90% confidence interval, 54.6-104%)) and the AUC_{0-24hr} was 70.3 and 71.0 ng·hr/mL, respectively (90.3% (66.3-123%)). SCH60663 C_{max} was 104 and 44.4 ng Eq/mL, respectively (228% (165-317%)), and the AUC_{0-24hr} was 828 and 344 ng Eq·hr/mL, respectively (237% (184-306%)), showing higher values in the elderly. Total Ezetimibe C_{max} was 108 and 48.8 ng Eq/mL, respectively (212% (157-285%)) and the AUC_{0-24hr} was 898 and 415 ng Eq·hr/mL,

respectively (210% (167-263%)), also showing higher values in the elderly.

2) Gender differences in the pharmacokinetics (Foreign Study C98-107)

Ezetimibe 20 mg was orally administered once daily for 10 days in healthy non-Japanese adult volunteers (12 males and 12 females) under the fasting conditions (on Days 1 and 10, the subjects continued fasting until 4 hours post-dose). As a result, there were no apparent gender differences in C_{\max} or AUC_{0-24hr} of Ezetimibe and SCH60663 after the first dose. On the other hand, after the last dose, the plasma Ezetimibe concentration and the plasma SCH60663 concentration were 20% and 15% higher, respectively, in women than in men.

3) Pharmacokinetics in healthy adolescent children (Foreign Study P00774)

Following multiple oral doses of Ezetimibe 10 mg once daily for 7 days to 18 healthy non-Japanese adolescent children (10-18 years) under fasting conditions, the C_{\max} values for Ezetimibe, SCH60663, and total Ezetimibe on Day 7 were 9.71 ng/mL, 54.8 ng Eq/mL, and 61.8 ng Eq/mL, respectively, the AUC_{0-24hr} values were 155 ng·hr/mL, 581 ng Eq·hr/mL, and 736 ng Eq·hr/mL, respectively, and the mean effective $t_{1/2}$ was 29.3, 19.8, and 21.5 hr, respectively. The mean accumulation ratios were 2.32, 1.72, and 1.82, respectively. The mean and individual plasma Ezetimibe concentrations were 1.3-2.7 fold higher in adolescent children than in adults and the mean exposure to Ezetimibe based on AUC was about 20% of the mean exposure to total Ezetimibe, which was higher than in adult subjects (about 10%).

4) Pharmacokinetics in subjects with hepatic impairment (Foreign Study P00251, Foreign Study P01912)

(a) Single-dose pharmacokinetics in subjects with various degrees of chronic liver disease (Foreign Study P00251)

After a single oral dose of Ezetimibe 10 mg was administered to healthy non-Japanese adult volunteers (8 males), subjects with mild hepatic impairment (Child-Pugh score 5 to 6, 3 males/1 female), subjects with moderate hepatic impairment (Child-Pugh score 7 to 9, 3 males/1 female), and subjects with severe hepatic impairment (Child-Pugh score 10 to 15, 4 males/0 female) under fasting conditions, the C_{\max} of Ezetimibe was 3.86, 4.10, 13.07, and 16.2 ng/mL, respectively, and the AUC_{0-t} was 54.6, 75.8, 316, and 265 ng·hr/mL, respectively. The C_{\max} of SCH60663 was 95.3, 138, 171, and 178 ng Eq/mL, respectively, and the AUC_{0-t} was 864, 1,468, 2,685, and 3,418 ng Eq·hr/mL, respectively. The C_{\max} of total Ezetimibe was 98.2, 141, 181, and 189 ng Eq/mL, respectively, and the AUC_{0-t} was 916, 1,543, 3,001, and 3,682 ng Eq·hr/mL, respectively. The increase in plasma exposure to Ezetimibe, total Ezetimibe, and SCH60663 observed with increasing liver impairment was considered attributable to increased bioavailability due to a decreased clearance.

(b) Multiple-dose pharmacokinetics in subjects with moderate chronic liver disease (Foreign Study P01912)

Multiple oral doses of Ezetimibe 10 mg were administered once daily for 14 consecutive days to non-Japanese subjects with moderate chronic liver disease (at least 1 year, Child-Pugh score 7 to 9, 11

subjects) and subjects with normal liver function (11 subjects) under fasting conditions. The C_{max} and AUC_{0-24hr} of Ezetimibe, SCH60663, and total Ezetimibe after 14 days of treatment were higher in subjects with chronic liver disease (C_{max} : 22.3 ng/mL, 257 ng Eq/mL, and 276 ng Eq/mL, respectively, AUC_{0-24hr} : 341 ng·hr/mL, 2,749 ng Eq·hr/mL, and 3,089 ng Eq·hr/mL, respectively) than in healthy adult subjects (C_{max} : 7.20 ng/mL, 95.4 ng Eq/mL, and 100 ng Eq/mL, respectively, AUC_{0-24hr} : 93.2 ng·hr/mL, 760 ng Eq·hr/mL, and 853 ng Eq·hr/mL, respectively). The accumulation of total Ezetimibe and SCH60663 on multiple dose administration was comparable between healthy subjects (accumulation ratio (R): 1.60 and 1.67, respectively) and subjects with chronic liver disease (R: 1.37 and 1.42, respectively), and R of Ezetimibe was 2.31 in healthy subjects and 1.94 in subjects with chronic liver disease. Based on the ratio of AUC values, the exposure to Ezetimibe was 2-22% of the exposure to total Ezetimibe in both healthy subjects and subjects with chronic liver disease, with no apparent differences between the two study populations.

5) Pharmacokinetics in subjects with renal insufficiency (Foreign Study P00749)

After a single oral dose of Ezetimibe 10 mg was administered to 9 non-Japanese subjects with chronic renal insufficiency (Creatinine clearance (CL_{cr})=10-29 mL/min/1.73m²) and 9 healthy adult subjects (CL_{cr} >80 mL/min/1.73m²) under fasting conditions, the exposure to total Ezetimibe and SCH60663 based on AUC_{0-t} was 47% higher in subjects with renal insufficiency. The mean Ezetimibe terminal phase $t_{1/2}$ was approximately 22 hours in healthy subjects and approximately 30 hours in subjects with severe renal insufficiency, showing a prolongation of the half-life in subjects with renal insufficiency. There was a negative correlation between CL_{cr} and AUC of total Ezetimibe and SCH60663, and a weak relationship was also observed between CL_{cr} and total body clearance for Ezetimibe. The increased AUC of total Ezetimibe in subjects with chronic renal insufficiency is not considered to be of clinical significance and no dosage adjustment of Ezetimibe should be required in patients with chronic renal insufficiency.

(4) Food effects

1) Food effects in Japanese subjects (Japanese Study JPC-02-335-16)

A 2×2 crossover study was conducted, where 23 healthy Japanese adult male subjects received a single oral dose of Ezetimibe (capsule-shaped tablets) 10 mg under fasting conditions on one occasion and at 30 minutes after a meal on the other occasion (washout period: at least 7 days). Twenty subjects excluding 3 subjects who were withdrawn from the study after the period 1 were included in the pharmacokinetic analysis. The t_{max} values for Ezetimibe administered in the fasted state and after a meal were 5.28 and 2.10 hr, respectively, the C_{max} values were 3.73 and 6.03 ng/mL, respectively, and the AUC_{0-t} values were 48.9 and 55.6 ng·hr/mL, respectively. For SCH60663, the t_{max} values were 1.80 and 1.48 hr, respectively, the C_{max} values were 44.4 and 72.3 ng Eq/mL, respectively, and the AUC_{0-t} values were 303 and 333 ng Eq·hr/mL, respectively. The presence of food affected the C_{max} of plasma Ezetimibe and SCH60663, but had no effect on the AUC.

2) The effects of a high-fat meal in non-Japanese subjects (Foreign Study P00751)

A 3×3 crossover study was conducted, where 18 healthy non-Japanese volunteers received Ezetimibe

(capsule-shaped tablets) 10 mg under fasting conditions, after a nonfat meal and after a high-fat meal. The 90% confidence intervals for the ratio of Ezetimibe given after a meal compared to given under the fasted state for the log-transformed AUC_{0-t} of Ezetimibe, SCH60663, and total Ezetimibe were 82-109%, which fell within the bioequivalence limits (0.8-1.25). Meanwhile, a difference in C_{max} was observed for Ezetimibe following administration of a high-fat meal (7.91 ng/mL) vs. the fasted state (5.48 ng/mL), and the point estimate based on the comparison of log-transformed C_{max} values following a meal vs. fasted subjects was 138% (90% confidence interval: 112-170%). The point estimates based on the comparison of log-transformed C_{max} values following a nonfat meal vs. fasted subjects were 82%, 102%, and 103% for Ezetimibe, SCH60663, and total Ezetimibe, respectively. Relative to the fasted state, there was a trend toward a higher Ezetimibe concentration when Ezetimibe was administered with a high-fat meal, and a trend toward a lower Ezetimibe concentration after a nonfat meal.

(5) Drug interactions

Potential Ezetimibe interactions with warfarin, digoxin, oral contraceptives (containing ethinyl estradiol and levonorgestrel), cimetidine, antacids, glipizide, various statins, fenofibrate, gemfibrozil, cholestyramine, and cyclosporine were investigated. Medications for which interactions with Ezetimibe have occurred and statins which are concomitantly used with Ezetimibe in clinical practice are mainly described below.

1) Interactions with cimetidine (Foreign Study P00746)

A crossover study was conducted, where 13 healthy non-Japanese adult subjects under fasting conditions received multiple oral doses of Ezetimibe 10 mg for 7 days on one occasion and multiple doses of Ezetimibe 10 mg and cimetidine 400 mg (twice daily administration at 8 a.m. and 8 p.m.) for 7 days on the other occasion. Cimetidine coadministration with Ezetimibe caused about 30% increases in plasma Ezetimibe C_{max} and AUC. The 90% confidence intervals for log-transformed AUC and C_{max} were 95-129% and 104-142%, respectively, for Ezetimibe, total Ezetimibe, and SCH60663. The 90% confidence interval for log-transformed AUC was 97-115% for total Ezetimibe and no significant inter-treatment differences were found based on the mean ratio for AUC and C_{max} for Ezetimibe, total Ezetimibe, and SCH60663.

2) Interactions with antacids (Foreign Study P00748)

A crossover study was conducted, where 12 healthy non-Japanese adult male and female subjects received a single oral dose of Ezetimibe 10 mg under fasting conditions on one occasion and Supralox antacid 20 mL (containing magnesium hydroxide 1.2 g and aluminum hydroxide 1.8 g) immediately prior to Ezetimibe 10 mg on the other occasion. When coadministered with Supralox, the rate of Ezetimibe absorption was slower, with t_{max} increasing from 1.5 hours to 3 hours in the presence of antacid. The point estimates based on the log-transformed C_{max} values following coadministration of Ezetimibe with antacid compared to Ezetimibe alone were 110%, 70%, and 67% for Ezetimibe, total Ezetimibe, and SCH60663, respectively, but the point estimates based on the log-transformed AUC values following coadministration of Ezetimibe with antacid compared to Ezetimibe alone were 108%, 96%, and 94% for Ezetimibe, total Ezetimibe, and SCH60663, respectively, and the corresponding 90% confidence intervals were within

80-125%.

3) Interactions with different statins (Foreign Study P00447; pravastatin, Foreign Study I98-311; simvastatin, Foreign Study P00755; fluvastatin, Foreign Study P00460; atorvastatin, Foreign Study P03317; rosuvastatin, Japanese Study JPC-04-335-18; pitavastatin, Foreign Study P01382; lovastatin, Foreign Study P00250; lovastatin, Foreign Study P00754; cerivastatin)

In order to evaluate the potential Ezetimibe interactions with pravastatin, simvastatin, fluvastatin, atorvastatin, rosuvastatin, lovastatin, and cerivastatin, parallel-group studies in non-Japanese adult subjects with mild hypercholesterolemia (serum LDL-C \geq 130 mg/dL) or healthy non-Japanese adult subjects were conducted. The treatment arms were Ezetimibe 10 mg once daily for 14 consecutive days; a statin at a clinical usual dose once daily for 14 consecutive days; Ezetimibe 10 mg+a statin at a clinical usual dose once daily for 14 consecutive days; and placebo.

When coadministered with pravastatin, fluvastatin, atorvastatin, lovastatin, and rosuvastatin, there was no significant effect on the pharmacokinetic parameters of Ezetimibe and SCH60663. When cerivastatin was coadministered with Ezetimibe, the point estimates for log-transformed plasma Ezetimibe C_{max} and AUC_{0-24hr} values following coadministration of Ezetimibe with cerivastatin compared to Ezetimibe alone were reduced to 69.5% (90% confidence interval: 50-96%) and 63.4% (47-86%), respectively, while there was no effect on the plasma SCH60663 concentration.

Ezetimibe did not significantly affect the pharmacokinetic parameters of pravastatin, simvastatin, atorvastatin, lovastatin, rosuvastatin, and cerivastatin, and their metabolites. When fluvastatin and Ezetimibe were coadministered, the point estimates for log-transformed plasma fluvastatin C_{max} and AUC_{0-24hr} values following coadministration of Ezetimibe with fluvastatin compared to fluvastatin alone were reduced to 73.0% (49-109%) and 61.1% (38-97%), respectively. When cerivastatin and Ezetimibe were coadministered, the point estimates for log-transformed plasma cerivastatin C_{max} and AUC values were increased to 133% (101-176%) and 127% (88-175%), respectively.

Using pitavastatin, a three-period crossover study in 18 healthy Japanese male adults (15 subjects completed the study) was conducted: Ezetimibe 10 mg once daily for 7 days; Ezetimibe 10 mg+pitavastatin 2 mg once daily for 7 days; and pitavastatin 2 mg once daily for 7 days. The point estimates based on the log-transformed Ezetimibe C_{max} and AUC_{0-24hr} values following coadministration of Ezetimibe with pitavastatin compared to Ezetimibe alone were 99.8% (88.3-113%) and 97.5% (90.5-105%), respectively. Likewise, the point estimates for log-transformed C_{max} and AUC_{0-24hr} for plasma pitavastatin lactone following coadministration of Ezetimibe with pitavastatin compared to pitavastatin alone were 97.5% (91.7-104%) and 98.0% (91.6-105%), respectively. Concomitant Ezetimibe did not affect the t_{max} of either pitavastatin or pitavastatin lactone. There were also no changes suggesting any effects of concomitant pitavastatin for plasma Ezetimibe or SCH60663 concentrations.

4) Interactions with fenofibrate (Foreign Study P00753)

Following multiple oral doses of fenofibrate 200 mg once daily for 14 days under fasting conditions to 8 healthy non-Japanese adult subjects with mild hypercholesterolemia (serum LDL-C \geq 130mg/dL), the effects of concomitant Ezetimibe (10 mg once daily for 14 days) on plasma fenofibric acid concentrations at the last dose (Day 14) were investigated. As a result, the point estimates based on the log-transformed C_{\max} and AUC_{0-24hr} values for Ezetimibe coadministered with fenofibrate vs. fenofibrate alone were 107% and 111%, respectively, and the 90% confidence intervals were 80-143% and 78-158%, respectively. Concomitant Ezetimibe had no effect on t_{\max} . On the other hand, as to plasma SCH 60663 concentrations, the coadministration of Ezetimibe with fenofibrate resulted in 68% and 52% increases in C_{\max} and AUC_{0-24hr} , respectively, which is not considered to be clinically significant, taking account of the 90% confidence interval. With respect to plasma Ezetimibe concentrations, there were no apparent changes suggesting any effects of concomitant fenofibrate.

5) Interactions with cholestyramine (Foreign Study P00776)

Following multiple doses of Ezetimibe 10 mg once daily for 14 consecutive days to 8 healthy non-Japanese adult male and female subjects with mild hypercholesterolemia (serum LDL-C \geq 130 mg/dL), the effects of concomitant cholestyramine (4 g administered twice daily every 12 hours for 14 consecutive days) on plasma Ezetimibe concentrations at the last dose (Day 14) were investigated. The total Ezetimibe C_{\max} was 72.8 ng Eq/mL in the Ezetimibe+cholestyramine coadministration group, which was not different from 76.5 ng Eq/mL in the Ezetimibe alone group while the AUC was 333 ng•hr/mL in the Ezetimibe+cholestyramine coadministration group, which was markedly lowered compared to 755 ng•hr/mL in the Ezetimibe alone group. A similar trend was observed also for SCH60663. The coadministration of cholestyramine with Ezetimibe resulted in reductions in plasma Ezetimibe C_{\max} (5.77→1.61 ng/mL) and AUC (86.7→17.0 ng•hr/mL). Also when simvastatin was coadministered in addition to Ezetimibe+cholestyramine, decreases in these pharmacokinetic parameters were observed, but the extent of the decreases was comparable to that when Ezetimibe was coadministered with cholestyramine only.

6) Interactions with cyclosporine (Foreign Study 027, Foreign Study 057)

The plasma concentration-time profiles for total Ezetimibe and Ezetimibe after a single oral dose of Ezetimibe 10 mg in 8 non-Japanese post-renal transplant patients with steady-state blood cyclosporine concentrations, were compared with historical data (data on cyclosporine-untreated healthy adults who received a single oral dose of Ezetimibe) (Foreign Study 027). The plasma total Ezetimibe concentration was about 3.4-fold higher in post-renal transplant patients treated with cyclosporine than in healthy adults untreated with cyclosporine.

A crossover study in 12 healthy non-Japanese adult male and female subjects was conducted, where the pharmacokinetics of cyclosporine was compared between once daily oral administration of Ezetimibe 20 mg for 8 days with a single 100-mg dose of cyclosporine on Day 7 and a single 100-mg dose of cyclosporine alone (Foreign Study 057). Multiple dose administration of Ezetimibe resulted in about a 15%

increase in cyclosporine AUC.

(6) Pharmacokinetics/Pharmacodynamics in patients with hyperlipidemia

1) Phase I clinical study in hyperlipidemic volunteers (Japanese Study JPC-99-335-15)

Multiple oral doses of Ezetimibe 0.25, 1, and 10 mg and placebo were administered for 4 weeks to 40 otherwise healthy Japanese male subjects with hyperlipidemia aged ≥ 20 years and < 65 years. The trough plasma Ezetimibe and total Ezetimibe concentrations after 1, 2, 3, and 4 weeks of treatment were quantifiable at all timepoints at 10 mg only, which were 2.553, 2.669, 2.822, and 3.432 ng/mL and 20.058, 20.360, 17.980, and 23.430 ng Eq/mL, respectively. There were no significant differences between the timings of assessment for either plasma Ezetimibe concentrations or plasma total Ezetimibe concentrations. Mean LDL-C levels reached the minimum values after 2 weeks of treatment at all doses and the mean levels became steady by the end of Week 2-4. The percent change from baseline to the end of treatment in LDL-C was $-1.2 \pm 9.8\%$ in the placebo group, $-9.5 \pm 8.1\%$ in the Ezetimibe 0.25 mg group, $-10.3 \pm 10.7\%$ in the Ezetimibe 1 mg group, and $-20.9 \pm 8.0\%$ in the Ezetimibe 10 mg group.

<Outline of the review by the PMDA>

The outline of review by the PMDA is as follows.

(1) Justification for once daily administration

The applicant explained the frequency of dosing of Ezetimibe as follows:

In a phase I single dose study in healthy non-Japanese male volunteers (I96-088), the plasma concentration-time profiles exhibited multiple peaks, which was considered to be due to enterohepatic circulation and it was difficult to estimate the elimination phase half-life of plasma Ezetimibe and total Ezetimibe. Therefore, a 24-hour dosing interval for multiple dosing was chosen and the theoretical $t_{1/2}$ was calculated based on the accumulation ratio predicted from the ratio of the AUC at the last measurement timepoint (AUC_{0-72hr}) to the AUC_{0-24hr} observed after a single dose administration. As a result, the theoretical $t_{1/2}$ was 19-31 hours (Ezetimibe) and 16-24 hours (total Ezetimibe). Thus, judging that a once-daily regimen of Ezetimibe was adequate, subsequent clinical studies were all conducted with a once daily regimen. The above inference on the basis of the half-life of plasma drug concentration was grounded on the assumption that the action of Ezetimibe is based on systemic exposure. However, basic data obtained thereafter demonstrated that the site of action of Ezetimibe is the small intestinal wall and that an active metabolite excreted in bile (SCH60663) contributes significantly. Following once-daily administration of Ezetimibe, the small intestinal wall is persistently exposed to Ezetimibe due to enterohepatic circulation of SCH 60663, an active metabolite, as well as the direct exposure of the small intestinal wall, i.e. the site of action, which results in persistent inhibition of cholesterol absorption in the small intestine and reductions in blood LDL-C levels. Therefore, it is unnecessary to administer Ezetimibe at every meal and administration in divided doses in order to maintain adequate plasma drug concentrations has little therapeutic benefits. A phase I multiple-dose study (JPC-98-335-13) showed that the total cholesterol and LDL-C lowering effects peaked at 6 days after the start of treatment and persisted until 3 days after the end of treatment. This suggests that the small intestinal wall, the site of action, is persistently

exposed to Ezetimibe for at least 3 days. Since the incidence, nature, and severity of adverse events were similar among 5, 10, and 20 mg in a phase II study, it is inferred that the safety is also similar between twice-daily administration of 5 mg and once-daily administration of 10 mg, and there are also no particular safety benefits of administration in divided doses. Furthermore, a phase III study has confirmed that once-daily administration of Ezetimibe 10 mg is safe and well tolerated. As an anti-hypercholesterolemia drug is used over a long period of time, a once-daily regimen is very convenient in terms of maintaining long-term medication compliance.

The PMDA considers that a once-daily regimen of Ezetimibe is justified from a pharmacokinetic point of view.

(2) Food effects

The PMDA asked why administration after a meal has not been selected as the recommended dosage regimen of Ezetimibe despite the fact that the plasma C_{max} values of Ezetimibe and SCH60663 were both higher after a meal, as compared to those at the fasting state, in Study JPC-02-335-16 with the proposed commercial formulation and that Ezetimibe was to be administered after either breakfast, lunch, or evening meal in Studies JPC-02-335-33 and JPC-02-335-34.

The applicant responded as follows:

In a food effect study conducted in Japan with the proposed commercial formulation (JPC-02-335-16), there was no apparent effect of food on the AUC_{0-t} of SCH60663, which is inferred to contribute to the persistence of the therapeutic effect of Ezetimibe by undergoing enterohepatic circulation and the 90% confidence interval for the ratio of after a meal/fasting was 98.1-117%, and the 90% confidence interval for the Ezetimibe AUC_{0-t} ratio of after a meal/fasting was also 106-129%. Therefore, even when Ezetimibe is administered under fasting conditions, the amount of the drug undergoing enterohepatic circulation is not decreased markedly and it was judged that the therapeutic effect is very unlikely to be diminished under fasting conditions, as compared to after a meal. Furthermore, it was judged that the C_{max} values of both Ezetimibe and SCH60663 were about 1.6 fold higher after a meal, which is very likely to be a transient elevation due to an increase in hepatic blood flow, instead of an increase in the absorption of the drug by the gastrointestinal tract. Therefore, at least, based on the pharmacokinetic assessment, our judgment that it is not necessary to recommend “administration after a meal” was not wrong. However, in all of the phase II study and phase III studies such as the comparative study with colestimide (JPC-02-335-33) and the long-term treatment study (JPC-02-335-34), Ezetimibe was to be taken once daily after either breakfast, lunch, or evening meal and the efficacy and safety of Ezetimibe were assessed under a condition of higher systemic exposure. Therefore, although there is at least no effect on the safety, the fact that an adequate therapeutic effect of Ezetimibe administered under fasting conditions has not been confirmed in Japan can not be denied. Based on the above, Ezetimibe administration after a meal is considered preferable and we will change the proposed dosage regimen from “The usual adult dosage for oral use is 10 mg of Ezetimibe once daily” to “The usual adult dosage for oral use is 10 mg of Ezetimibe once daily after a meal.”

The PMDA asked about the effects of not employing a consistent timing of dosing across Japanese and foreign clinical studies on efficacy and safety data of Ezetimibe.

The applicant responded as follows:

A foreign phase II dose regimen study where Ezetimibe was administered once daily before a morning meal or at bedtime for 12 weeks (C98-258), confirmed that Ezetimibe produces similar effects regardless of the timing of dosing. Among Japanese clinical studies, the Full Analysis Set (FAS) data from the phase II Ezetimibe monotherapy study (10 mg group), the comparative study with colestimide (Ezetimibe 10 mg group), the glucose metabolism study, and the long-term treatment study (10 mg monotherapy) were combined and then the data stratified by administration after breakfast, lunch, and evening meal was compared. As a result, the mean percent changes in LDL-C were -17.8, -17.3, and -16.5%, respectively, which were similar regardless of the timing of dosing, and it seemed that the timing of dosing does not affect the efficacy. The safety data were compared between subjects taking the drug after breakfast and those taking the drug after evening meal since only a few subjects took the drug after lunch. As a result, similar adverse events occurred regardless of the timing of dosing and it was considered that the timing of dosing does not affect the nature of adverse events.

The PMDA judged that once-daily administration of Ezetimibe after a meal without specifying the timing of dosing (after breakfast, lunch, or evening meal) is appropriate.

(3) Effects of age and gender

The PMDA asked for the applicant's view on the use of Ezetimibe in elderly women, based on the results from pharmacokinetic studies (JPC-02-335-17, C98-115, C98-107) and safety information etc. from clinical studies stratified by age and gender.

The applicant responded as follows:

Plasma drug concentration data from Japanese women are not available. In foreign human pharmacokinetic studies (C98-107, C98-115, P00774, P01912, P00746, P00447, P00755, P00460, P01382, P00754, P00753, P00252, P00776), the C_{max} and AUC values of plasma Ezetimibe and SCH 60663 were particularly high in none of the age groups in men or women. Although the elderly group of ≥ 65 years contained no female subject, none of 5 relatively old female subjects aged 51-63 years had particularly high values. Among all subjects identified (167 subjects), comparison was made between men and women. As a result, there was a trend towards higher values in female subjects for all parameters and it was confirmed that the mean values were about 14-45% higher in female subjects. However, taking account of inter-individual variability of data, such differences were unlikely to directly affect the clinical efficacy and safety. Although gender differences in glucuronidation ability in humans have been reported in several publications (*Br J Clin Pharmacol* 54: 246-250, 2002, *Clin Pharmacol Ther* 73: 61-70, 2003, etc.), its relationship with the observed gender differences in plasma Ezetimibe concentrations is unknown. However, as there were no apparent gender differences in the AUC ratio of Ezetimibe to SCH60663, it was judged that there are no gender differences in the ability of glucuronidating Ezetimibe into SCH60663. Moreover, as there was no

noteworthy elevation of plasma drug concentrations also in relatively old women (age: 51-63 years), it was not considered necessary to take measures such as imposing a restriction on the use in elderly women or dosage adjustment, at least from a pharmacokinetic standpoint. Meanwhile, the pooled data from 5 studies including the Japanese phase II study, the comparative study with colestimide, the glucose metabolism study, the study in severe hypercholesterolemia, and the homozygous FH study, were examined from a clinical point of view. As a result, adverse events tended to occur more frequently in elderly subjects than in non-elderly subjects in both men and women while the incidence of adverse drug reactions was similar between non-elderly and elderly subjects. As to the severity of adverse events in elderly women, none of the events was severe and there were more mild events than moderate events. Based on the above, since there was no trend towards higher exposure to Ezetimibe in elderly women from a pharmacokinetic standpoint and there were no adverse events causing concerns about the use in elderly women also from a clinical point of view, it was judged that it is unnecessary to advise special caution about the use in elderly women.

The PMDA considered that the plasma Ezetimibe and SCH60663 concentrations after multiple-dose administration are higher in women even taking account of individual differences, but judged that such differences are not significant enough to affect the efficacy and safety of Ezetimibe and accepted the above response.

(4) Drug interactions

The PMDA asked about the mechanism of interactions between Ezetimibe and cyclosporine.

The applicant responded as follows:

Interactions between cyclosporine and Ezetimibe may be associated with a drug transporter and the excipients. Since both cyclosporine and Ezetimibe are substrates of P-glycoprotein, drug interactions occur possibly due to competitive antagonism, but there have been no remarkable Ezetimibe interactions with cimetidine, digoxin, simvastatin, lovastatin, and atorvastatin which are also substrates of P-glycoprotein. Thus, this possibility seems low. As the cyclosporine product is in the form of microemulsion, which contains surfactants (glycerol esters of fatty acids, polyoxyethylene hydrogenated castor oil) and a solubilizer (propylene glycol), coadministration of cyclosporine and Ezetimibe may result in increased oral bioavailability of Ezetimibe due to increased solubility. As the effects of cyclosporine on transporters, a mechanism of inhibiting sodium-independent organic anion transporter involved in the uptake of drugs into the liver, OATP2 (OATP-C, LST-1) has been suggested, and elevations of plasma concentrations of pravastatin and pitavastatin, which are substrates of OATP2 when coadministered with cyclosporine have been reported. Ezetimibe and SCH60663 are metabolized in the liver and excreted in bile, suggesting the involvement of some transporters, but whether or not Ezetimibe and SCH60663 serve as substrates for OATP2 is unknown at present.

The PMDA asked about interactions with concomitant drugs affecting bile acid excretion.

The applicant responded as follows:

A clinical drug interaction study with cholestyramine was conducted to investigate the effects of a concomitant drug affecting bile acid excretion. Cholestyramine binds bile acid in the small intestinal lumen and excretes it in feces, resulting in the prevention of reabsorption of bile acid, i.e. enterohepatic circulation. When Ezetimibe was coadministered with cholestyramine, the plasma Ezetimibe and SCH60663 AUC values were decreased to 1/5 and 1/2, respectively, compared with Ezetimibe alone. The mechanism of this drug interaction is considered to be the prevention of intestinal absorption due to Ezetimibe or SCH60663 bound by cholestyramine in the gastrointestinal tract, and an *in vitro* study has confirmed that both Ezetimibe and SCH60663 are highly bound to cholestyramine. Therefore, although the potential diminution of the therapeutic effects of Ezetimibe was suggested from an efficacy standpoint, the cholesterol absorption inhibitory effect was not diminished in the clinical drug interaction study of Ezetimibe with cholestyramine. However, caution about concomitant administration of Ezetimibe with anion-exchange resins (colestimide, cholestyramine, etc.) is advised in the PRECAUTIONS section of the proposed package insert, stating that dosing of Ezetimibe should occur either ≥ 2 hours before or ≥ 4 hours after the administration of an anion-exchange resin.

The PMDA considers that it is appropriate to include patients receiving treatment with cyclosporine in “Careful Administration” because the effects of concomitant cyclosporine on the pharmacokinetics of Ezetimibe are not small and therapeutic drug monitoring has a significant meaning for cyclosporine therapy although the involvement of OATP etc. in the interactions with cyclosporine is unknown. In clinical practice, Ezetimibe is likely to be coadministered with statins and it is also necessary to be aware of the fact that clinical interactions between statins and cyclosporine have been reported. Concerning concurrent administration of Ezetimibe with statins, coadministration with pitavastatin, which is approved only in Japan, had not been evaluated at the time of regulatory submission and the PMDA instructed the applicant to conduct a coadministration study with pitavastatin in view of the possibility that Ezetimibe will be coadministered with pitavastatin, and a drug interaction study was conducted. As a result, it was judged that no interactions between Ezetimibe and pitavastatin occur. Also for statins approved in Japan other than pitavastatin, based on the results of drug interaction studies, it was considered that there are no clinically relevant interactions between Ezetimibe/SCH60663 and statins. Although information on drug interactions should continuously be collected also after marketing, it was judged at present that clinically significant interactions are unlikely to occur from a pharmacokinetic standpoint except for interactions with the drugs against which caution is to be advised. (See 4. (iii) <Outline of review> “(4) Justification for dosage and dose regimen” for the effects on patients receiving treatment with antibiotics)

(5) Use in patients with hepatic impairment

The PMDA asked the applicant to consider whether Ezetimibe should be contraindicated in patients with moderate or severe hepatic impairment, in view of the effects of hepatic impairment on the pharmacokinetics of Ezetimibe.

The applicant responded as follows:

Following a single dose of Ezetimibe, the C_{max} and AUC values were about 3-4 fold higher in subjects with moderate or severe hepatic impairment than in healthy subjects, but the plasma drug concentrations did not keep rising after multiple dosing. In addition, no apparent causal relationship between plasma concentrations and the occurrence of adverse events was found. Thus, we think that including a statement “Use of Ezetimibe in patients with moderate or severe hepatic impairment is not recommended” in the package insert should be adequate. However, Child-Pugh classification for the severity of hepatic impairment will be added in the package insert.

The PMDA believes that the use of Ezetimibe in patients with moderate or severe hepatic impairment is not desirable, but will further consider the appropriateness of the use of Ezetimibe in patients with hepatic impairment, taking account of comments from the Expert Discussion. (See 4. (iii) <Outline of the review by the PMDA> “(4) Justification for dosage and dose regimen”)

(6) Use in patients with renal impairment

The PMDA asked the applicant to explain the relationship between the plasma drug concentrations and adverse drug reactions in patients with renal impairment because the plasma drug concentrations were higher in patients with renal impairment than in healthy adult subjects.

The applicant responded as follows:

The plasma Ezetimibe C_{max} and AUC values following a single oral dose of Ezetimibe 10 mg, were compared between patients with severe renal impairment (CL_{Cr} : 10-29 mL/min) and healthy adult subjects (CL_{Cr} : >80mL/min). As a result, the median values were higher in patients with renal impairment than in healthy adult subjects, but there was overlap of individual values, and there were no apparent differences. There were no differences in the AUC ratio of Ezetimibe to SCH60663 (% Ezetimibe/SCH60663) between healthy adult subjects and patients with renal impairment, suggesting that there are no differences in glucuronidation ability between patients with renal impairment and healthy adult subjects. Also, there were no major differences in the plasma drug concentrations between 5 subjects with adverse events and those without adverse events in this study.

The PMDA accepted the above response, judging that no dosage adjustment is required for patients with renal impairment because the plasma Ezetimibe concentration in humans is 1/5-1/10 of the plasma SCH60663 concentration, there were no differences in the AUC ratio of Ezetimibe to SCH60663 between healthy adult subjects and patients with renal impairment, and adverse events were not correlated with the plasma drug concentrations in patients with renal impairment.

(iii) Summary of clinical efficacy and safety

<Summary of the submitted data>

As Evaluation Data, the results from 6 Japanese phase I studies, 1 Japanese phase II study, 3 phase III comparative studies (1 Japanese study, 2 foreign studies), and 5 open-label or long-term treatment studies (4 Japanese studies, 1 foreign study) were submitted. The summary of the submitted data is presented

below.

(1) Japanese studies

1) Phase I single dose study (JPC-98-335-12), Studied Period: May 1998 to July 1998

In order to evaluate the safety and disposition kinetics of a single oral dose of Ezetimibe, single doses of 10, 20, and 40 mg (6 subjects each) of Ezetimibe tablet or placebo (9 subjects) were administered to 27 healthy male adults or otherwise healthy male adults with hyperlipidemia. Adverse events reported were pain pharynx in 1 subject and stools watery in 1 subject in the Ezetimibe 40 mg group and headache in 1 subject in the placebo group, which were all assessed as possibly related to the study drug, but were mild in severity and resolved without treatment. There were no changes in clinical laboratory test values, vital signs, body weight, or ECG findings reported as adverse events.

2) Phase I multiple-dose study (JPC-98-335-13), Studied Period: November 1998 to January 1999

The safety and pharmacokinetics of Ezetimibe was evaluated in a randomized, double-blind, parallel-group comparative study where healthy male adults or otherwise healthy male adults with hyperlipidemia received multiple oral doses of Ezetimibe 20 mg (9 subjects) or placebo (3 subjects) once daily before breakfast for 14 days. Eleven adverse events were reported by 7/9 subjects in the Ezetimibe group and of which, mild feeling hot, moderate nausea, and moderate anorexia (occurring in the same subject), one event of mild lumbar pain, 3 events of serum ALT increased, one event of white blood cell increased, and one event of antinuclear antibody increased were those events for which a causal relationship to Ezetimibe could not be denied. Adverse events for which a causal relationship to Ezetimibe was denied were one event of cortisol increased and one event of TSH increased.

3) Phase I clinical pharmacology study (JPC-99-335-15), Studied Period: August 1999 to January 2000

The effective dose range and safety of Ezetimibe were evaluated in a double-blind, parallel-group, comparative study, where 40 otherwise healthy male adults with hyperlipidemia (a serum LDL-C value ≥ 120 mg/dL and ≤ 220 mg/dL and a triglycerides value ≤ 400 mg/dL) were orally administered Ezetimibe 0.25, 1, and 10 mg or placebo (10 subjects per group) once daily immediately before breakfast for 4 weeks. The percent changes from baseline in LDL-C (the primary efficacy endpoint) in the placebo and Ezetimibe 0.25, 1, and 10 mg groups were $-1.2 \pm 9.8\%$ (Mean \pm SD), $-9.5 \pm 8.1\%$, $-10.3 \pm 10.7\%$, and $-20.9 \pm 8.0\%$, respectively. The incidences of adverse events were 40% (4/10 subjects), 10% (1/10 subjects), 40% (4/10 subjects), and 30% (3/10 subjects), respectively. Adverse events occurring in at least 2 subjects treated with Ezetimibe were pharynx redness of in 3 subjects, and serum ALT increased, nasal discharge, white blood cell increased, lymphopenia, and feeling hot (generalized) in 2 subjects each, which all resolved or improved without treatment.

4) Food effect study (JPC-02-335-16), Studied Period: February 2003 to April 2003

The pharmacokinetics of Ezetimibe and the effects of food on its bioavailability were investigated in a crossover study where 23 healthy adults received a single oral dose of Ezetimibe 10 mg. Seven adverse

events were reported by 7 subjects, which include white blood cell count increased in 4 subjects, ALT increased in 2 subjects, and platelet count increased in 1 subject, all of which resolved or improved without treatment. There were no serious adverse events. One event of white blood cell count increased and one event of ALT increased were those events for which a causal relationship to Ezetimibe could not be denied. (See 4. (ii) <Summary of the submitted data> “(4) Food effects”)

5) Pharmacokinetic study in elderly and non-elderly subjects (JPC-02-335-17), Studied Period: January 2003 to March 2003

The steady-state pharmacokinetics of Ezetimibe was compared between the elderly (12 subjects) and the non-elderly (12 subjects) in an open-label, parallel-group, comparative study where 24 male adults received multiple oral doses of Ezetimibe 10 mg tablet once daily for 10 days. Six adverse events occurred in 5 elderly subjects and 6 adverse events occurred in 5 non-elderly subjects, which include vertigo, arthritis, γ -glutamyltransferase (γ -GTP) increased, AST increased, blood amylase increased, and protein urine present, one subject each in the elderly subjects, and blood glucose increased in 2 subjects, and queasy, white blood cell count increased, blood glucose decreased, and blood phosphate increased in one subject each in the non-elderly subjects. These events all resolved or improved without treatment and there were no serious adverse events. Those events for which a causal relationship to Ezetimibe could not be denied were vertigo, γ -GTP increased, AST increased, and blood amylase increased in the elderly subjects and queasy and white blood cell count increased in the non-elderly subjects. (See 4. (ii) <Summary of the submitted data> “(3) Human pharmacokinetics in special populations”)

6) Phase II dose-finding study (JPC-00-335-21), Studied Period: October 2000 to September 2001

In order to determine the dose for a phase III study, the efficacy and safety of Ezetimibe were evaluated in a double-blind, parallel-group, comparative study, where Ezetimibe 5, 10, and 20 mg or placebo were orally administered once daily after a meal for 12 weeks in patients with hypercholesterolemia (men aged between 20 and 75 years or postmenopausal women). Patients were included in the study if their LDL-C values at the start of the baseline observation period were ≥ 140 mg/dL in the presence of risk factors for arteriosclerosis or ≥ 160 mg/dL in the absence of risk factors for arteriosclerosis. The study drug was to be taken once daily after either breakfast, lunch, or evening meal, but the timing of dosing had to be consistent throughout the treatment period, wherever possible. Concomitant use of serum lipid-lowering agents (statins, anion-exchange resins, probucol, fibrates, nicotinic acid preparations, eicosapentaenoic acid (EPA) preparations, and other serum lipid-lowering agents), various hormones (excluding preparations to be used for hormone replacement therapy or local treatment), antidepressants, antipsychotics, anti-obesity drugs, and immunosuppressive drugs was prohibited throughout the baseline observation phase (4 weeks, but 8 weeks for probucol only due to the persistence of the effect), the treatment phase (12 weeks), and the follow-up phase (4 weeks).

Of 171 subjects from whom consent was obtained, 138 subjects were randomized to study treatment, 136 subjects (Placebo group: 36 subjects, Ezetimibe 5 mg group: 34 subjects, Ezetimibe 10 mg group: 32 subjects, Ezetimibe 20 mg group: 34 subjects) were included in the FAS, and 128 subjects (Placebo group:

34 subjects, Ezetimibe 5 mg group: 32 subjects, Ezetimibe 10 mg group: 29 subjects, Ezetimibe 20 mg group: 33 subjects) were included in the Per Protocol Set (PPS). Two subjects were excluded from the FAS because they failed to take the study drug for at least 2 days prior to the study visit and their efficacy data were excluded. Eight subjects were excluded from the PPS because of the use of prohibited concomitant drugs in 7 subjects and violation as to the exclusion criteria in 1 subject. Treatment was discontinued due to the occurrence of adverse events in 7 subjects, suspected hypothyroidism in 1 subject, LDL-C value at the start of the treatment phase <140 mg/dL in 1 subject, and genital haemorrhage in 1 subject.

The percent changes in LDL-C from baseline (at the start of the treatment phase) to the end of the treatment phase (or at withdrawal) in the FAS, the primary efficacy endpoint, are as shown in the following table.

Percent change in LDL-C

	Placebo (n=36)	5 mg (n=34)	10 mg (n=32)	20 mg (n=34)
LDL-C value at baseline (mg/dL)	181.2±37.51	178.1±34.80	181.0±29.34	179.1±23.70
LDL-C value at the end of the treatment (mg/dL)	175.1±36.47	149.9±28.24	147.4±27.64	143.5±21.29
Percent change (%)	-2.3±15.38	-14.9±12.07	-18.1±10.86	-19.2±11.49

Mean±SD

The proportion of subjects with a reduction of LDL-C to less than 140 mg/dL at the end of the treatment phase (or at withdrawal), which was the secondary endpoint, was 14% (5/36 subjects) in the placebo group, 35% (12/34 subjects) in the Ezetimibe 5 mg group, 44% (14/32 subjects) in the Ezetimibe 10 mg group, and 53% (18/34 subjects) in the Ezetimibe 20 mg group. The proportion of subjects with a ≥15% reduction in LDL-C from baseline to the end of the treatment phase (or at withdrawal) was 19% (7/36 subjects) in the placebo group, 56% (19/34 subjects) in the Ezetimibe 5 mg group, 66% (21/32 subjects) in the Ezetimibe 10 mg group, and 65% (22/34 subjects) in the Ezetimibe 20 mg group. There were no major changes in triglycerides or HDL-C in any of the treatment groups.

One hundred thirty-eight subjects treated with the study drug were included in the safety analysis. Adverse events occurred in 72% (26/36 subjects) of the placebo group, 57% (20/35 subjects) of the Ezetimibe 5 mg group, 69% (22/32 subjects) of the Ezetimibe 10 mg group, and 66% (23/35 subjects) of the Ezetimibe 20 mg group. Adverse events occurring in at least 2 subjects treated with Ezetimibe were blood CK increased, γ-GTP increased, blood testosterone decreased, ALT increased, blood amylase increased, white blood cell count increased, protein urine present, nasopharyngitis, abdominal pain, diarrhoea, dyspepsia, myalgia, arthralgia, headache, dizziness postural, contact dermatitis, seasonal allergy, and rhinitis seasonal. Blood CK increased occurred in 1 subject (3%) in the placebo group, 4 subjects (11%) in the Ezetimibe 5 mg group, 3 subjects (9%) in the Ezetimibe 10 mg group, and 2 subjects (6%) in the Ezetimibe 20 mg group, which were all mild in severity. Serious adverse events reported were varicella in the Ezetimibe 5 mg group and diverticulitis intestinal and arthralgia in the Ezetimibe 10 mg group and a causal relationship to the study drug was denied for all three cases. A total of 7 subjects discontinued treatment due to adverse

events: serious adverse events in 2 subjects (Ezetimibe 10 mg group: diverticulitis intestinal and severe arthralgia) and significant adverse events in 5 subjects (placebo group: acute abdomen in 1 subject, Ezetimibe 5 mg group: hepatic disorder aggravated in 1 subject, diarrhoea and queasy in 1 subject, anorexia and fatigue in 1 subject, Ezetimibe 20 mg group: abdominal pain in 1 subject). As for the five cases of significant adverse events, hepatic disorder aggravated was considered the natural history of concurrent illness and its causal relationship to the study drug was denied and in the other 4 cases, the symptoms resolved following the discontinuation of the study drug and a causal relationship to the study drug was not denied.

Taking account of the efficacy and safety results, the applicant judged that the recommended clinical dose of Ezetimibe is 10 mg, once daily and selected it as the dose for a phase III study.

7) Phase III double-blind comparative study (JPC-02-335-33), Studied Period: May 2002 to May 2003

A randomized, double-blind, parallel-group, comparative study in patients with hypercholesterolemia was conducted to confirm the non-inferiority of Ezetimibe 10 mg/day over colestimide 3g/day in terms of efficacy. The observation period was 4 weeks and the treatment period was 12 weeks. One Ezetimibe 10 mg tablet (or matching placebo) was taken once daily after either breakfast, lunch, or evening meal (consistent throughout the treatment phase). The inclusion criteria were 20 years or older; both LDL-C values obtained at two timepoints, i.e. at the start of the observation phase and at the start of the treatment phase, met the following criteria for initiating drug therapy and the difference between the two values was ≤ 35 mg/dL. Subjects were excluded from the study if their washout period was less than 4 weeks for statins, anion-exchange resins, fibrates, nicotinic acid, and EPA preparations or less than 8 weeks for probucol, at the start of the observation phase.

Criteria for initiating drug therapy

Category			LDL-C value
A	Coronary artery disease ^{a)} Other risk factors ^{b)}	No No	≥ 160 mg/dL
B	Coronary artery disease Other risk factors	No Yes	≥ 140 mg/dL
C	Coronary artery disease Other risk factors	Yes Yes or No	≥ 120 mg/dL

- A) Patients are determined to have “coronary artery disease” if any of the following apply.
 - (a) Myocardial infarction, (b) Angina pectoris, (c) Silent myocardial ischemia, (d) Coronary angiography shows a significant stenosis.
- B) Patients are determined to have “a risk factor for arteriosclerosis other than hypercholesterolemia” if any of the following apply.
 - (a) Aging (Male: ≥ 45 years, Female: Postmenopausal), (b) Family history of coronary artery disease,
 - (c) Smoking habit: even one cigarette, (d) Hypertension (≥ 140 and/or 90 mmHg, JNC-V criteria),
 - (e) Obesity (BMI ≥ 26.4), (f) Impaired glucose tolerance (Borderline type or Diabetic type according to the criteria issued by the Japan Diabetes Society),
 - (g) Hypertriglyceridemia (fasting triglycerides ≥ 150 mg/dL),
 - (h) Low HDL-cholesterol (< 40 mg/dL)

Of 307 subjects from whom consent was obtained, 235 subjects were randomized to study treatment (Ezetimibe group: 119 subjects, colestimide group: 116 subjects) and 42 subjects of the 235 subjects (21 subjects and 21 subjects, respectively) were withdrawn from the study. The reasons for withdrawal from the study were failure to meet the inclusion criteria in 31 subjects (18 subjects and 13 subjects, respectively), adverse events in 8 subjects (2 subjects and 6 subjects, respectively), difficulty in taking a medicine orally in 1 subject (Ezetimibe group), violations as to the study procedure in 1 subject (colestimide group), and consent withdrawal in 1 subject (colestimide group). After 19 subjects in the Ezetimibe group and 14 subjects in the colestimide group were excluded due to “failure to meet the inclusion criteria,” “no dose of Ezetimibe or colestimide taken” or “violations as to the formal registration procedure,” 202 subjects (100 subjects and 102 subjects, respectively) were included in the FAS. After excluding subjects with violations as to prohibited concomitant drugs (1 subject in the Ezetimibe group), those who took the study drug for an inadequate duration (2 subjects and 4 subjects, respectively), and those who had inadequate drug compliance (1 subject and 1 subject, respectively), 193 subjects (96 subjects and 97 subjects, respectively) were included in the PPS. The number of subjects classified as Category B of the criteria for initiating drug therapy was 92/100 subjects (92.0%) in the Ezetimibe group and 98/102 subjects (96.1%) in the colestimide group, and the number of subjects classified as Category C was 7/100 subjects (7.0%) in the Ezetimibe group and 1/102 subjects (1.0%) in the colestimide group. The number of subjects with concurrent diabetes was 27/100 subjects (27.0%) in the Ezetimibe group and 21/102 subjects (20.6%) in the colestimide group.

The percent changes from baseline (at the start of the treatment phase) to the end of study treatment (at the end of the treatment phase or at withdrawal) in LDL-C, the primary efficacy endpoint, are as shown in the following table. The between-treatment difference (Ezetimibe group - colestimide group) was 1.13% and its 95% confidence interval was -2.23 to 4.50%, which was less than the predefined upper equivalence margin for non-inferiority (7%). An equivalence margin of 7% was chosen as a value smaller than half the absolute value of the difference in the mean percent change from baseline in LDL-C at the end of treatment between Ezetimibe 10 mg and placebo in a Japanese phase II dose-finding study (-15.8%).

Percent change from baseline to the end of treatment in LDL-C

	Ezetimibe	colestimide	Difference between arms (95% confidence interval)
Baseline (mg/dL)	175.2±25.64(n=100)	179.5±28.36(n=102)	
End of the treatment (mg/dL)	143.1±26.26(n=97)	144.6±30.40(n=99)	
Percent change (%)	-18.05±10.96(n=97)	-19.18±12.82(n=99)	1.13(-2.23-4.50)

Mean±SD

The proportion of subjects with a $\geq 15\%$ reduction in LDL-C, which was the secondary endpoint, was 65.0% (65/100 subjects) in the Ezetimibe group and 62.7% (64/102 subjects) in the colestimide group and the between-treatment difference (95% confidence interval) was 2.3% (-10.99 to 15.50%). The proportion

of subjects achieving LDL-C goals was 13.0% (13/100 subjects) in the Ezetimibe group and 17.6% (18/102 subjects) in the colestimide group and the between-treatment difference (95% confidence interval) was -4.6% (-14.56 to 5.26%). With respect to serum lipids and serum proteins other than LDL-C, triglycerides were not altered by Ezetimibe ($141.9 \pm 81.89 \rightarrow 123.7 \pm 57.07$ mg/dL) and were elevated by colestimide ($134.2 \pm 59.63 \rightarrow 143.7 \pm 80.01$ mg/dL). HDL -C was increased in both the Ezetimibe group ($59.4 \pm 13.08 \rightarrow 62.4 \pm 13.26$ mg/dL) and the colestimide group ($59.2 \pm 13.04 \rightarrow 64.6 \pm 15.65$ mg/dL).

The safety analysis population included 234 subjects who received at least one dose of the study drug and the incidence of adverse events was 58.5% (69/118 subjects) in the Ezetimibe group and 69.0% (80/116 subjects) in the colestimide group. The adverse events occurring in the Ezetimibe group were all mild or moderate in severity. In the colestimide group, 5 severe adverse events were reported by 3 subjects, which include constipation aggravated, back pain, dizziness, anxiety, and insomnia exacerbated, and the remaining adverse events were mild or moderate. The main adverse events reported in the Ezetimibe group were nasopharyngitis (14.4%: 17/118 subjects), blood CK increased (5.9%: 7/118 subjects), constipation, diarrhoea, and ALT increased (4.2%: 5/118 subjects). The main adverse events reported in the colestimide group were nasopharyngitis (15.5%: 18/116 subjects), constipation and γ -GTP increased (11.2%: 13/116 subjects), ALT increased (10.3%: 12/116 subjects), upper respiratory tract inflammation (7.8%: 9/116 subjects), and back pain (4.3%: 5/116 subjects). There were no deaths or serious adverse events. Two subjects in the Ezetimibe group (“haematochezia,” “epigastric discomfort, anorexia”) and 6 subjects in the colestimide group (“skin rash,” “constipation aggravated, queasy, weakness, abnormal sensation in eye,” “queasy,” “constipation,” “back pain,” “dizziness aggravated”) discontinued study treatment and a causal relationship to the study drug could not be denied for all events other than skin rash in the colestimide group, but all improved following the discontinuation of study drug.

8) Uncontrolled study investigating the effects on glucose metabolism (JPC-02-335-35), Studied Period: May 2002 to May 2003

In order to investigate the effects of Ezetimibe on lipid metabolism and glucose metabolism, an uncontrolled study was conducted in hypercholesterolemic patients with type II diabetes (the difference between the HbA_{1c} values obtained at 2 timepoints, i.e. at the start of the observation phase and at the start of the treatment phase, was within $\pm 1\%$). The inclusion criteria as to hypercholesterolemia were the same as in a phase III double-blind comparative study (JPC-02-335-33) and a 4-week observation period was followed by a 12-week treatment with Ezetimibe 10 mg/day (orally administered after either breakfast, lunch, or evening meal). Thirty subjects received Ezetimibe and 27 subjects excluding 3 subjects who failed to meet the criteria for initiating drug therapy, completed treatment and were included in the analysis. Insulin preparations were used in 5/27 subjects (18.5%). The percent changes from baseline (at the start of the treatment phase) in LDL-C at the end of study treatment (at the end of the treatment phase or at withdrawal), which was the primary efficacy endpoint, are as shown in the following table.

Percent change from baseline in LDL-C at the end of treatment

Timepoints for measurement	N	Mean±SD (mg/dL)	Percent change (%)	95% confidence interval for percent change (%)
Baseline	27	169.1±17.33	-15.09	-19.92 to -10.26
End of the treatment	27	143.0±22.00		

Triglycerides level was 148.8±69.36 mg/dL at baseline and 115.3±42.89 mg/dL at the end of treatment, and HDL-C level was 50.4±11.92 mg/dL at baseline and 54.6±10.31 mg/dL at the end of treatment. The effects on glucose metabolism are as shown in the following table.

Change and Percent change from baseline in laboratory tests related to glucose metabolism at the end of treatment

Parameter	n	Timepoints for measurement	Mean±SD	Change		Percent change (%)	
				Mean	95% confidence interval	Mean	95% confidence interval
HbA _{1c} (%)	27	Baseline	6.86±0.873	0.15	-0.03 - 0.33	1.88	-0.54 - 4.30
		End of the treatment	7.00±1.123				
Glycoalbumin (%)	27	Baseline	20.42±3.581	-0.11	-0.75 - 0.52	-0.56	-3.45 - 2.32
		End of the treatment	20.31±3.902				
Fasting blood glucose (mg/dL)	27	Baseline	136.4±37.77	16.3	6.4 - 26.1	14.48	5.54 - 23.42
		End of the treatment	152.7±38.47				
Insulin (μU/mL)	22*	Baseline	9.99±6.299	-0.44	-2.60 - 1.72	12.50	-8.60 - 33.60
		End of the treatment	9.55±4.328				
HOMA index [†]	22*	Baseline	3.76±3.184	-0.08	-1.08 - 0.92	21.96	-4.45 - 48.36
		End of the treatment	3.68±2.086				

*: Subjects who did not use insulin preparations were assessed.

†: HOMA index = Fasting blood glucose × Insulin / 405

When subjects were stratified by the use of insulin preparations into subgroups, the change in HbA_{1c} from baseline to the end of treatment was 7.26±0.770 (Mean±SD)→7.74±1.313% with concomitant insulin preparations and 6.76±0.885→6.84±1.037% without concomitant insulin preparations. The change in glycoalbumin from baseline to the end of treatment was 21.20±2.941→22.04±3.611% with concomitant insulin preparations and 20.25±3.748→19.92±3.936% without concomitant insulin preparations. The change in fasting blood glucose from baseline to the end of treatment was 101.4±22.10→148.0±38.53 mg/dL with concomitant insulin preparations and 144.4±36.26→153.7±39.28 mg/dL without concomitant insulin preparations.

With regard to the safety, the proportion of subjects with any adverse event was 67% (20/30 subjects) and

there were no serious adverse events. Adverse events occurring in at least 2 subjects were blood CK increased (10%: 3/30 subjects), nasopharyngitis (10%: 3/30 subjects), abdominal distension (10%: 3/30 subjects), abdominal pain (7%: 2/30 subjects), constipation (7%: 2/30 subjects), flatulence (7%: 2/30 subjects), and hepatic cyst (7%: 2/30 subjects).

9) Ezetimibe+statin combination therapy study in patients with severe hypercholesterolemia (JPC-02-335-36), Studied Period: May 2002 to February 2003

In order to evaluate the efficacy and safety of Ezetimibe coadministered with a statin, an uncontrolled study was conducted in patients with severe hypercholesterolemia receiving a statin, where a 4-week observation period was followed by a 12-week combination therapy with Ezetimibe 10 mg (orally administered after either breakfast, lunch, or evening meal) and a statin. The inclusion criteria were patients with a diagnosis of heterozygous familial hypercholesterolemia (heterozygous FH) or patients with severe hypercholesterolemia other than FH (patients who previously had a total cholesterol level of ≥ 260 mg/dL, but was not diagnosed with FH); LDL-C values on statin therapy obtained at 2 timepoints, i.e. at the start of the observation phase and at the start of the treatment phase, did not meet the treatment targets as specified in the following table; patients had been taking a certain statin at a stable dosage regimen for at least 4 weeks at the start of the observation phase; and outpatients. Concomitantly used statins were pravastatin in 18 subjects (5 mg: 8 subjects, 10 mg: 6 subjects, 20 mg: 2 subjects, 30 mg: 2 subjects), atorvastatin in 20 subjects (5 mg: 1 subject, 10 mg: 12 subjects, 20 mg: 6 subjects, 40 mg: 1 subject), simvastatin in 1 subject (10 mg), and fluvastatin in 1 subject (20 mg).

Treatment targets (Subjects were categorized at the start of the observation phase)

Category			LDL-C value
A	Coronary artery disease	No	<140 mg/dL
	Other risk factors	No	
B	Coronary artery disease	No	<120 mg/dL
	Other risk factors	Yes	
C	Coronary artery disease	Yes	<100 mg/dL
	Other risk factors	Yes or No	

Ezetimibe was administered to 40 subjects (heterozygous FH: 30 subjects, other than FH: 10 subjects) and 39 subjects excluding 1 subject with heterozygous FH who failed to meet the inclusion criteria, completed the 12-week treatment.

The percent changes in LDL-C from baseline (at the start of the treatment phase) to the end of study treatment (at the end of the treatment phase or at withdrawal), the primary efficacy endpoint, are as shown in the following table.

Percent change from baseline in LDL-C at the end of treatment

Subjects	Timepoints for measurement	LDL-C ^a (mg/dL)	Percent change (%)	95% confidence interval for percent change (%)
All subjects (n=39)	Baseline	184.8±52.32	-22.97	-26.12 to -19.81
	End of the treatment ^b	142.8±42.87		
Heterozygous FH (n=29)	Baseline	199.9±51.25	-22.04	-24.99 to -19.10
	End of the treatment ^b	155.4±39.20		
Other than FH (n=10)	Baseline	141.1±22.93	-25.65	-35.82 to -15.48
	End of the treatment	106.1±31.09		

a: Mean±SD

b: Data at Treatment Week 8 was included for subjects 1-6.

The proportion of subjects with a $\geq 15\%$ reduction in LDL-C, which was the secondary endpoint, was 82% (32/39 subjects) in all subjects, 86% (25/29 subjects) in patients with heterozygous FH, and 70% (7/10 subjects) in patients with severe hypercholesterolemia other than FH. The proportion of subjects achieving their LDL-C goals was 28% (11/39 subjects), 14% (4/29 subjects), and 70% (7/10 subjects), respectively, and the 95% confidence interval was 14-42%, 1-26%, and 42-98%, respectively. The change in triglycerides from baseline to the end of treatment was 112.0±63.88 (Mean±SD)→97.6±44.05 mg/dL in all subjects, 104.7±49.34→92.4±35.79 mg/dL in patients with heterozygous FH, and 133.1±94.83→112.6±62.23mg/dL in patients with severe hypercholesterolemia other than FH, and the change in HDL-C from baseline to the end of treatment was 52.6±16.51→52.4±15.80 mg/dL, 51.5±17.03→50.2±15.34 mg/dL, and 55.9±15.26→58.7±16.15 mg/dL, respectively.

With regard to the safety, adverse events occurred in 75% (30/40 subjects) of the all subjects, 76.7% (23/30 subjects) of those with heterozygous FH, and 70% (7/10 subjects) of those with severe hypercholesterolemia other than heterozygous FH. There were no deaths or serious adverse events. Adverse events occurring in at least 2 subjects were nasopharyngitis in 8 subjects (20%), protein urine present in 4 subjects (10%), blood cortisol increased in 3 subjects (7.5%), abdominal distension in 2 subjects (5%), upper abdominal pain in 2 subjects (5%), dyspepsia in 2 subjects (5%), pharyngolaryngeal pain in 2 subjects (5%), stomatitis in 2 subjects (5%), ALT increased in 2 subjects (5%), blood CPK increased in 2 subjects (5%), and cough in 2 subjects (5%).

10) Ezetimibe+statin combination therapy study in patients with homozygous familial hypercholesterolemia (JPC-02-335-32), Studied Period: April 2002 to December 2002

An uncontrolled study of Ezetimibe 10 mg administered once daily after either breakfast, lunch, or evening meal for a total of 12 weeks in patients with homozygous FH on statin therapy undergoing LDL apheresis (6 subjects) was conducted to evaluate the efficacy and safety of Ezetimibe in combination with a statin. The inclusion criteria were patients with homozygous FH aged 16 years or older; patients undergoing LDL apheresis once weekly or once every 2 weeks under a certain condition; and patients who had been taking a

certain statin at a stable dosage regimen for at least 4 weeks at the start of the observation phase. A 2-week or 4-week observation phase was included according to the interval of LDL apheresis and the patients were to continue the same statin as used before throughout the study period. Concerning other serum lipid lowering agents, the concomitant use of anion-exchange resins and fibrates was prohibited while concomitant probucol was permitted if patients had been taking probucol at a stable dosage regimen for at least 8 weeks at the start of the observation phase.

Of the 6 subjects, 5 subjects excluding 1 subject who was withdrawn from the study at Treatment Week 11 due to LDL apheresis schedule, completed the 12-week treatment. Efficacy data for 1 subject was excluded because the condition of LDL apheresis, etc. was changed after the start of study treatment. Concomitantly used statins were atorvastatin in 5 subjects (10 mg: 1 subject, 20 mg: 3 subjects, 40 mg: 1 subject) and simvastatin in 1 subject (10 mg). The change in LDL-C from baseline to the end of treatment was 391.5 ± 43.40 (Mean \pm SD) \rightarrow 354.6 ± 47.39 mg/dL, and the percent change in LDL-C from baseline to the end of study treatment, which was the primary efficacy endpoint, was -9.57% and its 95% confidence interval was -14.11% to -5.03%. The change from baseline to the end of treatment in triglycerides was 107.3 ± 52.80 \rightarrow 113.6 ± 61.40 mg/dL and the change from baseline to the end of treatment in HDL-C was 30.7 ± 8.56 \rightarrow 28.3 ± 7.50 mg/dL.

With regard to the safety, 19 adverse events occurred in 5 out of 6 subjects, but there were no deaths or serious adverse events and no adverse events resulted in a subject's withdrawal from the study. There were queasy in 3 subjects, fatigue, cough, and protein urine present in 2 subjects each, AST increased, ALT increased, electrocardiogram QT prolonged, nasopharyngitis, upper respiratory tract infection, hypoesthesia, malaise, productive cough, supraventricular extrasystoles, and decreased appetite in 1 subject each.

11) Long-term treatment study (JPC-02-335-34), Studied Period: May 2002 to February 2004

A multicenter (34 study sites), uncontrolled study in 179 patients with hypercholesterolemia (Target number of cases: 150) was conducted to evaluate the safety and efficacy of long-term treatment with Ezetimibe and the safety and efficacy of Ezetimibe in combination with a statin. The inclusion criteria were at least 20 years old; both LDL-C values obtained at 2 timepoints, i.e. at the start of the observation phase and at the start of the treatment phase met the criteria for initiating drug therapy as in a phase III double-blind comparative study (JPC-02-335-33). Ezetimibe 10 mg was to be administered once daily after either breakfast, lunch, or evening meal for 52 weeks following a 4-week observation phase. If LDL-C levels after Treatment Week 12 were not reduced to less than the treatment targets, concomitant statin (either pravastatin 10 mg, simvastatin 5 mg, fluvastatin 20 mg, or atorvastatin 10 mg) was permitted after Treatment Week 16 as needed.

Consent was obtained from 219 subjects, 179 subjects were formally registered, 178 subjects received study treatment, and 140 subjects (Ezetimibe monotherapy: 77 subjects, combination therapy with pravastatin: 11 subjects, combination therapy with simvastatin: 7 subjects, combination therapy with

fluvastatin: 26 subjects, combination therapy with atorvastatin: 19 subjects) completed the 52-week treatment. Thirty-eight subjects were withdrawn from the study and of which, 25 subjects were withdrawn before the end of Week 16 (failure to meet the inclusion criteria in 15 subjects, the occurrence of adverse events in 9 subjects, consent withdrawal in 1 subject), and 13 subjects in total including 9 subjects on monotherapy and 4 subjects on combination therapy were withdrawn after Week 16 (the occurrence of adverse events in 7 subjects, consent withdrawal in 3 subjects, inadequate efficacy of Ezetimibe monotherapy in 2 subjects, inadequate efficacy even after concomitant use of statin in 1 subject). The efficacy analysis population included 163 subjects, since 15 subjects who failed to meet the inclusion criteria at the start of the treatment phase were excluded from total 178 subjects treated with Ezetimibe, and the safety analysis population included 178 subjects treated with Ezetimibe.

Regarding the subject background, 67 subjects received combination therapy with statins, and according to WHO phenotypic classification, the percentage of subjects with type IIa was 61.3% (100/163 subjects) in all subjects and 47.8% (32/67 subjects) in subjects on combination therapy, and the percentage of subjects with type IIb was 38.7% (63/163 subjects) in all subjects and 52.2% (35/67 subjects) in subjects on combination therapy. In terms of familial forms, the percentage of subjects with FH was 6.1% (10/163 subjects) in all subjects and 9.0% (6/67 subjects) in subjects on combination therapy, the percentage of subjects with familial combined hyperlipidemia was 1.2% (2/163 subjects) in all subjects and 3.0% (2/67 subjects) in subjects on combination therapy, and the percentage of subjects with non-familial hypercholesterolemia was 91.4% (149/163 subjects) in all subjects and 86.6% (58/67 subjects) in subjects on combination therapy. The percentage of subjects with concurrent diabetes was 27.0% (44/163 subjects) in all subjects and 25.4% (17/67 subjects) in subjects on combination therapy, and 57.7% (94/163 subjects) of all subjects and 67.2% (45/67 subjects) of subjects on combination therapy had used serum lipid lowering agents within 12 weeks prior to the start of the observation phase.

The percent changes from baseline (at the start of the treatment phase) to the end of study treatment in LDL-C, the primary efficacy endpoint, are shown in the following table.

Percent change in LDL-C

Analysis population	LDL-C			
	Baseline (mg/dL)	End of the treatment (mg/dL)	Percent change (%)	95% confidence interval for percent change (%)
Ezetimibe monotherapy (n=163)	184.6±35.92 (n=163)	152.5±32.19 (n=161)	-16.8	-18.5 to -15.1
Combination therapy with statins (n=67)	197.5±37.94 (n=67)	End of the monotherapy 165.7±32.33 (n=67)	-15.3	-18.2 to -12.3
		End of the combination therapy 128.8±33.31 (n=65)	-33.5	-37.5 to -29.5

Mean±SD

LDL-cholesterol values after 4-52 weeks of Ezetimibe monotherapy were within a range of 135.7-152.4 mg/dL and the percent changes in LDL-cholesterol were within a range of -21.6 to -16.9%, and there was no diminution of the effect during prolonged treatment.

The proportion of subjects with a $\geq 15\%$ reduction in LDL-C from baseline to the end of study treatment was 58.3% (95/163 subjects) for Ezetimibe monotherapy and 91.0% (61/67 subjects) for combination therapy and the 95% confidence interval was 50.7-65.9% and 84.2-97.9%, respectively. The proportion of subjects achieving their LDL-C goals was 8.0% (13/163 subjects) for Ezetimibe monotherapy and 35.8% (24/67 subjects) for combination therapy, and the 95% confidence interval was 3.8-12.1% and 24.3-47.3%, respectively. In the Ezetimibe monotherapy group, the change in triglycerides from baseline to the end of treatment was 144.4±68.00 (Mean±SD)→137.1±68.86 mg/dL and the change in HDL-C from baseline to the end of treatment was 58.5±15.66→60.8±15.24 mg/dL. In the combination therapy group, the change in triglycerides from baseline to the end of treatment was 160.3± 63.00→126.5±49.83 mg/dL and the change in HDL-C from baseline to the end of treatment was 55.0±13.15→58.5±11.93 mg/dL.

When broken down by concomitant statin, the baseline LDL-C levels for pravastatin 10 mg, simvastatin 5 mg, fluvastatin 20 mg, and atorvastatin 10 mg were 183.5±21.25, 206.1±30.61, 187.7±36.11, and 213.7±45.19 mg/dL, respectively, the LDL-C levels at the end of monotherapy were 157.5±30.82 (Percent change: -14.4%), 166.3±30.69 (-19.0%), 157.0±21.87 (-14.6%), and 181.4±40.66 mg/dL (-14.7%), respectively, and the LDL-C levels at the end of combination therapy were 130.6±16.82 (-28.4%), 125.7±29.18 (-37.8%), 130.5±30.70 (-29.1%), and 126.9±45.67 mg/dL (-40.5%), respectively.

The overall incidence of adverse events was 89.3% (159/178 subjects), and the incidence of adverse events during Ezetimibe monotherapy was 84.3% (150/178 subjects) and the incidence of adverse events during

combination therapy with statins was 80.6% (54/67 subjects). Adverse events occurring in at least 2% of subjects during Ezetimibe monotherapy were nasopharyngitis (36.0%, 64 subjects), blood CK increased (10.1%, 18 subjects), γ -GTP increased (9.0%, 16 subjects), arthralgia (8.4%, 15 subjects), back pain (7.9%, 14 subjects), ALT increased, headache, skin rash (5.6%, 10 subjects), upper respiratory tract inflammation (5.1%, 9 subjects), palpitations, abdominal distension, constipation, loose stools, white blood cell count increased, cough (3.9%, 7 subjects), diarrhoea, queasy, dental caries, blood LDH increased, insomnia (3.4%, 6 subjects), pharyngolaryngeal pain, stomatitis, chest pain, cystitis, laryngopharyngitis, AST increased, white blood cell count decreased, muscle stiffness, pain in extremity, eczema, contusion (2.8%, 5 subjects), cataract, toothache, abdominal pain lower, abdominal pain upper, malaise, tinea pedis, blood amylase increased, blood bilirubin increased, blood cortisol increased, blood pressure increased, blood urea increased, dizziness, and hypoaesthesia (2.2%, 4 subjects). Adverse events occurring during combination therapy with statins and at an incidence greater than Ezetimibe monotherapy were γ -GTP increased (13.4%, 9 subjects), blood CK increased, headache, ALT increased (10.4%, 7 subjects), arthralgia (9.0%, 6 subjects), seasonal allergy, AST increased (7.5%, 5 subjects), chest pain (6.0%, 4 subjects), blood amylase increased, hypoaesthesia (4.5%, 3 subjects), gingivitis, blood cortisol increased, blood TSH increased, protein urine present, and pruritus (3.0%, 2 subjects), etc.

The time to onset of adverse events was <3 months in 69.7% (124/178 subjects) of all subjects, \geq 3 months and <6 months in 67.7% (105/155 subjects) of all subjects, \geq 6 months and <9 months in 65.3% (98/150 subjects) of all subjects, and \geq 9 months in 60.7% (88/145 subjects) of all subjects, and <3 months in 69.7% (124/178 subjects) of those on monotherapy, \geq 3 months and <6 months in 61.9% (96/155 subjects) of those on monotherapy, \geq 6 months and <9 months in 50.0% (59/118 subjects) of those on monotherapy, and \geq 9 months in 58.5% (48/82 subjects) of those on monotherapy, and \geq 3 months and <6 months in 48.4% (15/31 subjects) of those on combination therapy, \geq 6 months and <9 months in 64.1% (41/64 subjects) of those on combination therapy, and \geq 9 months in 56.3% (36/64 subjects) of those on combination therapy.

One death occurred during the study (68-year-old man), but a causal relationship to the study drug was denied for observed adverse events as well as the death. In addition, eleven serious adverse events were reported by 10 subjects. Of the 11 serious adverse events, 10 events occurred in 9 subjects during Ezetimibe monotherapy, which includes angina unstable, sudden hearing loss, accident, cartilage injury, blood CK increased, prostate cancer and ileus paralytic (in the same subject), breast cancer, blepharoplasty, and hypertension. All of these events except for blood CK increased were those for which a causal relationship to Ezetimibe was denied. One serious adverse event reported by 1 subject during combination therapy was breast cancer recurrent. The following adverse events in 16 subjects led to the discontinuation of Ezetimibe: the above-mentioned death, prostate cancer, blood CK increased, breast cancer, accident (motor vehicle accident while crossing the road on a red signal due to carelessness, not consciousness disturbance or psychiatric disorder), abdominal pain lower and diarrhoea, photodermatitis, arthralgia and cystitis, diarrhoea, pompholyx, arthralgia, stomach erosion • reflux oesophagitis and abdominal pain lower, rash, AST • ALT • γ -GTP increased, queasy and loose stools, and prurigo. Of which, blood CK increased, abdominal pain lower and diarrhoea, diarrhoea, arthralgia, stomach erosion • reflux oesophagitis and

abdominal pain lower, rash, AST • ALT • γ -GTP increased, queasy and loose stools, and prurigo were those for which a causal relationship to Ezetimibe could not be denied.

Concerning the liver function, AST elevations to 2 to <3 times the upper reference limit were observed in 0.6% (1/178 subjects) during Ezetimibe monotherapy and 3.0% (2/67 subjects) during combination therapy, ALT elevations to 2 to <3 times the upper reference limit were observed in 3.4% (6/178 subjects) during Ezetimibe monotherapy and 6.0% (4/67 subjects) during combination therapy, and ALT elevations to ≥ 3 times the upper reference limit were observed in 0.6% (1/178 subjects) during Ezetimibe monotherapy. γ -GTP elevations to 2 to <3 times the upper reference limit were observed in 11.8% (21/178 subjects) during Ezetimibe monotherapy and 16.4% (11/67 subjects) during combination therapy, and γ -GTP elevations to ≥ 3 times the upper reference limit were observed in 5.6% (10/178 subjects) during Ezetimibe monotherapy and 6.0% (4/67 subjects) during combination therapy.

Blood CK elevations to 3 to <5 times the upper reference limit were reported by 1.1% (2/178 subjects) during Ezetimibe monotherapy and 3.0% (2/67 subjects) during combination therapy, and blood CK elevations to 5 to <10 times the upper reference limit were reported by 0.6% (1/178 subjects) during Ezetimibe monotherapy, and blood CK elevations to ≥ 10 times the upper reference limit were reported by 0.6% (1/178 subjects) during Ezetimibe monotherapy.

(2) Foreign studies

1) Rising, single-dose safety and tolerance study in healthy male volunteers (I96-088), Studied Period: June 1996 to July 1996, Single study site in the UK (Reference Data)

The safety, tolerability, and pharmacokinetics of rising single oral doses of 1-50 mg of Ezetimibe were investigated in 45 healthy male volunteers. The incidence of adverse events in the subjects who received Ezetimibe was 20% (6/30 subjects), which was similar to 27% (4/15 subjects) in the placebo group, and all adverse events were mild in severity. There was no apparent increase in the incidence of adverse events as the dose of Ezetimibe increased. Clinically significant abnormalities in clinical laboratory tests from pretreatment baseline were observed in one subject. This subject had a mildly elevated concentration of ALP at baseline, and mild increases in ALT (<3-fold increase from the upper reference limit) and AST (to a lesser extent compared to ALT), but the values returned toward baseline within 3 weeks after dosing.

2) Rising, multiple-dose safety and tolerance study in healthy male volunteers (I96-139), Studied Period: October 1996 to January 1997, Single study site in the UK (Reference Data)

The safety, tolerability, and pharmacokinetics of rising multiple oral doses of 10-50 mg of Ezetimibe were investigated in 36 healthy male volunteers. The incidence of adverse events in the subjects who received Ezetimibe was 41% (11/27 subjects), which was similar to 56% (5/9 subjects) in the placebo group. There were no serious adverse events or deaths. Ten subjects (8 subjects treated with Ezetimibe, 2 subjects treated with placebo) had elevations in liver function tests and one subject (Ezetimibe 50 mg dose) discontinued treatment when his ALT values reached 3 times the upper reference limit.

3) Dose response study in patients with primary hypercholesterolemia (C98-010), Studied Period: November 1998 to July 1999, 27 study sites in the US (Reference Data)

A randomized, double-blind, parallel group, comparative study of Ezetimibe 0.25, 1, 5, and 10 mg or placebo orally administered once daily before a morning meal for 12 weeks was conducted in order to evaluate the efficacy and safety and find the optimal dose of Ezetimibe in patients with primary hypercholesterolemia. The main inclusion criteria were patients with primary hypercholesterolemia who had calculated LDL-C (by using Friedewald equation) of 130-250 mg/dL and triglycerides \leq 300 mg/dL, and followed the National Cholesterol Education Program (NCEP) Step 1 diet or stricter. Two hundred forty-three subjects were randomly assigned to the study treatments (Placebo group: 52 subjects, 0.25 mg group: 47 subjects, 1 mg group: 49 subjects, 5 mg group: 49 subjects, 10 mg group: 46 subjects).

The efficacy results are as shown in the following table. Ezetimibe at all doses significantly decreased direct LDL-C compared with placebo and the dose-response relationship was observed.

Percent change from baseline in direct LDL-C at the end of treatment

	Placebo	Ezetimibe 0.25 mg	Ezetimibe 1 mg	Ezetimibe 5 mg	Ezetimibe 10 mg
Baseline (mg/dL)	170.4(n=52)	166.4(n=47)	171.2(n=49)	172.2(n=49)	176.2(n=46)
End of treatment (mg/dL)	177.8(n=51)	150.2(n=46)	149.7(n=49)	143.9(n=49)	143.9(n=46)
Percent change (%)*	+4.3 \pm 1.4	-9.9 \pm 1.5	-12.6 \pm 1.5	-16.4 \pm 1.4	-18.7 \pm 1.5

*Least-square mean \pm standard error (based on a two-way ANOVA model that extracted sources of variation due to treatment and study sites)

The proportion of subjects with a \geq 15% reduction in LDL-C was 3.9% (2/51 subjects) in the placebo group, 41.3% (19/46 subjects) in the Ezetimibe 0.25 mg group, 46.9% (23/49 subjects) in the Ezetimibe 1 mg group, 55.1% (27/49 subjects) in the Ezetimibe 5 mg group, and 78.3% (36/46 subjects) in the Ezetimibe 10 mg group. Ezetimibe had no effect on triglycerides or HDL-C.

With regard to the safety, 57.6% of all subjects had adverse events and the incidence of adverse events was 51.9% (27/52 subjects) in the placebo group, 57.4% (27/47 subjects) in the Ezetimibe 0.25 mg group, 63.3% (31/49 subjects) in the Ezetimibe 1 mg group, 53.1% (26/49 subjects) in the Ezetimibe 5 mg group, and 63.0% (29/46 subjects) in the Ezetimibe 10 mg group. A total of 3 subjects discontinued treatment because of adverse events: 1 subject treated with placebo (liver function test abnormal, Day 65), 1 subject treated with Ezetimibe 0.25 mg (arthralgia, edema, nightmare, and skin disorder [macular rash on face]; Day 43), and 1 treated with Ezetimibe 1 mg (thrombocytopenia, Day 35). There were no deaths or serious adverse events occurring after the start of study treatment.

The applicant explained that 10 mg was chosen as the recommended dose of Ezetimibe for the following reasons: According to the results of pooled analysis from this study and a dose regimen study (Study C98-258: a placebo-controlled study of Ezetimibe 5 mg or 10 mg administered once daily before a

morning meal or at bedtime for 12 weeks), Ezetimibe 5 mg (percent change in LDL-C (the least-square mean±standard error based on ANOVA taking the study sites effect into account): $-15.7\pm 0.9\%$) and 10 mg ($-18.5\pm 0.9\%$) decreased LDL-C significantly compared with placebo ($-0.4\pm 1.1\%$); the degree of decrease in LDL-C was significantly greater with 10 mg compared with 5 mg; the proportion of subjects with a $\geq 15\%$ reduction in LDL-C was increased by 16% when the dose was doubled from 5 mg to 10 mg, but did not rise when the dose was doubled from 10 mg to 20 mg; and as to the safety, the incidence of adverse events did not increase with increasing doses.

4) Study in patients with homozygous familial hypercholesterolemia (P01030), Studied Period: May 2000 to May 2001, 4 U.S. study sites and 13 non-U.S. study sites

A randomized, double-blind, parallel group, comparative study was conducted in order to evaluate the efficacy and safety of Ezetimibe 10 mg in patients with homozygous FH already receiving atorvastatin or simvastatin. Patients who had been receiving dietary therapy and medication therapy with atorvastatin 40 mg or simvastatin 40 mg for 6-14 weeks were randomized to one of the following: (a) Ezetimibe placebo+atorvastatin or simvastatin 80 mg, (b) Ezetimibe 10 mg+atorvastatin or simvastatin 40 mg, (c) Ezetimibe 10 mg+atorvastatin or simvastatin 80 mg (atorvastatin: administered once daily in the morning, simvastatin: administered once daily in the evening (before or after a meal)) and were treated for 12 weeks. The main inclusion criteria were (a) patients with homozygous FH, (b) patients who had received atorvastatin 40 mg or simvastatin 40 mg for at least 4 weeks before the first qualifying lipid determination, (c) the mean of LDL-C values at the first and second qualifying lipid determinations ≥ 100 mg/dL, (d) patients who were following NCEP Step1 diet or stricter. As a rule, those patients had to demonstrate adequate stabilization of their serum lipid lowering therapy at the qualifying lipid determinations 2 weeks and 1 week prior to randomization, and the stabilization period (the subjects on a stable regimen) was at least 6 weeks for anion-exchange resins and nicotinic acid preparations, at least 1 year for probucol, and at least 8 weeks for LDL apheresis, and a 12-week washout of fibrates was required.

Fifty subjects (21 men, 29 women) were randomized and 33 subjects received Ezetimibe 10 mg + statin 40/80 mg and 17 subjects received statin 80 mg. One subject in the Ezetimibe 10 mg + atorvastatin 40 mg group (complicated by hepatic hydatid cysts) and one subject in the Ezetimibe 10 mg + simvastatin 80 mg group (protocol violation) discontinued treatment in an earlier stage.

The percent changes from baseline at the end of treatment in LDL-C, the primary endpoint, are shown in the following table.

Percent change in direct LDL-C

Treatment group	Ator 80mg n=12	EZ 10mg + Ator 40mg n=12	EZ 10mg + Ator 80mg n=12	Sim 80mg n=5	EZ 10mg + Sim 40mg n=4	EZ 10mg + Sim 80mg n=5
Baseline (mg/dL)	353.78	381.58	281.56	326.87	324.33	267.73
End of treatment (mg/dL)	342.58	321.42	208.00	288.40	285.75	191.20
Percent change (%)	-3.5	-13.0	-24.7	-11.0	-12.0	-29.8

EZ: Ezetimibe, Ator: atorvastatin, Sim: simvastatin

The percent change in LDL-C (the least-square mean±standard error based on ANOVA that extracted sources of variation due to treatment and statin) was -20.73±3.15% in the Ezetimibe+statin 40/80 mg group and -6.65%±4.21% in the statin 80 mg group, showing a significant reduction by Ezetimibe+statin 40/80 mg compared to statin 80 mg. The percent change in triglycerides was -10.78±5.17% in the Ezetimibe+statin 40/80 mg group and -5.77±6.90% in the statin 80 mg group, and the percent change in HDL-C was -2.79±2.59% in the Ezetimibe+statin 40/80 mg group and 4.43±3.46% in the statin 80 mg group.

With regard to the safety, the incidence of adverse events was 73% (24/33 subjects) in the Ezetimibe+statin 40/80 mg group and 65% (11/17 subjects) in the statin 80 mg group. Although there were no deaths, serious adverse events occurred in 4 subjects, which include AST increased (consecutive elevations to ≥3 times the upper reference limit) (1 subject in the Ezetimibe 10 mg + simvastatin 80 mg group), severe chest pain, angina pectoris, abdominal pain, moderate hepatic function abnormal (consecutive elevations of AST to ≥3 times the upper reference limit), and darkened urine (1 subject in the Ezetimibe 10 mg + atorvastatin 40 mg group), severe hemiparesis (1 subject in the Ezetimibe 10 mg + atorvastatin 40 mg group), mild asthenia, chest pain, cardiac dilatation, pericardial effusion, cough, epistaxis, pleural effusion, moderate urinary tract infection, and advanced procedure (cardiac surgical procedure) (1 subject in the simvastatin 80 mg group).

Subjects with ALT increased are tabulated as follows.

Number of subjects by the degree of elevation in hepatobiliary tests

Category	EZ + Statin* 40/80 mg (n=33)	Statin* 80mg (n=17)	EZ + Ator 40mg (n=12)	EZ + Ator 80mg (n=12)	Ator 80mg (n=12)	EZ + Sim 40mg (n=4)	EZ + Sim 80mg (n=5)	Sim 80mg (n=5)
ALT (reference range: 5-25 mU/mL)								
2 to <3 times the upper reference limit	4(12%)	1(6%)	0	3(25%)	1(8%)	0	1(20%)	0
≥3 times the upper reference limit	2(6%)	1(6%)	1(8%)	0	1(8%)	0	1(20%)	0

*atorvastatin or simvastatin

Blood CK increased was observed in 1 subject in the Ezetimibe 10 mg + atorvastatin 80 mg group, 1 subject in the Ezetimibe 10 mg + simvastatin 40 mg group, 1 subject in the Ezetimibe 10 mg + simvastatin 80 mg group, and 2 subjects in the atorvastatin 80 mg group, which were all increases to <3-5 times the upper reference limit and there were no elevations to ≥ 5 times the upper reference limit.

Based on the above results, the applicant explained as follows:

It was confirmed that the addition of Ezetimibe 10 mg in patients with homozygous FH receiving statin 40 mg produced an incremental effect equal to or greater than an increased dose of 80 mg of statin, and the LDL-C lowering effect was further enhanced by increasing the dose of statin to 80 mg in line with the addition of Ezetimibe 10 mg. Also, combination therapy with Ezetimibe 10 mg and atorvastatin or simvastatin 40/80 mg was well tolerated in patients with homozygous FH, which was similar to the tolerability in subjects treated with statin 80 mg alone.

5) Study in patients with homozygous sitosterolemia (P02243/P02257), Studied Period: February 2001 to September 2001 (Circulation 109: 966-971, 2004)

A randomized, double-blind, unbalanced-parallel-group, comparative study assessed the efficacy and safety of Ezetimibe 10 mg (administered when getting out of bed in the morning) in patients with homozygous sitosterolemia with an elevated plasma sitosterol level >5 mg/dL. The study consisted of 1-5 weeks screening period followed by 3-week single-blind placebo run-in period before 8-week double-blind treatment period.

Thirty-seven subjects (13 males, 24 females) were randomized in a 4:1 ratio to Ezetimibe or placebo, and 30 subjects received Ezetimibe and 7 subjects received placebo. The primary endpoint was the percent change between baseline (defined as the average of the values obtained during the single-blind placebo run-in period and the one obtained at the start of double-blind treatment) and endpoint (defined as the average of values at Weeks 6 and 8) in plasma sitosterol. Efficacy analysis was performed for the MITT (Modified Intent-to-Treat) population consisting of subjects with at least one value at both baseline and endpoint who did not receive apheresis and 36 subjects excluding one subject in the Ezetimibe group treated with apheresis therapy were included in the MITT population. Concomitant therapy for sitosterolemia was statin therapy in 7/30 subjects (23.3%) in the Ezetimibe group and 1/7 subjects (14.3%) in the placebo group, anion-exchange resins in 8/30 subjects (26.7%) in the Ezetimibe group and 2/7 subjects (28.6%) in the placebo group, and ileal bypass surgery in 3/30 subjects (10.0%) in the Ezetimibe group and 2/7 subjects (28.6%) in the placebo group.

With respect to the efficacy, the change in the mean plasma sitosterol from baseline to endpoint was 21.0→16.2 mg/dL in the Ezetimibe group and 18.5→17.8 mg/dL in the placebo group and the percent change in sitosterol between baseline and endpoint, which was the primary endpoint, was $-22.6 \pm 2.2\%$ in the Ezetimibe group (least square mean \pm standard error from the ANOVA model). When subgroup analysis was performed in subjects treated with Ezetimibe, the percent change from baseline to endpoint in sitosterol was $-20.4 \pm 10.6\%$ (Mean \pm SD) with concomitant anion-exchange resin and $-23.5 \pm 12.3\%$ without

concomitant anion-exchange resin, and $-23.7\pm 3.9\%$ with concomitant statin therapy and $-22.3\pm 13.4\%$ without concomitant statin therapy.

As to the safety, the incidence of adverse events was 70% (21/30 subjects) in the Ezetimibe group and 29% (2/7 subjects) in the placebo group. Adverse events reported by at least 2 subjects in the Ezetimibe group were dizziness, fatigue, abdominal pain, diarrhoea, queasy, toothache, upper respiratory tract infection, and musculoskeletal pain. There were no deaths or treatment discontinuation due to adverse events. Serious adverse events reported were arteriosclerosis in 1 subject treated with Ezetimibe and hypertension in 1 subject treated with placebo, which were assessed as unrelated to the study drug and the both events improved. The incidence of gastrointestinal disorder was higher in the Ezetimibe group than in the placebo group. Abnormalities in hepatobiliary tests observed were γ -GTP elevations to 2 to <3 times the upper reference limit in 2 subjects in the Ezetimibe group, AST elevations to ≥ 3 times the upper reference limit in 1 subject, ALT elevations to ≥ 3 times the upper reference limit in 2 subjects, and γ -GTP elevations to ≥ 3 times the upper reference limit in 1 subject in the placebo group. None of the subjects had consecutive elevations of blood CK value to ≥ 10 times the upper reference limit during the treatment period.

Based on the above results, the applicant explained that Ezetimibe reduced plant sterols in patients with homozygous sitosterolemia and was well tolerated and there were no particular safety problems.

6) Long-term treatment study in patients with primary hypercholesterolemia (P00476), Studied Period: February 2000 to August 2002

A multicenter, uncontrolled extension study evaluated the safety and tolerability of Ezetimibe 10 mg orally administered once daily (in the morning) for 24 months in patients with primary hypercholesterolemia who completed the 12-week, double-blind phase III study (P00474 or P00475). The main criteria for inclusion in Study P00474 and Study P00475 were patients with primary hypercholesterolemia; LDL-C value after washout of serum lipid lowering medication ≥ 130 mg/dL and ≤ 250 mg/dL; triglycerides ≤ 350 mg/dL; adherence to NCEP Step1 diet with a Ratio of Ingested Saturated fat and Cholesterol to Calories (RISCC) score < 24 during the study period. If NCEP ATP II target LDL-C levels had not been reached after at least 1 month of Ezetimibe monotherapy, or LDL-C exceeded 130 mg/dL, a statin was to be added. If combination therapy with statins was required, both Ezetimibe and 10, 20, or 40 mg tablet of simvastatin were to be orally taken once daily (in the evening with a meal) or both Ezetimibe and 10 or 20 mg tablet of lovastatin were to be orally taken once daily (in the evening with a meal), and the maximum daily doses of simvastatin and lovastatin were 80 mg and 40 mg, respectively.

Of 1,719 subjects who received Ezetimibe or placebo in Study P00474 or P00475, 1,313 subjects participated in this study. Among which, 336 subjects were assigned to receive placebo in Study P00474 or P00475 and received their first dose of Ezetimibe in this study. Statin was combined with Ezetimibe in 612 subjects (lovastatin in 192 subjects, simvastatin in 420 subjects). Concurrent diabetes was present in 5.0% (65/1313 subjects) and the proportion of subjects with concurrent diabetes in the Ezetimibe+statin combination therapy group was 6.2% (38/612 subjects).

With regard to the efficacy, in the Ezetimibe monotherapy group, LDL-C was 158.05 ± 0.76 mg/dL (Mean \pm standard error) at baseline and 131.39 ± 1.61 mg/dL at 24 months of treatment, and the percent change was $-18.00 \pm 0.87\%$. In the Ezetimibe+statin combination therapy group, LDL-C was 180.87 ± 1.63 mg/dL at baseline and 114.47 ± 1.73 mg/dL at 24 months of treatment and the percent change was $-36.25 \pm 0.92\%$. The study demonstrated long-term durability of response to Ezetimibe either as monotherapy or in combination with a statin for LDL-C throughout the treatment period.

The safety analysis included 1,624 subjects containing 311 subjects who had received Ezetimibe in Study P00474 or P00475 but did not participate in Study P00476. Three subjects in the Ezetimibe monotherapy group and 1 subject in the Ezetimibe+lovastatin combination therapy group died during the study period, but their causal relationship to the study drug was denied. The overall incidence of serious adverse events was 12.6% (205/1,624 subjects), and the incidences of serious adverse events during Ezetimibe monotherapy and during Ezetimibe+statin combination therapy were 10.5% (106/1012 subjects) and 12.9% (79/612 subjects: 18.8% (36/192 subjects) for lovastatin, 10.2% (43/420 subjects) for simvastatin), respectively.

Treatment discontinuations due to adverse events occurred in 15.7% of subjects during Ezetimibe monotherapy (159/1,012 subjects) and 6.2% of subjects during combination therapy with statins (38/612 subjects). The main adverse events leading to discontinuation during Ezetimibe monotherapy included asthenia, chest pain, dizziness, fatigue, headache, coronary artery disease, hypertension, myocardial infarction, abdominal distension, abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, loose stools, queasy, bradycardia, palpitations, γ -GTP increased, hepatic function abnormal, AST increased, ALT increased, blood CK increased, arthralgia, back pain, muscle cramp, musculoskeletal pain, myalgia, pruritus, and skin rash. The main adverse events leading to discontinuation during combination therapy included dizziness, angina pectoris, myocardial infarction, abdominal pain, diarrhoea, dyspepsia, γ -GTP increased, liver function test abnormal, blood CK increased, muscle cramp, and myalgia. Treatment discontinuations due to adverse events did not increase with prolonged duration of treatment with either Ezetimibe alone or Ezetimibe in combination with a statin. Subjects with elevations in hepatobiliary tests are tabulated as follows.

Number of subjects by degree of elevation of ALT

Category	All subjects (n=1,624)	During Ezetimibe monotherapy (n=1,624)	During combination therapy with statins	
			Events not reported during Ezetimibe monotherapy and occurring only during combination therapy (n=612)	Events occurring during combination therapy, regardless of whether these were reported during Ezetimibe monotherapy (n=612)
ALT (Reference range: 5-25 mU/mL)				
2 times the upper reference limit to <3 times the upper reference limit	64/1,603(4.0%)	53/1,603(3.3%)	12/611(2.0%)	19/611(3.1%)
≥3 times the upper reference limit	25/1,603(1.6%)	21/1,603(1.3%)	4/611(0.7%)	4/611(0.7%)
≥3 times the upper reference limit (consecutive)	9/1,603(0.6%)	8/1,603(0.5%)	2/611(0.3%)	2/611(0.3%)
≥5 times the upper reference limit	3/1,603(0.2%)	3/1,603(0.2%)	0	0
≥10 times the upper reference limit	0	0	0	0

Subjects with blood CK increased are tabulated as follows. There were 16 subjects with blood CK increased (a value ≥ 10 times the upper reference limit, or a value ≥ 5 times the upper reference limit with associated muscle symptoms) and their blood CK values all returned to baseline values or to within the reference limits.

Number of subjects by degree of elevation of blood CK

Category (Reference range: 0-120 mU/mL)	All subjects (n=1,624)	During Ezetimibe monotherapy (n=1,624)	During combination therapy with statins	
			Events not reported during Ezetimibe monotherapy and occurring only during combination therapy (n=612)	Events occurring during combination therapy, regardless of whether these were reported during Ezetimibe monotherapy (n=612)
3 times the upper reference limit to <5 times the upper reference limit	45/1,603(2.8%)	32/1,603(2.0%)	15/611(2.5%)	16/611(2.6%)
5 times the upper reference limit to <10 times the upper reference limit	18/1,603(1.1%)	14/1,603(0.9%)	4/611(0.7%)	6/611(1.0%)
≥10 times the upper reference limit	8/1,603(0.5%)	6/1,603(0.4%)	2/611(0.3%)	2/611(0.3%)

<Outline of review>

The outline of review by the PMDA is as follows.

(1) Clinical positioning of Ezetimibe in the treatment of hyperlipidemia

The applicant claimed that as Ezetimibe selectively inhibits the absorption of cholesterol and plant sterols with a similar structure to cholesterol in the small intestine, when treatment goals can not be achieved with statin monotherapy, combination therapy with Ezetimibe is expected to produce high efficacy, offering more options for drug therapy, which is of high clinical significance.

According to the Japan Atherosclerosis Society Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Disease 2002, low HDL-cholesterol, aging, diabetes, hypertension, smoking, and a family history of coronary artery disease are listed as the major coronary risk factors other than high LDL-cholesterol, and lipid goals are specified by the number of these risk factors and the presence or absence of coronary artery disease. The 2004 NCEP recommends that the treatment target for LDL-C should be <70 mg/dL for high-risk patients and that more aggressive therapy should be instituted for particularly high-risk patients, based on the results of clinical studies, and advocates statin therapy for patients with diabetes or cardiovascular disease, regardless of their LDL-C values. In view of the above, the PMDA considers that the applicant's claim is justified because statin monotherapy, which is mainly used for the treatment of hypercholesterolemia, has limitations in terms of achievable LDL-C levels and furthermore, high-dose statin increases the risk for hepatic or skeletal muscle adverse reactions etc. although Ezetimibe is unlikely to be a first-choice drug for the treatment of hypercholesterolemia. In addition, as statin therapy may not be suitable for some patients due to adverse reactions etc., Ezetimibe is considered to have clinical usefulness.

(2) Indications

1) Ezetimibe monotherapy

The PMDA asked for the applicant's view on the appropriateness of Ezetimibe monotherapy and combination therapy with statins or other anti-hyperlipidemia drugs, on the basis of the fact that in Europe, Ezetimibe monotherapy is limited to patients with primary hypercholesterolemia in whom a statin is considered inappropriate or is not tolerated.

The applicant responded as follows:

The approved indications in Europe are based on the European regulatory authority's opinion that all "non-statin products" should be considered a second choice unless its clinical benefit has been proven. On the other hand, the U.S. authority has approved Ezetimibe monotherapy. When choosing a treatment option, it is necessary to carefully review the current treatment guidelines and individual risk factors, and if more aggressive lipid-lowering therapy is required, high-dose statin or Ezetimibe in combination with a statin needs to be administered. Furthermore, for patients with abnormalities in blood lipids in addition to increased LDL-C, other combination therapies also need to be considered.

The PMDA considers as follows:

The effect of Ezetimibe on the survival prognosis is unknown and there is little evidence for recommending Ezetimibe monotherapy compared to statins, which have the data supporting the improvement of the survival prognosis. However, since patients in whom a statin is considered inappropriate etc. should receive Ezetimibe monotherapy and Ezetimibe has a mechanism of action that differs from those of other antihyperlipidemia drugs, offering an alternative therapeutic option, Ezetimibe monotherapy can be approvable. But, it is necessary to provide information about the cases in which Ezetimibe monotherapy is considered appropriate, and the target patient population for Ezetimibe as well as the appropriateness of monotherapy, will be further considered, taking comments from the Expert Discussion also into account.

2) Familial hypercholesterolemia

The applicant explained about its limited experience in Japanese patients with FH as follows:

As FH is a rare disease and it was difficult to secure a sufficient number of subjects in a Japanese clinical study, it was decided to use the data from a foreign comparative study in addition to Japanese clinical study data. The prevalence of homozygous FH is similar between Japan and Europe/the U.S., and the severity of the disease is determined by the type of abnormal receptor function (defective type or negative type) and is unaffected by lifestyle such as diet. In addition, as the LDL-C lowering effect of Ezetimibe was very similar between Japanese and non-Japanese subjects and there were no ethnic differences in the pharmacodynamic effects of Ezetimibe, extrapolation of foreign data to Japan was considered possible. In both Japanese and foreign studies involving patients with homozygous FH, Ezetimibe 10 mg/day was added to ongoing statin therapy. As a result, the percent change in LDL-C in the Japanese study was -9.6% and the percent change in LDL-C when Ezetimibe was added to ongoing therapy with atorvastatin 40 mg/day or simvastatin 40 mg/day in the foreign study was -13.0% and -12.0%, respectively, demonstrating similar effects between Japan and overseas.

The PMDA considers as follows:

Based on the Japanese and foreign clinical study data, the administration of Ezetimibe to FH patients is justified to some extent. However, these clinical studies included patients who responded inadequately to other therapies such as statins and LDL apheresis, and FH patients other than these cases have not been studied. Thus, treatment with Ezetimibe should be limited to patients who respond inadequately to statins etc. The appropriateness of the use of Ezetimibe in FH patients and the details of information provision/cautioning will be further considered, taking also account of comments from the Expert Discussion.

3) Homozygous sitosterolemia

The applicant explained the basis for judging that the efficacy and safety of Ezetimibe in the treatment of homozygous sitosterolemia can be evaluated in spite of no patients treated with Ezetimibe in Japan, as follows:

Homozygous sitosterolemia is an autosomal recessive hereditary disease characterized by accumulation of plant sterols in the body due to increased intestinal absorption and decreased excretion of plant sterols which are scarcely absorbed in healthy people. As with cholesterol, plant sterols accumulated in the body lead to the development of xanthoma or premature arteriosclerosis. Non-clinical studies have confirmed that Ezetimibe inhibits the absorption of sitosterol from the small intestinal lumen. There are an estimated about 50 family lines with homozygous sitosterolemia worldwide and 9 family lines across Japan and the estimated number of patients in Japan is very limited, i.e. approximately 15-20 patients and it was difficult to conduct a clinical study in Japan. Mutations in either the ABCG5 or ABCG8 genes encoding ABC transporters have been identified to be responsible for the disease and there are no ethnic differences in etiology at a genetic level between Japanese and non-Japanese patients and there should be no differences in clinical symptoms between Westerners and Japanese patients. Therefore, the efficacy of Ezetimibe in Japanese patients with homozygous sitosterolemia is considered to be similar to the efficacy observed in the foreign clinical study. The safety profile of Ezetimibe in patients with hypercholesterolemia is similar between Japan and overseas and the safety profile is also similar between patients with hypercholesterolemia and those with homozygous sitosterolemia overseas. Thus, the safety profile of Ezetimibe in Japanese patients with homozygous sitosterolemia is considered to be similar to the safety profile observed in the foreign clinical study, and we have added the disease to the proposed indications in order to establish a treatment for the disease.

The PMDA considers as follows:

A report that elevations of serum plant sterols are associated with the incidence of coronary artery disease (Metabolism 40: 842-848, 1991) and a report that the severity of coronary artery lesion is increased with higher serum sitosterol level or higher ratio to cholesterol in women (Nutr Metab Cardiovasc Dis 8: 386-391, 1998), support the possibility of involvement of serum plant sterols in the development of arteriosclerosis. Ezetimibe has never been used in patients with homozygous sitosterolemia in Japan and whether or not a reduction in serum plant sterols by Ezetimibe improves the cardiovascular prognosis is unknown. However, as a foreign study has shown the potential for the reduction of Achilles tendon xanthoma and there is also an overseas report that the plasma sitosterol and campesterol levels were decreased by about 50% in patients with sitosterolemia receiving cholestyramine after 1 year of combination therapy with Ezetimibe, where the diminution of carotid bruit, platelet count increased, and regression of xanthoma were also noted (Gastroenterology 130: 1853-1857, 2006) etc., Ezetimibe may produce efficacy, e.g. the reduction of arteriosclerosis or xanthoma. Taking into account the rarity of the disease, the pharmacological action of Ezetimibe, foreign clinical study data for homozygous sitosterolemia, and clinical study data for hypercholesterolemia etc., the usefulness of Ezetimibe in the treatment of homozygous sitosterolemia can be recognized, but the handling of homozygous sitosterolemia will be finalized, taking account of comments from the Expert Discussion.

(3) Efficacy

1) A relationship between the primary endpoint and the true endpoint

The applicant explained about a relationship between the primary endpoint for clinical studies of Ezetimibe

and the true endpoint as follows:

Japanese and foreign long-term treatment studies were not designed to evaluate the efficacy of Ezetimibe in the prevention of arteriosclerotic disease, the true endpoint, and the efficacy of Ezetimibe against the true endpoint can not be discussed based on the results from these studies. Also, the effects of Ezetimibe on arteriosclerosis or vascular lesions have not been investigated to date. The US and European guidelines recognize LDL-C as a validated surrogate endpoint for clinical outcome. The Japanese “guideline for the clinical evaluation of anti-hyperlipidemia agents” also recognizes a link between arteriosclerosis and cholesterol, which is widely accepted worldwide, and justifies the assessment of the therapeutic effect of the drug primarily based on changes in serum cholesterol.

Although the ultimate target of treating hypercholesterolemia is the prevention of arteriosclerotic disease, it is difficult to assess the prevention of arteriosclerotic disease in the development stage in terms of the duration of study and the sample size, etc. Taking account of such circumstances, the PMDA considers that the applicant’s explanation is appropriate, and judges that the LDL-cholesterol lowering effect observed in the clinical studies of Ezetimibe is adequate enough to infer the clinical efficacy of Ezetimibe.

2) Effects on serum lipids other than LDL-C

The applicant explained the effects of Ezetimibe on serum lipids other than LDL-C as follows:

When monotherapy data from 4 studies where Ezetimibe 10 mg/day was administered to patients with hypercholesterolemia (the phase II study, the comparative study with colestimide, the glucose metabolism study, and the long-term treatment study) were combined (n=312), the percent change in triglycerides was -1.3% (95% confidence interval: -5.13 to 2.53%) while the percent change in total cholesterol was -14.1 to -12.8%, showing that Ezetimibe had no evident effect on triglycerides. In a comparative study with colestimide, colestimide significantly increased triglycerides from baseline, whereas Ezetimibe did not increase triglycerides. The percent change in HDL-C from baseline to the end of Ezetimibe 10 mg/day monotherapy was +5.2% (3.74-6.72%), which was a significant increase from baseline.

The PMDA considers that Ezetimibe is unlikely to have clinically unfavorable effects on triglycerides and HDL-C.

(4) Justification for dosage and dose regimen

1) Dosage

The applicant explained the rationale for selecting 10 mg/day as the dose of Ezetimibe as follows:

In the phase II study (JPC-00-335-21), placebo or Ezetimibe 5, 10, and 20 mg were administered once daily after either breakfast, lunch, or evening meal for 12 weeks to 138 patients with hypercholesterolemia and the percent changes from baseline to the end of treatment in LDL-C were -2.3, -14.9, -18.1, and -19.2%, respectively. The efficacy of Ezetimibe virtually peaked at 10 mg and the doses of 20 mg or higher are unlikely to provide a greater effect and 10 mg seemed appropriate as the initial dose. On the other hand, the incidences of adverse events were 72.2% (26/36 subjects), 57.1% (20/35 subjects), 68.8% (22/32 subjects), and 65.7% (23/35 subjects), respectively, and there were no increases in the incidence of adverse

events with increasing doses. In the comparative study with colestimide (JPC-02-335-33), the percent change from baseline to the end of treatment in LDL-C was -18.1% in the Ezetimibe 10 mg/day group and -19.2% in the colestimide 3g/day group and the non-inferiority of Ezetimibe over colestimide was verified. Based on the above, 10 mg/day was considered appropriate as the recommended dose of Ezetimibe.

The PMDA considers that there are no major problems with selecting a once-daily 10 mg regimen of Ezetimibe since the overseas approved dosage and administration is 10 mg once daily in all countries, 20 mg/day did not provide an effect clearly exceeding that of 10 mg/day in the Japanese clinical study, and also from a safety point of view, there is no reason for recommending a dose other than 10 mg/day.

2) Dosage adjustment

The PMDA asked the applicant to explain about any patient groups that are considered to require dosage adjustment as well as the specific dosage adjustment method.

The applicant explained as follows:

Based on the pharmacokinetic property of Ezetimibe, chronic administration of anti-bacterial drugs (antibiotics) is predicted to affect the efficacy of Ezetimibe. Intestinal bacterial flora is considered deeply associated with in deglucronidation of SCH60663 in the small intestinal lumen, and if intestinal bacterial flora remains imbalanced over a long period of time due to chronic administration of anti-bacterial drugs (antibiotics), the percentage of the dose excreted in feces as SCH60663 will be increased due to decreased deglucronidation ability, which may affect the persistence of the therapeutic effect of Ezetimibe. However, anti-bacterial drugs (antibiotics) intended to treat infections are unlikely to be administered over a long period of time and intestinal bacterial flora is also expected to recover from the influence of an anti-bacterial drug within several days after the end of treatment. Therefore, there should be no need to consider dose increase from an efficacy point of view. The cases in which there are safety concerns due to increased systemic exposure may include the use of Ezetimibe in patients with hepatic impairment. However, a caution statement has been included in the PRECAUTIONS section of the proposed package insert: "The use of Ezetimibe in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment is not recommended." The effects of the patients' age, gender, and renal function on BA are small and are considered to be of little clinical significance, and no dosage adjustment depending on these factors should be required. Meanwhile, as the response to treatment is not necessarily the same between individual patients in routine clinical practice, it is envisaged that the dosage may be increased or decreased as appropriate.

The PMDA asked the applicant to explain the rationale for stating that the dosage may be increased or decreased according to the patient's age and symptoms in the DOSAGE AND ADMINISTRATION section of the proposed package insert despite the fact that the phase II dose-finding study (Study JPC-00-335-21) showed no apparent benefit of increasing the dose from 10 mg to 20 mg, as well as the criteria for increasing the dose of Ezetimibe, based on the data from clinical studies.

The applicant responded as follows:

As an increased dose of 20 mg is not considered to be more effective than the 10 mg dose based on the percent change in LDL-C and the proportion of subjects with a $\geq 15\%$ reduction in LDL-C in the phase II dose-finding study, the wording in the DOSAGE AND ADMINISTRATION section of the proposed package insert will be changed from “may be increased or decreased” to “may be reduced.”

The PMDA considers as follows:

Since patients in whom dose reduction is recommended have not been specified, if dose reduction is allowed, it will be necessary to adequately caution not to easily prescribe Ezetimibe to patients who should avoid receiving Ezetimibe, such as patients with moderate or severe hepatic impairment. It is also necessary to appropriately collect and review information after marketing. The details of dosage and administration and necessary cautioning etc. will be further considered, taking account of comments from the Expert Discussion.

(5) The efficacy and safety of Ezetimibe in combination with statins

The PMDA asked the applicant to explain the efficacy of Ezetimibe in combination with a statin based on the results of Japanese and foreign clinical studies.

The applicant responded as follows:

In a foreign coadministration study with atorvastatin in patients with primary hypercholesterolemia (P00692), Ezetimibe 10 mg in combination with the usual dose (10 mg) of atorvastatin produced an effect that is similar to the effect of the highest dose (80 mg) of atorvastatin. In a Japanese clinical study, Ezetimibe 10 mg was coadministered to patients with heterozygous FH or severe hypercholesterolemia other than FH on statin therapy not achieving their treatment targets in order to evaluate the add-on effect. As a result, the percent change in LDL-C was -23.0% in overall subjects (39 subjects), -22.0% in patients with heterozygous FH (29 subjects), and -25.6% in patients with severe hypercholesterolemia other than FH (10 subjects). The proportion of patients with a $\geq 15\%$ reduction in LDL-C was 82% (32/39 subjects) and the proportion of patients achieving their LDL-C goals was 28% (11/39 subjects), showing that about 30% of patients on statin monotherapy not achieving their treatment goals met the treatment goals when Ezetimibe was added. In the long-term treatment study where subjects with untreated LDL-C not meeting the criteria for initiating drug therapy were administered Ezetimibe 10 mg and if the treatment goals were unmet after 16 weeks of treatment, concomitant statin was permitted, the percent changes in LDL-C with combination therapy with statins were assessed in 54 subjects for whom the data was made available from at least 4-week combination therapy. As a result, the percent changes from baseline (untreated) in LDL-C with Ezetimibe in combination with atorvastatin, simvastatin, fluvastatin, or pravastatin were -40.5, -37.8, -29.1, and -28.4%, respectively. As the percent changes in LDL-C at the end of Ezetimibe monotherapy in patients who received combination therapy with atorvastatin, simvastatin, fluvastatin, or pravastatin were -14.7, -19.0, -14.6, and -14.4%, respectively, the incremental percent changes in LDL-C gained by combination therapy with atorvastatin, simvastatin, fluvastatin, and pravastatin were -25.7%, -18.9%, -14.5% and -13.9%, respectively, as compared with Ezetimibe monotherapy. Thus, the effectiveness of

Ezetimibe+statin combination therapy has been demonstrated.

The PMDA asked about differences in the efficacy and safety of Ezetimibe between different types/doses of combined statin in the Japanese long-term treatment study.

The applicant responded as follows:

The breakdown of 67 subjects who received combination therapy with statins in this study was as follows: pravastatin 10 mg: 11 subjects, atorvastatin 10 mg: 20 subjects, simvastatin 5 mg: 10 subjects, fluvastatin 20 mg: 26 subjects. The 95% confidence intervals for the percent change in LDL-C from baseline to the end of Ezetimibe and statin combination therapy were -34.3 to -22.4% for pravastatin, -49.1 to -31.8% for atorvastatin, -46.7 to -29.0% for simvastatin, and -35.8 to -22.4% for fluvastatin, and the percent changes in LDL-C from the end of Ezetimibe monotherapy to the end of combination therapy with statins were -13.9% for pravastatin, -25.7% for atorvastatin, -19.8% for simvastatin, and -14.5% for fluvastatin. It seems that differences in the percent change in LDL-C between different statins in combination with Ezetimibe largely reflect differences in the percent change in LDL-C between different statin monotherapies. There were no adverse events or adverse reactions specific to any of these statins in combination with Ezetimibe and there should be no differences in the safety of Ezetimibe between different types of statin combined.

The PMDA asked about differences in the efficacy and safety of Ezetimibe between different types/doses of combined statin in the Japanese Ezetimibe+statin combination therapy study in patients with severe hypercholesterolemia.

The applicant responded as follows:

Combined statins in the safety analysis population for this study were pravastatin in 18 subjects (5 mg: 8 subjects, 10 mg: 6 subjects, 20 mg: 2 subjects, and 30 mg: 2 subjects), atorvastatin in 20 subjects (5 mg: 1 subject, 10 mg: 12 subjects, 20 mg: 6 subjects, and 40 mg: 1 subject), simvastatin in 1 subject (10 mg), and fluvastatin in 1 subject (20 mg). The percent changes in LDL-C with combination therapy were compared among the different statin dose groups containing at least 2 subjects. As a result, the percent changes in LDL-C were -19.9 to -26.8% in the pravastatin 5, 10, 20, and 30 mg groups and -21.4 to -27.6% in the atorvastatin 10 and 20 mg groups, and there was no consistent trend between the doses of each statin and the percent change in LDL-C with Ezetimibe. With respect to the safety, there were no particular differences in the type or incidence of adverse events between pravastatin and atorvastatin when combined with Ezetimibe, and there were no increases in the type or incidence of adverse events with increasing doses of each statin.

The PMDA asked the applicant to explain whether there are any differences in the safety profile between Ezetimibe monotherapy and combination therapy with statins, based on the results from Japanese and foreign clinical studies.

The applicant responded as follows:

In Japanese and foreign clinical studies, the safety profile of Ezetimibe+statin combination therapy was largely similar to that of statin monotherapy, but the incidence of increased abnormal liver function tests was higher in the combination therapy group. The incidence of adverse events related to liver function (hepatic function abnormal, hepatic dysfunction, AST increased, ALT increased, and γ -GTP increased) in Japanese clinical studies was 3% (1/36 subjects) in the placebo group, 9% (3/35 subjects) in the Ezetimibe 5 mg group, 9.2% (33/358 subjects) in the Ezetimibe 10 mg group, 6% (2/35 subjects) in the Ezetimibe 20 mg group, and 15.0% (17/113 subjects) in the Ezetimibe 10 mg + statin combination therapy group, and the incidence was higher with combination therapy compared with Ezetimibe monotherapy. When the data from 4 foreign studies with combination therapy with statins including the Ezetimibe monotherapy group (P00679, P00680, P00691, P00692) were combined (statin monotherapy: 936 subjects, statin+Ezetimibe combination therapy: 925 subjects), AST increased and ALT increased (≥ 3 times the upper reference limit) were reported more frequently with statin+Ezetimibe combination therapy compared to statin monotherapy (combination therapy: 1.3%, statin monotherapy: 0.4%). In all of these patients, AST or ALT increased was transient and returned to baseline levels after the discontinuation of treatment or during continued treatment.

The PMDA asked the applicant to reconsider a caution statement in the package insert concerning liver function monitoring during Ezetimibe+statin combination therapy, including a statement in “the Precautions for combined use,” in view of the following facts: According to the results of pooled analysis from the Japanese long-term studies and foreign studies, the incidence of adverse events related to liver function was increased with Ezetimibe+statin combination therapy; and the Company Core Data Sheet and the U.S. labeling also specify when liver function tests should be performed in the case of Ezetimibe coadministered with a statin.

The applicant responded as follows:

All statins marketed in Japan are contraindicated in pregnant women or women of child-bearing potential according to their package inserts, and we decided to indicate this point clearly in the package insert for Ezetimibe. In relation to this, the following statement will be included in the “Important Precautions”:

“When Ezetimibe is coadministered with an HMG-CoA reductase inhibitor, always refer to the package insert for the HMG-CoA reductase inhibitor and check the statements in “CONTRAINDICATIONS,” “Careful Administration,” “Important Precautions,” and “Clinically significant adverse reactions” etc. of the PRECAUTIONS section. Being fully aware of, especially, a caution statement about patients with hepatic impairment in the CONTRAINDICATIONS section and a caution statement about pregnant women or women who may possibly be pregnant, and nursing mothers, liver function testing should be performed at the initiation of coadministration and according to the recommendations of the package insert for the HMG-CoA reductase inhibitor.”

The PMDA considers as follows:

As the Japanese and foreign clinical studies etc. have demonstrated the usefulness of Ezetimibe+statin

combination therapy and LDL-C goals are becoming more stringent, Ezetimibe will be coadministered with a statin after marketing. Compared with Ezetimibe or statin alone, hepatic dysfunction may be increased with combination therapy, and it is necessary to adequately caution about hepatic dysfunction associated with coadministration and perform periodic liver function monitoring. Relevant caution statements including the frequency of liver function tests during coadministration, will be further considered, taking account of comments from the Expert Discussion.

(6) The safety of Ezetimibe in combination with other antihyperlipidemia drugs

1) Combination therapy with fibrates

The PMDA asked the applicant to explain combination therapy with Ezetimibe and fibrates in Japan, based on the results of a foreign coadministration study with fenofibrate.

The applicant responded as follows:

A foreign coadministration study with fenofibrate (Study P036) evaluated the efficacy and safety of 12-week coadministration of fenofibrate 160 mg+Ezetimibe 10 mg compared with fenofibrate 160 mg alone in patients with mixed hyperlipidemia. The percent change from baseline to the end of study in LDL-C, the primary endpoint, was 0.2% in the placebo group (63 subjects), -13.4% in the Ezetimibe monotherapy group (185 subjects), -5.5% in the fenofibrate monotherapy group (188 subjects), and -20.4% in the fenofibrate+Ezetimibe coadministration group (183 subjects). Persistent ALT and/or AST elevations were observed in 2.1% (4/188 subjects) of the fenofibrate monotherapy group and 2.2% (4/183 subjects) of the Ezetimibe+fenofibrate coadministration group while the incidence was 1.6% (1/63 subjects) in the placebo group and 0.5% (1/184 subjects) in the Ezetimibe monotherapy group. Discontinuations due to laboratory adverse events occurred in 3 subjects in the fenofibrate monotherapy group and 4 subjects in the Ezetimibe+fenofibrate coadministration group, which were all due to liver transaminases increased and the increased values returned to baseline levels following the discontinuation of the study drug. Adverse events related to gallbladder/bile duct reported were acute cholecystitis and cholelithiasis in 1 subject in the fenofibrate+Ezetimibe coadministration group and the subject underwent cholecystectomy. Based on the combined data from Study P036 and the extension study (Study P036X1), the incidence of performed or planned cholecystectomy (patient/year) was 14.2 in the placebo group, 40.3 in the Ezetimibe monotherapy group, 178.3 in the fenofibrate monotherapy group, and 292.7 in the fenofibrate+Ezetimibe coadministration group. In the U.S., combination therapy with fenofibrate was approved based on the above study results while coadministration with fibrates other than fenofibrate is still “not recommended.” Since there is no data on coadministration with bezafibrate, which is a fibrate most commonly prescribed in Japan, and there is no data on coadministration with fenofibrate in Japanese patients, it seems appropriate to include the following statement in the PRECAUTIONS section of the proposed package insert, regardless of the presence or absence of the risk for cholelithiasis: “Coadministration with fibrates is not recommended until the efficacy and safety in Japan have been confirmed adequately. [Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. It has been reported that Ezetimibe increased cholesterol concentration in the gallbladder bile in dogs.]”

The PMDA considers that the applicant's opinion that coadministration of Ezetimibe with fibrates is not recommended is appropriate for the following reasons: Although there is a possibility that Ezetimibe is coadministered with fibrates in patients with high cholesterol and triglycerides levels, there is no data on coadministration of Ezetimibe with fibrates in Japan; fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis; it has been reported that Ezetimibe increased cholesterol concentration in the gallbladder bile in dogs; and foreign study data suggests the potential for increased gallbladder diseases with coadministration of Ezetimibe and fibrates. The details of information provision/cautioning about this matter will be further considered, taking also account of comments from the Expert Discussion.

2) Coadministration with anion-exchange resins

Concerning the coadministration of Ezetimibe with anion-exchange resins, the PMDA asked the applicant to explain the rationale and appropriateness of stipulating that "Dosing of Ezetimibe should occur either ≥ 2 hours before or ≥ 4 hours after the administration of an anion-exchange resin" in the PRECAUTIONS section.

The applicant responded as follows:

As Ezetimibe binds an anion-exchange resin, leading to possible delay or decrease of absorption, an adequate dosing interval is needed if Ezetimibe and colestimide are used concomitantly. Since pharmacokinetic interactions between Ezetimibe and cholestyramine have been reported, the U.S. labeling states that the incremental LDL-C reduction due to adding Ezetimibe to cholestyramine may be reduced by the drug interaction and that dosing of Ezetimibe should occur either ≥ 2 hours before or ≥ 4 hours after administration of a bile acid sequestrant (an anion-exchange resin). On the other hand, the "Drug Interactions" of the PRECAUTIONS section in the Japanese package insert for cholestyramine reads "These listed drugs should be administered carefully at least 4 hours before or 4-6 hours after the administration of cholestyramine, or at an interval as long as possible, in order to avoid the inhibition of the absorption of these drugs." Therefore, referring to the above statement in the package insert for cholestyramine and taking account of the t_{\max} of SCH60663 or total Ezetimibe of 1-2 hours, it has been decided to state "Dosing of Ezetimibe should occur either ≥ 2 hours before or ≥ 4 hours after the administration of an anion-exchange resin" also in the Japanese package insert for Ezetimibe.

The PMDA accepted the response.

(7) Safety

1) Rhabdomyolysis, myopathy, and CK elevations

The PMDA asked the applicant to compare the cases of CK elevations between Japanese and foreign clinical studies and describe rhabdomyolysis, myopathy, muscle disorder, and CK elevations from overseas post-marketing safety information.

The applicant compared the cases of CK elevations associated with Ezetimibe between a Japanese long-term treatment study (at the end of 52-week treatment) and a foreign long-term treatment study (at the

end of about 24-month treatment) and tabulated as follows.

Number of subjects by degree of elevation of CK

Parameter	Category (relative to the upper limit of normal)	All subjects		Monotherapy	
		Japan n=178	Overseas n=1603	Japan n=178	Overseas n=1603
CK	3 to <5 times	4(2.2%)	45(2.8%)	2(1.1%)	32(2.0%)
	5 to <10 times	2(1.1%)	18(1.1%)	1(0.6%)	14(0.9%)
	≥10 times	1(0.6%)	8(0.5%)	1(0.6%)	6(0.4%)

The applicant also explained about overseas post-marketing information as follows:

Between the initial approval of Ezetimibe (October 17, 2002) and January 17, 2005, there were 22 cases of rhabdomyolysis among patients who did not receive combination therapy with statins: the details were unknown in 8 cases; CK elevations to <10 times the upper limit of normal in 5 cases; and CK elevations to ≥10 times the upper limit of normal in 9 cases, of which, 3 cases were crush injury, McArdle's disease, and autoimmune phenomenon of unknown type, and in another 3 cases, the symptoms recurred after rechallenge. Between October 17, 2002 and December 31, 2004, there were 46 cases of myopathy among patients who did not receive combination therapy with statins, of which 1 case had a CK value ≥10 times the upper limit of normal. The reporting rates of rhabdomyolysis and myopathy were estimated at approximately 0.7 and 1.4 cases per 100,000 patients-year, respectively.

The PMDA asked for the applicant's view on the necessity of cautioning about rhabdomyolysis or muscle disorder and CK elevations and of monitoring CK, muscle symptoms, etc. because the U.S. and European package inserts mention the risk of rhabdomyolysis even with Ezetimibe monotherapy and indicate actions to be taken if symptoms such as myalgia occur or myopathy is suspected; and the Canadian package insert states that patients with a history of statin intolerance (myalgia with or without elevated CK levels) should be closely monitored for adverse muscle events during treatment with Ezetimibe.

The applicant responded as follows:

The risk of muscle adverse events is not considered to be increased with Ezetimibe monotherapy or in combination with a statin. Also in a report evaluating Ezetimibe in combination with simvastatin and simvastatin monotherapy (Am J Cardiol 97: 223-228, 2006), there were no exacerbation of muscle adverse events or elevations of muscle enzymes with Ezetimibe+simvastatin combination therapy compared to simvastatin monotherapy, and it seems that either Ezetimibe alone or in combination with a statin does not promote or exacerbate muscle disorder. CK monitoring is not recommended because its sensitivity is not high and it can not predict muscle adverse events. The proposed package insert states "Although a causal relationship to Ezetimibe has not been established, rhabdomyolysis and myopathy may occur rarely, and the patient should be carefully monitored. If myalgia, feelings of weakness, CK (CPK) increased, and blood and urine myoglobin increased etc. are observed, administration of the drug should be discontinued and appropriate therapeutic measures taken. Most of the patients who developed rhabdomyolysis had taken a statin prior to initiating Ezetimibe."

The PMDA asked the applicant to reconsider the necessity of monitoring CK and muscle symptoms etc. and a means of cautioning including a statement in the package insert, in view of the fact that 44 cases of suspected adverse reactions to Ezetimibe reported to New Zealand's Centre for Adverse Reactions Monitoring (CARM) up to June 30, 2006, include 1 case of suspected myopathy, 1 case of myalgia and muscle weakness, and 9 cases of myalgia, of which, 6 cases were not treated with a statin or a fibrate and 4 cases including muscle weakness recovered after the discontinuation of Ezetimibe.

The applicant responded as follows:

Although the current statements in the proposed package insert are considered adequate to caution doctors about possible occurrence of myopathy, the following statement will be added: "When Ezetimibe is coadministered with an HMG-CoA reductase inhibitor, refer to the monitoring recommendation in the package insert for the HMG-CoA reductase inhibitor."

The PMDA asked the applicant to compare the background factors (underlying diseases, concomitant medications, etc.) between subjects with and without skeletal muscle adverse events (including CK elevations) in Japanese and foreign clinical studies (regardless of causality assessment) and discuss the risk factors for skeletal muscle adverse events.

The applicant responded as follows:

In order to investigate the background factors affecting the occurrence of skeletal muscle adverse events (including CK elevations), logistic regression analysis was performed with a stepwise method for variable selection, using the pooled data from the Japanese phase II clinical study (Ezetimibe 10 mg), the comparative study with colestimide (Ezetimibe 10 mg), the glucose metabolism study, the study in patients with severe hypercholesterolemia, the study in patients with homozygous FH, and the long-term treatment study (Ezetimibe 10 mg monotherapy). Based on the pooled data (n=404), the total number of subjects with musculoskeletal and connective tissue disorders or blood CK elevations was 80, and logistic regression analysis could not find a risk factor for skeletal muscle adverse events (including CK elevations) in subjects treated with Ezetimibe.

The PMDA asked the applicant to discuss when CK elevations associated with Ezetimibe are likely to occur, based on the results from Japanese and foreign clinical studies.

The applicant responded as follows:

Among all subjects in the Japanese long-term treatment study, the frequency of CK deviations from the reference range was almost constant regardless of the duration of treatment, and the incidence of abnormal values did not rise with prolonged duration of treatment. In foreign studies, the number of patients with CK elevations to ≥ 5 times the upper reference limit in the Ezetimibe monotherapy group (1,691 subjects) over time was 4/1,626 subjects in Weeks 0-2, 5/1,628 subjects in Weeks 2-4, 4/1,593 subjects in Weeks 4-8, and 5/1,507 subjects in Weeks 8-12. The number of patients with CK elevations to ≥ 5 times the upper reference

limit in the Ezetimibe+statin combination therapy group (925 subjects) over time was 1/877 subjects in Weeks 0-2, 1/891 subjects in Weeks 2-4, 2/861 subjects in Weeks 4-8, and 0/820 subjects in Weeks 8-12. In the foreign long-term treatment study, the number of patients with CK elevations to ≥ 5 times the upper reference limit in the Ezetimibe monotherapy group (1,624 subjects) over time was 15/1,603 subjects in <6 months, 2/910 subjects in 6 to <12 months, 1/622 subjects in 12 to <18 months, 3/486 subjects in 18 to <24 months, and 0/456 subjects in ≥ 24 months. The number of patients with CK elevations to ≥ 5 times the upper reference limit in the Ezetimibe+statin combination therapy group (612 subjects) over time was 6/611 subjects in <6 months, 3/494 subjects in 6 to <12 months, 2/453 subjects in 12 to <18 months, 2/274 subjects in 18 to <24 months, and 0/3 subjects in ≥ 24 months. Based on the above, it is considered that the duration of treatment with Ezetimibe has no effect on CK elevations.

The PMDA considers that it is important to caution about the risk of rhabdomyolysis or myopathy because a causal relationship to Ezetimibe is suspected for some of the patients who experienced rhabdomyolysis or myopathy based on the recurrence of the symptoms after rechallenge, etc. The details of cautioning about this matter and post-marketing information collection for CK and muscle symptoms etc., will be further considered, taking account of comments from the Expert Discussion.

2) Hepatic dysfunction

The applicant compared laboratory changes related to hepatic dysfunction between the Japanese long-term treatment study (at the end of 52-week treatment) and the foreign long-term treatment study (at the end of about 24-month treatment) and explained that persistent elevations of transaminases were not observed in Japan, and the incidence was 0.8% in overall subjects and 0.7% in subjects treated with Ezetimibe monotherapy even overseas.

Number of subjects by the degree of elevation of AST and ALT

Parameter	Category (relative to the upper reference limit)	All subjects		Monotherapy	
		Japan n=178	Overseas n=1,603	Japan n=178	Overseas n=1,603
AST and/or ALT	≥ 3 times	1(0.6%)	31(1.9%)	1(0.6%)	26(1.6%)
	consecutive elevations to ≥ 3 times	0	13(0.8%)	0	11(0.7%)
	≥ 5 times	0	5(0.3%)	0	4(0.2%)
	≥ 10 times	0	0	0	0

The PMDA asked the applicant to explain the occurrence of hepatic dysfunction in post-marketing experience in foreign countries.

The applicant responded as follows:

Between October 17, 2002 and October 16, 2005, 94 hepatic adverse reactions including 58 serious adverse reactions were reported. There were 63 reports of hepatitis, acute hepatitis, autoimmune hepatitis, and toxic hepatitis, and the cumulative reporting rate of hepatitis in patients receiving Ezetimibe was

estimated at 13.1 cases per million patients-year. The time to onset was reported in 40 out of the 63 cases and the median time to onset was 46 days (range: 1-363 days). Ezetimibe was coadministered with a statin in 33 out of the 63 cases (52%). Out of the 63 cases, the symptoms improved after the discontinuation of treatment in 34 cases, but did not improve even after the discontinuation of treatment in 7 cases. In one follow-up report, a relationship between the discontinuation of Ezetimibe and the outcome was unknown, but the patient was recovering. In the remaining 21 cases, the outcome was unknown.

The PMDA asked the applicant to discuss the risk factors for adverse events related to hepatic function based on clinical study data.

The applicant responded as follows:

Based on the pooled data from Japanese clinical studies (n=404), a total of 36 subjects had adverse events related to hepatic function. Logistic regression analysis detected WHO phenotypic classification of hyperlipidemias as a background factor affecting the occurrence of adverse events related to hepatic function, and the odds ratio comparing type IIb with type IIa was 2.5 (1/0.400) and subjects with type IIb were considered more likely to experience adverse events related to hepatic function. However, the incidence of adverse drug reactions was similar between type IIb and type IIa and we have judged that this is unlikely to be an obvious risk factor during treatment with Ezetimibe.

The PMDA asked the applicant to explain when hepatic dysfunction associated with Ezetimibe is likely to occur, based on the results from Japanese and foreign clinical studies.

The applicant responded as follows:

In the Japanese long-term treatment study, the frequency of deviations from the reference range in liver function tests (AST, ALT, γ -GTP) was almost constant up to Week 52, regardless of the duration of treatment, and the incidence of abnormal values did not rise with prolonged duration of treatment. In foreign studies, the number of patients with persistent elevations of liver function tests to ≥ 3 times the upper reference limit during Ezetimibe monotherapy (1691 subjects) over time was 2/1626 subjects in Weeks 0-2, 2/1628 subjects in Weeks 2-4, 1/1,593 subjects in Weeks 4-8, and 5/1,507 subjects in Weeks 8-12. The number of patients with persistent elevations of liver function tests to ≥ 3 times the upper reference limit during combination therapy with Ezetimibe and a statin (925 subjects) over time was 1/877 subjects in Weeks 0-2, 6/891 subjects in Weeks 2-4, 4/863 subjects in Weeks 4-8, and 5/820 subjects in Weeks 8-12. In the foreign long-term treatment study, the number of patients with elevations of liver function tests to ≥ 3 times the upper reference limit during Ezetimibe monotherapy (1624 subjects) over time was 7/1,603 subjects in <6 months, 2/910 subjects in 6 to <12 months, 0/622 subjects in 12 to <18 months, 0/486 subjects for 18 to <24 months, and 2/456 subjects in ≥ 24 months. The number of patients with elevations of liver function tests to ≥ 3 times the upper reference limit during combination therapy with Ezetimibe and a statin (612 subjects) over time was 0/611 subjects in <6 months, 2/494 subjects in 6 to <12 months, 0/453 subjects in 12 to <18 months, 0/274 subjects in 18 to <24 months, and 0/3 subjects in ≥ 24 months. Thus, it was suggested that elevations of liver function tests occurred primarily within 12

months after the start of treatment. In foreign studies, Ezetimibe in combination with a statin resulted in an increased incidence of adverse events of hepatic function abnormal, but there was no clear relationship between the duration of treatment and hepatic function abnormal.

The PMDA asked for the applicant's view on the necessity of cautioning and monitoring for adverse events related to hepatic function.

The applicant responded as follows:

In Japanese clinical studies, adverse events related to hepatic function associated with Ezetimibe monotherapy were all mild. In foreign clinical studies, the incidence of consecutive elevations of hepatic enzymes to >3 times the upper reference limit was comparable between the Ezetimibe monotherapy group and the placebo group. Therefore, cautioning or monitoring for adverse events related to hepatic function associated with Ezetimibe monotherapy is considered unnecessary.

Although adverse reactions related to hepatic dysfunction after treatment with Ezetimibe are mentioned in the proposed package insert, there were subjects who did not recover after the discontinuation of Ezetimibe. Thus, the PMDA will further consider caution statements, taking comments from the Expert Discussion also into account. In addition, it is necessary to collect and review information appropriately after marketing, but the details will be considered, taking also account of comments from the Expert Discussion (See (5) for hepatic dysfunction during combination therapy with statins).

3) Effects on blood glucose levels

The PMDA asked about the effects of Ezetimibe on glucose tolerance because treatment with Ezetimibe did not cause clear increases in HbA_{1c} or glycoalbumin, but resulted in elevations of fasting blood glucose in a Japanese glucose metabolism study (Study JPC-02-335-35).

The applicant responded as follows:

The fasting blood glucose levels in subjects with concomitant insulin (5/27 subjects) were 101.4±22.10 mg/dL (Mean±SD) at baseline and 148.0±38.53 mg/dL at the end of treatment (the mean change: 46.6, 95% confidence interval: 11.5-81.7), and those in subjects without concomitant insulin (22/27 subjects) were 144.4±36.26mg/dL at baseline and 151.7±38.01 mg/dL at the end of treatment (the mean change: 10.4, 95% confidence interval:1.4-19.3). The possibility that elevations of fasting blood glucose in subjects receiving concomitant insulin affected the assessment of fasting blood glucose in this study can not be denied. However, HbA_{1c} and glycoalbumin are more reliable indicators compared with fasting blood glucose and the time course of HbA_{1c} and glycoalbumin may diverge from that of fasting blood glucose. Since there were no changes in HbA_{1c} or glycoalbumin in subjects receiving concomitant insulin in the glucose metabolism study with Ezetimibe, there should be no concerns that blood glucose is likely to be increased in patients with diabetes requiring control with insulin preparations.

The PMDA asked the applicant to present the results of analysis of the effects of Ezetimibe on glucose

metabolism parameters in the foreign long-term treatment study by the patient background (with or without concomitant insulin preparations, presence or absence of diabetes, etc.) and then assess whether there are any differences from the results of the Japanese long-term treatment study.

The applicant responded as follows:

In the foreign long-term treatment study (P00476), as shown in the following table, the fasting blood glucose levels in subjects with concurrent diabetes (66 subjects) were 137 ± 34.5 mg/dL (Mean \pm SD) at the start of treatment with Ezetimibe and 153 ± 32.8 mg/dL after ≥ 24 months of treatment (Change: 7.89), and those in subjects without concurrent diabetes (1,247 subjects) were 95.7 ± 12.5 mg/dL at the start of treatment with Ezetimibe and 96.8 ± 13.3 mg/dL after ≥ 24 months of treatment (Change: 1.75). In those receiving concomitant insulin among subjects with concurrent diabetes (7 subjects), the fasting blood glucose levels were 134 ± 63.6 mg/dL at the start of treatment with Ezetimibe and 177 ± 75.4 mg/dL after ≥ 24 months of treatment (Change: -11). In those without concomitant insulin among subjects with concurrent diabetes (59 subjects), the fasting blood glucose levels were 137 ± 30.3 mg/dL at the start of treatment with Ezetimibe and 148 ± 18.6 mg/dL after ≥ 24 months of treatment (Change: 11.7). In the Japanese long-term treatment study, as shown in the following table, the changes in fasting blood glucose were greater in subjects with concurrent diabetes than in those without concurrent diabetes and in those receiving concomitant insulin than in those without concomitant insulin.

Fasting blood glucose and change in fasting blood glucose over time in the foreign long-term treatment study: with or without diabetes

Concurrent diabetes	Summary statistic	Duration of treatment with Ezetimibe (months)							
		Baseline	<3	3 to <6	6 to <9	9 to <12	12 to <18	18 to <24	≥24
Present	n	66	51	60	35	29	24	19	18
	Mean ±SD	137 ± 34.5	141 ± 43.0	144 ± 36.2	146 ± 38.0	150 ± 44.3	157 ± 38.7	144 ± 33.9	153 ± 32.8
	Median	131	133	142	145	143	148	137	153
	Min-Max	51-232	42-325	57-249	92-275	95-287	90-264	79-213	91-233
	Change	-	6.55	7.15	5	6.52	6.13	-3.42	7.89
Absent	n	1,247	1,020	1,120	769	659	597	466	438
	Mean ±SD	95.7 ± 12.5	96.2 ± 12.5	99.7 ± 17.3	98.2 ± 15.9	99.1 ± 18.2	98.2 ± 18.9	96.6 ± 13.7	96.8 ± 13.3
	Median	95	95	97	96	97	96	94	94
	Min-Max	52-180	60-179	71-445	62-361	58-326	60-431	64-199	70-173
	Change	-	0.405	3.73	2.34	3.31	2.98	1.62	1.75

The unit of measurement of fasting blood glucose: mg/dL

Fasting blood glucose and change in fasting blood glucose over time in the foreign long-term treatment study: with or without concomitant insulin preparations

Concomitant insulin	Summary statistic	Duration of treatment with Ezetimibe (months)							
		Baseline	<3	3 to <6	6 to <9	9 to <12	12 to <18	18 to <24	≥24
Present	n	7	5	6	5	4	4	3	3
	Mean ±SD	134 ± 63.6	196 ± 92.6	144 ± 55.4	168 ± 72.8	181 ± 95.1	168 ± 58.4	163 ± 69.8	177 ± 75.4
	Median	123	157	152	166	168	178	192	206
	Min-Max	51-232	90-325	57-205	92-275	100-287	90-226	83-213	91-233
	Change	-	73.8	8.5	15.4	15.5	2.75	-25	-11
Absent	n	59	46	54	30	25	20	16	15
	Mean ±SD	137 ± 30.3	135 ± 30.5	144 ± 34.2	142 ± 29.3	145 ± 31.3	155 ± 35.2	141 ± 25.4	148 ± 18.6
	Median	136	130	142	145	143	146	137	148
	Min-Max	87-214	42-200	88-249	99-234	95-222	111-264	79-171	111-178
	Change	-	-0.761	7	3.27	5.08	6.8	0.625	11.7

The unit of measurement of fasting blood glucose: mg/dL

Fasting blood glucose and change in fasting blood glucose over time in the Japanese long-term treatment study: with or without diabetes

Concurrent diabetes	Summary statistic	Duration of treatment with Ezetimibe (weeks)									
		-4	Baseline	4	8	12	20	28	36	44	52
Present	n	26	26	27	26	24	24	24	23	23	23
	Mean ±SD	133.0 ±37.1	127.5 ±33.3	128.0 ±27.0	131.2 ±37.7	133.9 ±40.8	142.3 ±25.2	130.9 ±25.1	128.9 ±22.1	134.6 ±29.0	137.2 ±31.2
	Median	126.5	116	123	124.5	131.5	140.5	130.5	128	128	140
	Min-Max	68-208	72-223	85-187	57-233	60-246	91-189	85-188	92-174	99-193	76-193
	Change	1.9	-	-1.6	-1.5	-0.9	10.0	-1.9	1.2	6.7	8.6
Absent	n	69	69	68	65	64	62	56	57	56	53
	Mean ±SD	96.3 ±9.1	97.0 ±15.3	96.2 ±11.3	96.1 ±11.6	96.1 ±11.1	96.9 ±11.5	94.9 ±10.6	95.8 ±11.0	94.9 ±10.4	96.0 ±10.9
	Median	95	96	95.5	95	95	95	94	95	95	95
	Min-Max	78-124	68-185	69-121	74-125	68-125	68-128	71-126	68-133	68-117	71-123
	Change	-0.7	-	-0.8	-0.8	-0.9	-0.4	-1.8	-1.2	-2.2	-0.5

The unit of measurement of fasting blood glucose: mg/dL

Fasting blood glucose and change in fasting blood glucose over time in the Japanese long-term treatment study: with or without concomitant insulin preparations

Concomitant insulin	Summary statistic	Duration of treatment with Ezetimibe (weeks)									
		-4	Baseline	4	8	12	20	28	36	44	52
Present	n	6	6	6	6	6	6	6	6	6	6
	Mean ±SD	109.5 ±41.4	116.0 ±35.4	116.5 ±30.7	115.8 ±50.3	101.0 ±38.3	141.2 ±30.9	117.3 ±25.0	108.5 ±13.7	125.5 ±35.1	121.2 ±42.5
	Median	95.5	110.5	115	110.5	91.5	134	125.5	105	111.5	117
	Min-Max	68-162	72-179	85-165	57-204	60-172	104-186	85-142	92-129	99-190	76-180
	Change	-6.5	-	0.5	-0.2	-15.0	25.2	1.3	-7.5	9.5	5.2
Absent	n	20	20	21	20	18	18	18	17	17	17
	Mean ±SD	140.0 ±33.6	131.0 ±32.8	131.3 ±25.7	135.8 ±33.3	144.9 ±36.1	142.7 ±24.0	135.4 ±24.2	136.1 ±20.1	137.8 ±27.0	142.9 ±25.4
	Median	132	120	123	127	134.5	141.5	131	137	130	140
	Min-Max	96-208	95-223	100-187	97-233	98-246	91-189	91-188	103-174	105-193	104-193
	Change	4.6	-	-2.2	-1.9	4.1	4.7	-3.0	4.4	5.6	9.9

The unit of measurement of fasting blood glucose: mg/dL

The PMDA asked the proportion of patients with concurrent diabetes or abnormal glucose tolerance in the target patient population for Ezetimibe.

The applicant responded as follows:

According to an updated report on type II diabetes (Decision Resource Pharmacor May 2004), 50.7% of patients with confirmed diabetes (1,480 subjects) had a LDL-C value ≥ 130 mg/dL and 66.8% had a total cholesterol value ≥ 200 mg/dL. Although poorly controlled diabetic patients were excluded from Japanese clinical studies, the proportion of subjects with concurrent diabetes was 25% (135/546 subjects) across all Japanese clinical studies, 28% (38/136 subjects) in the phase II study, 24% (48/202 subjects) in the comparative study with colestimide, and 27% (44/163 subjects) in the long-term treatment study, and these

studies had a similar number of patients with concurrent diabetes. Thus, it seems appropriate to assume that the proportion of patients with concurrent diabetes in the target patient population for Ezetimibe is about 25%.

The PMDA considers as follows:

Although subjects receiving concomitant insulin showed no significant changes in HbA_{1c} or glycoalbumin in either the glucose metabolism study or the Japanese/foreign long-term treatment studies, there was a trend towards higher fasting blood glucose levels at the end of treatment compared with baseline, and it is necessary to appropriately caution about the risk of increased blood glucose during treatment with Ezetimibe in diabetic patients.

The PMDA asked for the applicant's view.

The applicant responded as follows:

Since the possibility that Ezetimibe may increase blood glucose in some diabetic patients can not be ruled out, the following statement will be included in "2. Important Precautions" of the PRECAUTIONS section of the package insert: "As elevations of fasting blood glucose in diabetic patients have been reported, adequate caution should be exercised."

The PMDA considers as follows:

As there are a large number of patients with diabetes and a considerable proportion of diabetic patients have concurrent hypercholesterolemia, it is envisaged that Ezetimibe will be administered to diabetic patients, and the occurrence of abnormal glucose tolerance associated with Ezetimibe and the effects of Ezetimibe on glycemic control in diabetic patients are important issues to be studied and it is necessary to appropriately collect and review information after marketing. The details of information provision/cautioning and post-marketing surveillance etc. on this matter will be further considered, taking also account of comments from the Expert Discussion.

4) Adverse events associated with the inhibition of cholesterol absorption

The PMDA asked the applicant to discuss anticipated adverse events associated with an increase in unabsorbed dietary components in feces resulting from the inhibition of intestinal absorption of cholesterol etc. by Ezetimibe.

The applicant responded as follows:

The main adverse events classified as gastrointestinal disorders occurring following treatment with Ezetimibe (the pooled data from the phase I clinical pharmacology study, the phase II study, the comparative study with colestimide, the glucose metabolism study, the homozygous FH study, and the study in patients with severe hypercholesterolemia, n=326) were constipation (2.1%), abdominal distension (1.8%), and queasy (1.2%), as well as dyspepsia, abdominal pain, flatulence, etc. were also observed. In foreign countries, 1 event of faecal incontinence was reported during the period covered by the 1st Periodic Safety Update Report for marketed drugs (PSUR) for Ezetimibe (October 17, 2002 to April 16, 2003) and

4 events of steatorrhea were reported during the period covered by the 2nd PSUR (April 17, 2003 to October 16, 2003). Drugs that inhibit the intestinal absorption of lipids, like Ezetimibe, include anion-exchange resins, orlistat, ethyl icosapentate, plant sterol, and gamma-oryzanol, and adverse reactions commonly reported with these drugs are, on the whole, similar to the symptoms observed with Ezetimibe, which are presumably attributable to increased excretion of lipids.

Since gastrointestinal adverse events such as constipation and abdominal distension occurred relatively commonly, the PMDA asked the applicant to assess the background factors etc. predisposing to these adverse events and then explain the necessity of cautioning.

The applicant responded as follows:

In order to assess the background factors affecting gastrointestinal adverse events such as constipation and abdominal distension, logistic regression analysis was performed using the pooled data from the Japanese phase II clinical study (Ezetimibe 10 mg), the comparative study with colestimide (Ezetimibe 10 mg), the glucose metabolism study, the study in patients with severe hypercholesterolemia, the homozygous FH study, and the long-term treatment study (Ezetimibe 10 mg monotherapy), but no clinically relevant background factor was detected. The incidence of adverse reactions of constipation/constipation aggravated with Ezetimibe 10 mg was 3.4% (12/358), which is about one-third of that with colestimide, and their severity was mostly mild. Thus, these symptoms have been just mentioned as “Other adverse reactions.”

The PMDA considers that it is necessary to collect information on gastrointestinal adverse events associated with Ezetimibe after marketing, but the details of post-marketing surveillance will be further considered, taking also account of comments from the Expert Discussion.

5) The risk of promoting gallstone formation

The PMDA asked about the cases of cholelithiasis and cholecystitis reported to date in foreign countries, in view of the fact that Ezetimibe increased the cholesterol concentration in the gallbladder bile by about 2 to 3-fold in dogs and that the U.S. labeling states that cholelithiasis and cholecystitis have been reported in post-marketing experience. The PMDA also asked for the applicant’s view on the possibility that Ezetimibe may promote gallstone formation.

The applicant responded as follows:

Gallbladder adverse events collected between the initial approval of Ezetimibe overseas (October 17, 2002) and April 16, 2005 were 18 events of cholelithiasis, 5 events of cholestasis, 3 events of cholecystitis, 2 events of gallstone colic, 2 events of bile duct stone, and 1 event of gallbladder disorder, and the reporting rate of gallbladder adverse events was estimated at 7.7 cases per million patients-year, which was far below the background incidence rate of cholelithiasis (6.3-9.3 cases per 1000 patients-year). Fenofibrate was concomitantly used in 2 among the 13 cases with documented concomitant medications. According to pooled analysis of all foreign controlled studies with Ezetimibe as monotherapy and in combination with

statins, the incidence of all gallbladder adverse events was 7.41 cases per 1000 patients-year (95% confidence interval: 3.7-13.3) with Ezetimibe, 4.53 (2.8-6.9) cases per 1000 patients-year with Ezetimibe+statin, 7.76 (0.9-28.0) cases per 1000 patients-year with placebo, and 6.26 (3.2-10.9) cases per 1000 patients-year with all statins, and it seems that Ezetimibe does not increase the risk of gallbladder adverse events.

The PMDA considers that it is necessary to collect and review information on biliary adverse events associated with Ezetimibe after marketing. The details of post-marketing surveillance will be further considered, taking also account of comments from the Expert Discussion.

(Combination therapy with fibrates has already been described in the earlier section.)

6) The risk for acute pancreatitis

The PMDA asked the applicant to explain the overseas reports of acute pancreatitis to date and then discuss the cause of the occurrence of acute pancreatitis associated with Ezetimibe, since acute pancreatitis has been reported in post-marketing experience overseas; the U.S. labeling also notes acute pancreatitis; acute pancreatitis is associated with cholelithiasis; and there is a relationship between abnormal glucose metabolism and acute pancreatitis.

The applicant responded as follows:

According to the clinical trial database for Ezetimibe (including combination therapy with statins), there was no report of acute pancreatitis, whereas there were 27 reports of pancreatitis between the initial approval of Ezetimibe overseas (October 17, 2002) and April 16, 2004 and the reporting rate was estimated at approximately 1.2 cases per 100,000 patients-year. The symptoms recurred after rechallenge in 2 out of the 27 cases. One case of pancreatitis had documented adverse events including diabetes or hyperglycaemia. This patient had hyperglycaemia, borderline diabetes, obesity, metabolic syndrome, and previous use of fenofibrate, who developed pancreatitis 3 weeks after the start of treatment with Ezetimibe and was found to have hyperglycaemia (208 mg/dL) on the day of onset of pancreatitis. Seventeen cases of pancreatitis were reported in patients with a history of diabetes and there were no changes in their condition of diabetes.

Although pancreatitis is mentioned in the Adverse Reactions section of the proposed package insert, there has been more than one report of acute pancreatitis possibly related to Ezetimibe. Thus, the PMDA will further consider the necessity of additional cautioning and post-marketing information collection/review, taking also account of comments from the Expert Discussion.

7) The potential for psychiatric symptoms such as depression

In Australia, since the approval of Ezetimibe as of June 2003, 265 adverse reactions possibly related to Ezetimibe have been reported. Of which, 12 adverse reactions are depression (9 events) or depressed mood (3 events), and it has been reported that the only suspected medicinal product in all cases is Ezetimibe (Australian Adverse Drug Reactions Bulletin (October 2006)). Of these, 7 events occurred within 4 days

and 3 events occurred at 4-6 weeks of treatment, and the symptoms resolved following the dose reduction of Ezetimibe in 1 case, concurrent depression worsened after the second administration in 1 case, and the symptoms improved after the discontinuation of Ezetimibe, but recurred after rechallenge in 5 subjects. In view of these clinical courses, a relationship between Ezetimibe and depression is strongly suspected and close monitoring is recommended in the early phase of treatment with Ezetimibe, especially in elderly patients. Based on the above, the PMDA asked the applicant to investigate the presumed mechanism of action relevant to depression associated with Ezetimibe (the inhibition of absorption of tryptophan, a serotonin precursor, etc.) and then show the applicant's view on the relationship between Ezetimibe and depression.

The applicant responded as follows:

When the data from post-marketing adverse reaction reports on Ezetimibe received from the medical institutions during the first 3 years after marketing (October 17, 2002 to October 16, 2005) were studied, a total of 48 patients experienced depressed mood, depression, or depressive symptom. The time to the onset of depression was documented for 25 patients and the median was 22 days (1 day to 2 years). Previous and concurrent illnesses were documented for 25 patients, of whom 6 patients had concurrent depression or a disease that can contribute to the onset of depression (hypothyroidism, prostate cancer, etc.). Concomitant medications were documented for 32 patients, of whom 24 patients were receiving antidepressants or medications with which the onset of depression has been reported. The outcome was documented for 28 patients, of whom 20 patients recovered/were recovering after the discontinuation of Ezetimibe and 8 patients did not recover. 5 patients experienced recurrence after rechallenge and 2 patients did not experience recurrence after rechallenge. Since the estimated cumulative number of patients exposed to ezetimibe after marketing between October 17, 2002 and September 30, 2005 was 4,806,861 patients-year, the reporting rate of depressive adverse events with Ezetimibe is estimated at approximately 10 in a million. However, as the prevalence of depressive disorder in the U.S. is approximately one in 14 (6.91%), the background incidence rate of depression exceeds the incidence of depression as an adverse reaction in patients treated with Ezetimibe. Although a study assessing the effects of Ezetimibe on the absorption of tryptophan has not been performed, Ezetimibe affects only the absorption of cholesterol and plant sterols by specifically inhibiting NPC1L1, and has no effect on the absorption of other nutrients. So far, there has been no evidence showing a relationship between Ezetimibe and depression.

The PMDA asked the applicant to explain the occurrence of psychiatric symptoms including depression in Japanese and foreign clinical studies and then show the applicant's view on the potential for the occurrence of psychiatric symptoms associated with Ezetimibe and the necessity of a caution statement in the package insert.

The applicant responded as follows:

Of 504 subjects treated with Ezetimibe in Japanese clinical studies with a treatment duration of at least 4 weeks, only 8 subjects experienced adverse events classified as the "psychiatric disorders" System Organ Class ("insomnia"), and a causal relationship to Ezetimibe was denied for all cases. The safety data from 3

foreign phase II and 6 foreign phase III clinical studies with Ezetimibe monotherapy were classified into the three groups of placebo, Ezetimibe 10 mg, and all doses of Ezetimibe (0.25, 1, 5, 10, 20, and 40 mg) for evaluation. As a result, the percentage of subjects who experienced psychiatric adverse events during the treatment period was 3.1% (25/795 subjects) in the placebo group, 3.5% (59/1,691 subjects) in the Ezetimibe 10 mg group, and 3.3% (66/1,983 subjects) in the group of all doses of Ezetimibe, the percentage of subjects who experienced depression was 0.4% (3/795 subjects) in the placebo group, 0.5% (9/1,691 subjects) in the Ezetimibe 10 mg group, and 0.6% (11/1,983 subjects) in the group of all doses of Ezetimibe, and the percentage of subjects who experienced depression aggravated was 0.1% (1/795 subjects) in the placebo group, 0.2% (4/1,691 subjects) in the Ezetimibe 10 mg group, and 0.2% (4/1,983 subjects) in the group of all doses of Ezetimibe. It seems that Ezetimibe does not increase the risk for psychiatric adverse events compared to placebo and although monitoring for reports of depression-related events occurring in patients treated with Ezetimibe will be continued, there should be no problems with the current proposed package insert.

Although the reporting frequency of depression etc. is low also in overseas post-marketing surveillance and clinical studies showed no trend towards increases in depression with Ezetimibe, there have been cases where the symptoms recurred after rechallenge with Ezetimibe as well as cases of suicidal ideation. Therefore, the PMDA considers that it is necessary to collect and review information on the potential for depression etc. during treatment with Ezetimibe after marketing. This matter will be further considered, taking also account of comments from the Expert Discussion.

(8) Post-marketing clinical studies and post-marketing surveillance

The PMDA considers as follows:

In view of the characteristics of the disease, Ezetimibe is expected to be administered over a long period of time, and it is necessary to collect information on the efficacy and safety of long-term treatment with Ezetimibe as a monotherapy and in combination with statins or other antihyperlipidemia drugs after marketing. In addition, surveillance should be focused on rare adverse reactions such as rhabdomyolysis, the time course of fasting blood glucose in diabetic patients, the administration of a reduced dose (especially in patients with decreased hepatic function), the occurrence of hepatic dysfunction, gastrointestinal adverse events due to the inhibition of absorption of cholesterol etc., biliary adverse events associated with coadministration of Ezetimibe with fibrates, the onset of acute pancreatitis and depression, and thrombocytopenia, which is noted as an adverse reaction in foreign countries. It is also necessary to collect detailed information on the efficacy and safety in patients with familial hypercholesterolemia. Ezetimibe has never been administered to patients with homozygous sitosterolemia in Japan and if this indication is approved, it is necessary to collect information on patients with homozygous sitosterolemia treated with Ezetimibe.

The PMDA asked the applicant to submit an outline of post-marketing surveillance (draft).

The applicant responded as follows:

In order to confirm the safety and efficacy of Ezetimibe in patients with hypercholesterolemia or familial

hypercholesterolemia under routine drug uses, the following Specified Drug Use Investigations are planned to be conducted: a survey on a 12-week treatment with target numbers of cases of 5,000 for Ezetimibe monotherapy and 5,000 for combination therapy and a survey on a 52 week-treatment with target numbers of cases of 500 for Ezetimibe monotherapy and 500 for combination therapy. With regard to the safety, in addition to overall evaluation, the occurrence of adverse drug reactions, especially blood glucose levels, hepatic dysfunction, rhabdomyolysis, CK increased, muscle symptoms, urine protein, hormones such as blood cortisol, gastrointestinal symptoms, thrombocytopenia, pancreatitis, cholelithiasis, cholecystitis, and depression and depressed mood will be identified. Concerning homozygous sitosterolemia, we will identify medical institutions treating the patients and ask for cooperation with the Specified Drug Use Investigation, and collect information. To investigate effects of Ezetimibe on glucose metabolism in hypercholesterolemic patients with concurrent diabetes or abnormal glucose tolerance, we will discuss with diabetes specialists and develop a plan, for example, investigating such effects in a post-marketing clinical study.

The PMDA will further consider the details of post-marketing surveillance, taking also account of comments from the Expert Discussion.

III. Results of Compliance Review Concerning the Documents Appended to New Drug Application and Conclusion by the PMDA

1. The PMDA's conclusion on the results of document compliance review

Document compliance review was conducted in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application. As a result, although some protocol deviations were found, there were no serious problems and the sponsor handled them appropriately. Therefore, the PMDA concluded that there should be no problem with conducting regulatory review based on the submitted documents.

2. The PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to the new drug application (5.3.5.1.1.1, 5.3.5.1.2.1, 5.3.5.2.1, 5.3.5.2.2, 5.3.5.4.1). As a result, at some medical institutions, a review conducted by the Institutional Review Board in the absence of doctors and non-compliance with the protocol-specified exclusion criteria for case registration, etc. were found (the clinical trial sites) and failure to detect these issues due to the sponsor's non-compliance with the monitoring procedure were identified (the sponsor), but there were no serious problems. Thus, the PMDA concluded that there should be no problem with conducting regulatory review based on the submitted documents.

IV. Overall Evaluation

As a result of the above review, based on the submitted data, although Ezetimibe is unlikely to be considered as a first-choice drug for the treatment of hypercholesterolemia, the PMDA has judged that the

efficacy of Ezetimibe in the treatment of hypercholesterolemia has been demonstrated, also taking into consideration the overseas experience where Ezetimibe has been already widely used. Currently, there are some patients in whom HMG-CoA reductase inhibitors, which are mainly used for the treatment of hypercholesterolemia in Japan, provide inadequate efficacy or are undesirable due to adverse reactions etc., and when Ezetimibe, which has a novel mechanism of action, is coadministered with an HMG-CoA reductase inhibitor, incremental LDL-C lowering effects are also expected. In view of these aspects, Ezetimibe is considered to have clinical usefulness. As Ezetimibe is a drug with a novel mechanism of action, it should be important to collect information during actual clinical use including a long-term treatment.

Review Report (2)

January 19, 2007

I. Product Submitted for Registration

[Brand name]	Zetia Tablets 10 mg
[Non-proprietary name]	Ezetimibe
[Name of applicant]	Schering-Plough K.K.
[Date of application]	October 31, 2003 (application for marketing approval for imported drugs)

II. Content of the Review

The PMDA sought the expert advisors' opinions based on the Review Report (1). The results of review taking account of a discussion with the expert advisors are reported as follows.

1. Clinical positioning and indications

The LDL-cholesterol lowering effect of Ezetimibe monotherapy and the LDL-cholesterol lowering effect of Ezetimibe in combination with statins have been demonstrated and Ezetimibe is expected to be effective in treating hypercholesterolemia, with a mechanism of action that differs from those of existing drugs. Providing Ezetimibe to the clinical practice is significant in terms of offering more choices of anti-hypercholesterolemia drugs. In addition to coadministration of Ezetimibe with statins, Ezetimibe monotherapy may be useful in some cases including the case of patients who can not tolerate statins. Therefore, the expert advisors agreed that both combination therapy with statins and Ezetimibe monotherapy are justified. The following comments were raised from the expert advisors: Ezetimibe can be used for the treatment of familial hypercholesterolemia, which should basically be considered in the same manner as the treatment of high risk patients with hypercholesterolemia; familial hypercholesterolemia requires a potent cholesterol-lowering effect and if Ezetimibe is used for severe familial hypercholesterolemia, a statin will generally be coadministered in clinical practice; in view of the mechanism of action of Ezetimibe, the indication of homozygous sitosterolemia is also justified although it is necessary to ensure information collection after marketing; it is necessary to appropriately provide information that there is no available data supporting that Ezetimibe reduces cardiovascular events or improves survival prognosis.

Taking account of the comments from the Expert Discussion, the PMDA judged that the proposed indications are justified and asked the applicant to appropriately provide information that there is no available clinical study data showing that Ezetimibe reduces the risk of coronary artery disease and cerebrovascular disorder.

The applicant responded as follows:

The following statement will be included in the CLINICAL STUDIES section of the package insert: “The effects of Ezetimibe as a monotherapy or in combination with a statin in reducing cardiovascular morbidity and mortality have not been established.”

The PMDA accepted the response.

2. Dosage and administration

The expert advisors discussed and agreed as follows:

Based on the results of the dose-finding study, the difference in the percent reduction in LDL-cholesterol between the doses of 5 mg and 10 mg was not large and the possibility that Ezetimibe even at a dose lower than 10 mg may be effective in Japanese patients can not be ruled out. If Ezetimibe is approved for a 10 mg dose, collecting post-marketing adverse drug reaction information is important. However, as long as contraindications and the recommendations for “Careful Administration” as to patients with hepatic impairment are established and due caution is advised, the dosage and administration based on the results of Japanese clinical studies, “The usual adult dosage for oral use is 10 mg of Ezetimibe once daily after a meal. The dosage may be reduced according to the patient’s age and symptoms.” is justified.

3. Combination therapy with statins or fibrates

The PMDA judged that combination therapy with statins is justified based on the results of Japanese and foreign clinical studies although adequately cautioning about hepatic dysfunction and periodic liver function monitoring are necessary. This PMDA’s judgment was supported by the expert advisors.

There is a possibility that Ezetimibe is coadministered with fibrates in hypercholesterolemic patients with hypertriglyceridemia, but coadministration of Ezetimibe with fibrates has not been studied in Japan and it potentially causes increased gallbladder diseases. Thus, the PMDA judged that coadministration with fibrates should not be recommended. This PMDA’s judgment was also supported by the expert advisors and there was a comment that coadministration of Ezetimibe with fibrates can not be recommended unless further information becomes available.

Taking account of comments from the Expert Discussion, the PMDA judged that coadministration of Ezetimibe with a statin should be contraindicated in patients with severe hepatic impairment and that it should be clearly noted that coadministration of Ezetimibe with fibrates is not recommended as its efficacy and safety have not been adequately confirmed, and asked the applicant to amend the relevant sections in the package insert.

The applicant responded that the relevant sections in the package insert would be amended in accordance with the PMDA’s instruction.

The PMDA judged the applicant’s response was appropriate.

4. Provision of safety information, etc.

At the Expert Discussion, the following issues were mainly discussed: cautioning about rhabdomyolysis or myopathy; the appropriateness of the use of Ezetimibe in patients with moderate or severe hepatic impairment and cautioning about the use of Ezetimibe in patients with hepatic impairment; cautioning about hepatic dysfunction during Ezetimibe monotherapy and hepatic dysfunction during combination therapy with statins; cautioning about the effects of Ezetimibe on the occurrence of abnormal glucose tolerance and glycemic control in diabetic patients; and cautioning about gastrointestinal adverse events associated with Ezetimibe. Based on these discussions, the PMDA required the followings: coadministration of Ezetimibe with a statin should be contraindicated in patients with severe hepatic impairment; patients with hepatic impairment should be included in the Careful Administration section of the package insert; the statement about liver function tests recommended during coadministration of Ezetimibe with a statin should be reconsidered; diabetic patients should be included in the Careful Administration section of the package insert. At the same time, the PMDA asked the applicant to improve the statements in the proposed package insert, e.g. reconsider appropriate caution statements in the package insert, taking also account of overseas labeling.

In accordance with the PMDA's instructions, the applicant improved the statements in "CONTRAINDICATIONS," "Precautions of Indications," "Careful Administration," "Important Precautions," "Interactions," and "Adverse Reactions" of the proposed package insert.

The PMDA judged that the applicant's response was appropriate.

5. Post-marketing information collection

The following comments were raised from the expert advisors: it is necessary to collect efficacy and safety information on long-term treatment with Ezetimibe after marketing; it is necessary to collect information on long-term coadministration with other antihyperlipidemia drugs, and the effects of Ezetimibe on the occurrence of abnormal glucose tolerance and on glycemic control in diabetic patients; it is also necessary to collect information about patients who received a reduced dose; an appropriate sample size for long-term treatment should be determined after defining the objectives of the survey; surveillance should be focused on adverse events anticipated at present; care should be exercised so as to prevent unnecessary combination therapy for collecting patients for the combination therapy group. Based on these discussions, the PMDA asked the applicant to reconsider the sample size required to confirm the safety and efficacy of long-term treatment with Ezetimibe in a survey on a 52-week treatment.

The applicant responded as follows:

Based on the incidence of adverse drug reactions in the Japanese long-term clinical study, the sample size for a survey on long-term treatment of 52 weeks is determined to be 500 patients each for monotherapy and combination therapy and the target number of recruitment is 700 patients each for monotherapy and combination therapy, allowing for dropouts.

The PMDA judged that the outline of post-marketing surveillance (draft) presented by the applicant was basically appropriate although the details needed to be further considered.

III. Overall Evaluation

As a result of the above review, the PMDA has concluded that it is appropriate for the application to be discussed at the First Committee on New Drugs, considering that the product may be approved for the following indications and dosage and administration.

Since this application is classified as drugs containing a new active ingredient, a re-examination period of 6 years should be appropriate.

Either the drug substance or the drug product is not classified as a poisonous drug or a powerful drug and the product is not classified as a biological product or a specified biological product.

[Indications]

Hypercholesterolemia, familial hypercholesterolemia, homozygous sitosterolemia

[Dosage and administration]

The usual adult dosage for oral use is 10 mg of Ezetimibe once daily after a meal. The dosage may be reduced according to the patient's age and symptoms.