24th December 1999

EVALUATION REPORT

[Evaluated Articles]	Product name: Lipitor, Lipitor 5mg Tablet, Lipitor 10mg Tablet Generic name: atorvastatin calcium hydrate
[Submission Date]	24th August 1998 (Import approval of the drug substance, manufacturing approval of the drug product)
[Applicant]	Drug substance: Warner-Lambert Drug product: Yamanouchi Pharmaceutical Co., Ltd
[Evaluation]	Evaluation Division II, Pharmaceuticals and Medical Device Evaluation Centre, National Institute of Health Sciences
[Subcommittee]	2nd Subcommittee on New Drugs

[Evaluation Result]

As a result of evaluation by the Pharmaceuticals and Medical Device Evaluation Centre and discussion by the 2nd Subcommittee on New Drugs, we have no objection in granting an approval of the articles.

[Indications]

Hypercholesterolemia

Familial hypercholesterolemia

[Dosage and Administration Method]

Hypercholesterolemia

Usually for adults, orally administer 10mg of atorvastatin once daily

Familial hypercholesterolemia

Usually for adult, orally administer 10mg of atorvastatin once daily

The dose should be adjusted according to age and symptoms. In severe cases, the dose may be increased to up to 40mg per day.

18th May 1999

EVALUATION SUMMARY (PART 1)

Pharmaceuticals and Medical Device Evaluation Centre

1. SUMMARY OF THE ARTICLES

[Product name] Lipitor, Lipitor tablet 5mg, Lipitor tablet 10mg

[Generic name] Atorvastatin calcium hydrate

[Submission Date] 24th August 1998 (Import approval of the drug substance, manufacturing approval of the drug product)

[Applicant] Drug substance: Warner-Lambert

Drug product: Yamanouchi Pharmaceutical Co., Ltd

[Formulation and content]

Film coat tablets containing 5mg or 10mg of atorvastatin per tablet

[Indications] Hypercholesterolaemia

Familial hypercholesterolaemia

[Dosage and Administration Method]

Hypercholesterolaemia

Usually for adults, orally administer 10mg of atorvastatin once daily

Familial hypercholesterolaemia

Usually for adults, orally administer 10mg of atorvastatin once daily

The dose should be adjusted according to age and symptoms. In severe cases, the dose may be increased to up to 40mg per day.

2. SUMMARY OF THE SUBMITTED DATA AND EVALUATION BY THE EVALUATION CENTRE

A. Data On Origin, Details of Discovery, Use in Overseas Countries, etc.

Atorvastatin is a HMG-CoA reductase inhibitor for treatment of hyperlipidemia, which was synthesised by Warner-Lambert (US) in 1986. It is approved in 68 countries including the UK, Germany and the USA (as of March 1999).

In addition to non-clinical and clinical studies implemented by Warner-Lambert (US), non-clinical studies were implemented in Japan. The Japanese clinical study program was started in November 1992. In November 1993, Warner-Lambert and Yamanouchi Pharmaceuticals concluded a joint development contract. Since then, the two companies implemented joint non-clinical and clinical studies and came to apply for an importing approval of the drug substance for Warner-Lambert and a manufacturing approval of the drug products for Yamanouchi Pharmaceutical.

In December 1994, the production method of the drug substance was improved and the amorphous drug substance was replaced with a more stable and purer crystalline drug substance. In Japan, the Applicant used formulations with the crystalline drug substance from phase IIb clinical studies onward.

B. Data on Physical and Chemical Properties, Specifications and Test Methods, etc.

With regard to specifications and test methods of the drug substance, the Evaluation Centre instructed the Applicant to specify optical rotation as a specific physical and chemical value for the Identification Test and to review the specification of heavy metal in the Purity Test. In addition, they asked for more detailed discussion on the safety of related substances. Referring to a replacement of the amorphous drug substance with the crystalline drug substance, the Evaluation Centre instructed the Applicant to provide information on their differences in stability and dissolution speed. Furthermore, they instructed the Applicant to amend the *Gaiyo* according to data from analysis validations. The Applicant supplied appropriate responses to those instructions and the Evaluation Centre verified that appropriate specifications and test methods were set up.

C. Data on Stability

With the drug substance, slight degradation due to temperature, and slight degradation and colouring due to light were observed. No change due to storage was observed in the long-term storage study (24 months) and the accelerated study. The drug substance was considered to be stable for a minimum of two years at ambient temperature.

Changes in the drug products were observed under open temperature/humidity conditions. However, when the drug products were packed in sealed plastic bottles with desiccators or PTP/metal strips, few changes were observed in the long-term storage study and accelerated study. Change due to light was negligible at 1,440,000 lux/hour. In conclusion, the formulated products were considered to be stable for a minimum of one year at ambient temperature.

The long-term study of the drug substance and the drug products is still on-going.

D. Data on Acute Toxicity, Subacute Toxicity, Chronic Toxicity, Teratogenicity and Other Toxicity

Acute toxicity studies were implemented in rats and dogs.

LD50 of a single oral dose in rats was 5000mg/kg or over and approximate lethal dose of a two-week dose escalation in dogs was 400mg/kg or over.

Subacute toxicity and chronic toxicity studies were implemented in rats and dogs with oral dose. Main toxicological findings were increases in serum transaminase and skeletal muscle degeneration/necrosis. Increases in the liver weight and cornification of mucosa of forestomach in rats and suppression of body weight gain and cholestasis in the liver in dogs were observed, but they were reversible after withdrawal except for the liver histology. In the subacute toxicity study, the no toxicity doses were 5mg/kg/day in male

rats, 20mg/kg/day in female rats and 10mg/kg in dogs. In the chronic toxicity study, the no toxicity doses were 5mg/kg/day in rats and 10mg/kg/day in dogs.

The Evaluation Centre instructed the Applicant to provide a clarification on safety because the no toxicity dose in rats was relatively low. The Applicant argued that an intrinsic no toxicity dose was 70mg/kg/day, which was approximately 88 times higher as a dose amount than the human clinical dose (0.2 to 0.8 mg/kg). The Evaluation Centre instructed the Applicant to provide an account for the liver effect. The Applicant replied that hepatic impairments in rats and dogs were not qualitatively serious and dosage within a normal range was unlikely to cause serious hepatic impairment in humans. We would like to hear the Subcommittee's comments on this response.

Reproductive and developmental toxicity studies were implemented in rats and rabbits.

In the male fertility study in rats and the female fertility study in rats, suppressions of body weight gain and reductions of food consumptions were observed in parent animals, however, effect on reproductive potentials and early embryonic development was not observed. The no toxicity dose in male parent animals was estimated at 20mg/kg/day and that for female parent animals was at 100mg/kg/day.

In the organogenesis study in rats, dams showed suppression of bodyweight gain, reduction in food consumption and hypersalivation. At 300mg/kg/day, reduction in foetal bodyweight and embryonic lethality were observed, but teratogenicity was absent. The estimated no toxicity dose was 100mg/kg/day in both dams and foetuses.

The rabbit organogenesis study showed suppression of bodyweight gain in dams and an increase in the mortality of dams after nidation, but teratogenicity was absent. The no toxicity dose was estimated at 10mg/kg/day in dams and 50mg/kg/day in foetuses.

In the organogenesis, peri- and postnatal study in rats, suppression of bodyweight gain and reduction in food consumption were observed in dams. Bodyweight reduction in offspring, developmental delay in offspring and reduced responses in some behavioural

function tests were observed in the second generation. The no toxicity dose was estimated at 100mg/kg/day in dams and 20mg/kg/day in the second generation.

Results of antigenicity tests were negative.

In the mutanogenicity study, microbial reverse mutation tests, chromosome aberration tests with mammalian cell cultures and mouse micronucleus tests were performed, and all test results were negative.

Carcinogenicity studies were carried out in mice and rats. An increase in the incidence of hepatocellular tumours in mice was observed at 400mg/kg/day.

The Evaluation Centre instructed the Applicant to discuss carcinogenic potential in humans. The Applicant believed that the increase in hepatocellular tumours was due to the liver effect which was specific to rodents and possibility of increase in hepatocellular tumours in humans was low. The Evaluation Centre accepted the response.

Neither a dependency study nor a local irritation study were carried out.

The amorphous drug substance was used in the above toxicity studies. In order to confirm that the crystalline drug substance was not toxicologically different from the amorphous drug substance, which was replaced with the crystalline drug substance during the development, bridging toxicity studies were implemented in mice, rats and dogs.

In mice and rats, there was no difference in the toxicology of these drug substances. However, in dogs, the crystalline drug substance had a tendency to show higher plasma concentrations and stronger toxicity.

Compared with the toxicity of other agents, the toxicity seen in atorvastatin was common to other HMG-CoA reductase inhibitors and specific toxicity was not observed.

E. Data on Pharmacological Action

In vitro studies (human hepatocellular carcinoma HepG2 cells, rat liver microsome fraction and rat liver, spleen and testis tissue preparations) demonstrated that atorvastatin had HMG-CoA reductase inhibitory effect and inhibitory effect on cholesterol synthesis and it increased LDL receptor activities and LDL receptor mRNA expression. Strengths of tissue selectivity of cholesterol synthesis inhibitions of various agents in the liver tissue preparations were compared on a base of their relative IC50. The agent with the strongest selectivity was pravastatin (2 to 3) followed by atorvastatin (1), and the lowest was lovastatin (1/7 to 1/5).

When normal guinea pigs, which were believed to have cholesterol metabolisms similar to humans, received repeated oral doses of atorvastatin for two weeks, an increase in the LDL receptor activity in the liver microsome fraction, a decrease in the total cholesterol (TC) levels in the liver and reduced plasma TC levels were observed. When sucrose-fed hypertriglyceridaemia rats received repeated oral doses of atorvastatin for two weeks, reductions in serum triglyceride (TG) levels and TG secretion speed were observed. Repeated oral dose studies in *Watanabe* heritable hyperlipidemic rabbits and cholesterol-fed rabbits showed serum TC lowering, reduction in percentages of diseased area and cholesterol contents in the thoracic aorta, and reduced area with intimal thickening in the iliofemoral aorta. Repeated oral doses of atorvastatin in cholestyramine-fed dogs lowered plasma TC levels. In cholesterol-fed miniature pigs, the speed of LDL and VLDL apoprotein B synthesis in the liver was reduced. When atorvastatin was repeatedly administered orally for three weeks, plasma TC levels, LDL-cholesterol (LDL-C) levels, TG levels and VLDL-TG levels were reduced.

In a study with rat liver microsome fractions, the main metabolites in humans, which were hydrated at the 4^{th} position (M-1) and 2^{nd} position (M-2) of the amide band of the benzene ring, demonstrated HMG-CoA reductase inhibitory effect. The degree of the inhibitory effect was similar to the parent form.

In conclusion, it was suggested that atorvastatin inhibited cholesterol synthesis in the liver and induced hypermetabolism of blood lipoprotein by LDL-receptors. At the same time, it prevented arteriosclerosis associated with hyperlipidemia by improving blood kinetics of lipids through reducing the speed of secretion and synthesis of lipoproteins.

As a part of the general pharmacological actions, atorvastatin reduced motor activities in rats. The metabolite (M-2) transiently reduced the urine volumes and K^+ excretion levels in urine.

The Evaluation Centre compared the PK/PD in order to assess appropriateness of the clinical dose against the effective dose in animals. IC_{50} of inhibitory effect on cholesterol synthesis in rat liver tissue preparations was 39mM (45ng/mL). IC_{50} of inhibitory effect on cholesterol synthesis in the liver microsome of cholestyramine-fed rats were 13nM (15ng/mL). When a single dose of atorvastatin (3mg/kg) was given to cholestyramine-fed rats, the rate of the cholesterol synthesis inhibition was 43% and the cholesterol synthesis was significantly inhibited for up to four hours after dosing. Rat plasma free parent-form concentrations at four hours after dosing were approximately 0.2 to 0.5ng/mL (plasma protein binding rate: 94.9 to 97.7%) and the tissue-plasma concentration ratio in the liver was around 130. Therefore, the free parent-form concentration in the liver was estimated at around 27 to 60ng/mL. This was roughly in agreement with IC_{50} of the inhibitory effect on cholesterol synthesis in the rat liver tissue preparations. The free M-2 concentration in the liver (plasma protein binding rate in humans: 96.6 to 98.9%) was estimated at around 30 to 93ng/mL.

IC_{50} of inhibitory effect on cholesterol synthesis in HepG2 cells was 70nM (81ng/mL). The Applicant set the dose for hyperlipidemia patients at 10mg/dose/day (0.17mg/kg/day), which may be increased to 20mg/dose/day. In a seven-day repeated dose study in the clinical phase I program, serum lipid tests were performed before breakfast and 10mg of atorvastatin was administered after breakfast. Compared to predose levels, postdose serum lipid levels were significantly reduced (22% reduction in the TC value). When healthy volunteers received repeated doses of the crystalline formulation, estimated concentrations of plasma free parent-form before breakfast on

Day 7 were approximately 0.01 to 0.06ng/mL (plasma protein binding rate: 95.6 to 99.0%). Presuming transposition of atorvastatin to organs was similar in rats and humans, the free parent-form concentration in the liver before breakfast was estimated at approximately 3 to 13ng/mL and the free M-2 concentration in the liver was estimated at approximately 2 to 5ng/mL (plasma protein binding rate: 96.6 to 98.9%). Even if their effects were additive, they were closer than IC_{50} of inhibitory effect on cholesterol synthesis in HepG2 cells. However, after administration, the IC_{50} values were closer.

In a Japanese study in homozygotic familial hypercholesterolemia patients, atorvastatin with or without concurrent probcol was effective in lowering TC and LDL-C in two patients with a partial deficit of LDL receptors (48.37%) with high receptor activities, but the number of patients was insufficient for making efficacy assessment. Therefore, the Evaluation Centre requested a justification of the indication to homozygotic patients. The Applicant replied that because plasma TC levels and the speed of cholesterol excretion were reduced in LDL receptor deficient mice (a model for familial hypercholesterolemia), atorvastatin's effect was not restricted to LDL receptors and homozygotic patients were rare (one in one million), they added a precaution for homozygotic patient treatment in the Precautions for Use. Furthermore, the Evaluation Centre instructed the Applicant to provide details of currently available information on the mode of the TG lowering effect. The Applicant replied that the amount of TG in the liver did not show changes despite the inhibitory effect on TG excretion and details about the mode of action were unknown.

F. Data on Absorption, Distribution, Metabolism and Excretion

Results in Humans:

When healthy volunteers received a single oral dose of 5 to 40mg atorvastatin, plasma parent-form concentrations reached the maximum (C_{max}) at 0.6 to 0.9 hours from the administration and the biological half-life ($t_{1/2}$) was 9.4 to 10.7 hours. The C_{max} and the area under the plasma concentration-time curve ($AUC_{0-\infty}$) increased roughly proportionally to the dosed amount. The bioavailability of atorvastatin (as the parent

form) was 12.2%. Compared with administration under fasting conditions, time to the maximum plasma concentration (T_{max}) of administration after meals was prolonged and the C_{max} was reduced to less than a half, but $t_{1/2}$ and $AUC_{0-\infty}$ were almost unchanged. C_{max} and AUC of the plasma parent-form after repeated oral doses of 10mg/day were 1.2 times to 0.9 times of those after a single dose and a steady state was achieved within four days of administration. T_{max} and $t_{1/2}$ of the plasma active metabolite M-2 concentrations after an oral dose of 10mg atorvastatin in healthy volunteers were 6.2 hours and 8.0 hours, respectively. The AUC_{0-48hr} was about a half of that of the parent form, suggesting contribution of M-2 to the manifestation of a therapeutic response. The plasma M-1 concentration was extremely low.

In elderly population, C_{max} and $AUC_{0-\infty}$ of the plasma parent-form were about twofold higher than in younger population. Their plasma M-2 concentrations were also about twofold higher than in the younger population, demonstrating effects of aging. In hyperlipidemia patients (foreign population), C_{max} and AUC of plasma HMG-CoA reductase inhibition active substances (the active forms) were about two times higher than in healthy volunteers (Japanese). Plasma active-form concentrations in subjects with cirrhosis were significantly higher than subjects with normal liver function (both in foreign population).

When 40mg of 14C-atorvastatin was orally administered to subjects (foreign) after cholecystectomy, the excretion rates of the parent form, M-1 and M-2 in the bile were 5.3%, 5.7% and 2.7% of the dosed amount respectively, and the total excretion rate in the bile was 57.0%. When 20mg of 14C-atorvastatin was orally administered to healthy volunteers (foreign), 8.3%, 11.7% and 18.2% of radioactivity in the faeces were the parent form, M-1 and M-2, respectively. The total volume of excretion was 1.2% in urine and 89.4% in faeces. In human, atorvastatin was mainly metabolised in the liver and involvement of CYP3A4 as the main metabolising enzyme was suggested.

Drug interactions were investigated abroad. Concurrent use of aluminium hydroxide gel/ magnesium hydroxide preparations or negative ionic exchange resins inhibited atorvastatin absorption. Concomitant use of erythromycin increased plasma active-

atorvastatin concentrations. It also increased plasma norethindrone/ethinylestradiol concentrations, digoxin concentrations and terfenadine concentrations.

During the clinical program, the drug substance was changed from amorphous to crystalline. With regard to studies in hyperlipidemia patients, the amorphous formulation was only used in the phase IIa studies. Comparison of pharmacokinetic parameters of a single dose in healthy volunteers showed $AUC_{0-\infty}$ of the crystalline formulation was 32% higher than the amorphous formulation. Formulations with different contents were also compared. Two 5mg tablets and one 10mg tablet of atorvastatin (the crystalline formulations) were biologically equivalent.

Results in Animals:

The absorption rate of 14C-atorvastatin in the *in situ* rat digestive tract was the highest in the duodenum, followed by the jejunum then the stomach, and the lowest in the ileum. When male rats received 3mg/kg of atorvastatin orally, C_{max} was 40ng/mL and $t_{1/2}$ was 1.5 hours. Within a dose range of 1 to 10mg/kg, C_{max} and $AUC_{0-\infty}$ of the plasma parent-form increased roughly proportionally to the dosed amount. C_{max} was lower in females than in males and showed durable changes in females. When dogs received oral doses, an increase in plasma parent-form concentrations was bigger than an increase in the dosed amounts, but there was no sex difference. Bioavailability of an oral dose was between 9 and 14% in rats, and between 13 and 25% in dogs.

When rats received a single oral dose of 14C-atorvastatin, radioactivity was accumulated specifically in the liver and it was 130 times of the highest plasma concentration at four hours after administration. Between 34 and 53% of radioactivity was located in blood cells, and the *in vitro* plasma protein bonding rate of 14C-atorvastatin in mice, rats, dogs and human was between 95 and 99% in all species. Main bonding proteins were LDL, HDL and albumin. In humans, the *in vitro* plasma protein bonding rate of the active metabolite M-2 was similar to that of the parent form and a protein binding interaction between the parent form and M-2 was not observed. It was considered that atorvastatin did not have a protein binding interaction with any of concurrent drugs examined.

Rat, dog and human *in vitro* liver microsome metabolisms produced M-1 and M-2, showing no difference among species. The main metabolite in plasma after an oral dose in rats and dogs was M-2 in both species and the $AUC_{0-\infty}$ was bigger than that of the parent form.

In rats and dogs, the rate of radioactivity excretion in urine after oral administration of 14C-atorvastatin was 2.0% and 3.0% respectively, and the rate of excretion in faeces was 98.5% and 96.2% respectively. The rate of excretion in bile was 66.9% in rats, suggesting a presence of enterohepatic circulations. In rats, there was no sex difference in excretion rates via urine, bile and faeces.

At four hours after pregnant rats received an oral dose, radioactivity in the foetuses was 5% of plasma concentrations in dams, showing a slight transmigration. When lactating rats received 14C-atorvastatin orally, radioactivity was eliminated faster from milk than from plasma. In the liver of weaning pups, a low level of radioactivity was found, suggesting absorption of compounds in milk in the digestive tract.

As the plasma concentrations in cirrhosis patients were significantly higher, the Evaluation Centre requested the Applicant to compare it with other HMG-CoA reductase inhibitors. It was suggested that atorvastatin, lovastatin, simvastatin, pravastatin and fluvastatin were likely to be affected by changes in liver function, because all of them were mainly metabolised in the liver and excreted to the bile. Pravastatin and fluvastatin were also reported to have significantly higher C_{max} and AUC in cirrhosis patients than in the healthy population. The Applicant argued that C_{max} and AUC in cirrhosis patients were significantly higher because a proportion of orally administered atorvastatin entered the systemic circulation directly from the portal system avoiding the first pass effect. However, the 9.8-fold increase of AUC in moderate cirrhosis patients was not fully accounted for by this because the absolute bioavailability of atorvastatin was 12.2% and even if 100% of atorvastatin was absorbed and entered the systemic circulation directly, the AUC increase would be only around 8-fold. In addition, based on the distribution after repeated doses in rats, assuming only the parent form was

accumulated in the liver, an estimated free parent form concentration in moderate cirrhosis patients was approximately 850ng/mL. The Michaelis constant of atorvastatin metabolism based on free atorvastatin was estimated at 52 to 58 mM, therefore, the increases were not caused by saturated metabolisms.

The Evaluation Centre asked the Applicant to provide details of drug interactions of atorvastatin including comparisons with other HMG-CoA reductase inhibitors. It was considered that plasma active atorvastatin concentrations were increased with concomitant use of erythromycin because erythromycin formed p-450-macrolide metabolite complex, which deactivated P450 enzymes. This was also observed in other HMG-CoA reductase inhibitors. The Applicant stated that atorvastatin, simvastatin and cerivastatin were mainly metabolised by CYP3A4 and therefore care should be taken when a CYP3A4 matrix such as terfenadine was used concomitantly. Concomitant use of itraconazol increased AUC of unchanged atorvastatin threefold. The Evaluation Centre believed that in some cases, a dose adjustment might be required when a strong inhibitor of CYP3A4 was used concurrently.

The mode of action of the increase in blood digoxin concentration with a concurrent use of atorvastatin and digoxin had not been explained. The Evaluation Centre requested an interpretation of a possibility of active excretion to the digestive tract cavity. The Applicant responded that an investigation using the human colon cancer Caco-2 cell culture suggested a membrane transport via the monocarboxylate transport system (proton co-transporters) on the brush border membrane of epithelocyte of small intestine and secretion to the digestive tract cavity via the p-glycoprotein transport system.

The incidence of abnormal changes in lab test values with atorvastatin was 38%, which was higher than those observed with existing HMG-CoA reductase inhibitors (7 to 19%). The 21-day repeated oral dose distribution study in rats showed that accumulation of radioactivity in the liver at four hours after administration on Day 21 was 1.7 times higher than after a single dose, raising concerns over hepatopathy. The plasma protein-binding rate was extremely high but the Evaluation Centre believed that

there would be no clinically significant effect because the distribution volume at the steady state was large (7.1L/kg).

G. Data on Clinical Study Results

The clinical program was carried out from November 1992 till May 1998 targeting 1112 subjects in total.

Combining a phase I single dose study and a phase I single/repeated dose study, safety assessment of 2.5mg to 40 mg atorvastatin was carried out in 30 subjects. Four out of five subjects in the 40mg group had adverse events including heavy head and stomach pain, one out of six subjects in the 20mg group showed elevated bilirubin and one out of six subjects in the 10mg group showed elevated GOT and GPT.

A phase IIa study targeted 121 hyperlipidemia patients with TC levels of 220mg/dL or over and TG levels of not more than 400mg/dL which were measured more than twice in the predose-observation period. The study was in the double-blind parallel-groups design with four groups at the dose levels of placebo, 5mg, 10mg and 20mg, receiving the study treatment for eight weeks. The percentage change of TC and LDL-C levels were -0.7±10.7% and -1.5±11.6% in the placebo group, respectively, whereas they were -28.0±8.6% and -27.4±12.2%; -37.9±8.5% and -36.5±12.5%; and -38.4±15.7% and -49.6±9.7% in the 5mg, 10mg and 20mg groups, respectively. The percentage change of TG levels was 20.9±42.3% in the placebo group, whereas they were -19.0±28.5%, -17.2±31.3% and -24.2±27.2% in the 5mg, 10mg and 20mg groups, respectively. The incidences of adverse events other than abnormal changes in lab test values were 3.3% (1/30 cases), 3.8% (1/26 cases), 12.5% (4/32 cases) and 9.7% (3/31 cases) in the placebo, 5mg, 10mg and 20mg groups, respectively. Abnormal changes in lab test results were seen in 26.7% (8/30), 26.9% (7/26), 40.6% (13/32) and 25.8% (8/31) of patients in the placebo, 5mg, 10mg and 20mg groups, respectively.

A phase IIb study targeted 243 hyperlipidemia patients with TC levels of 220mg/dL or over in all measurements which were taken more than twice in the observation period.

The study design was in a double-blind fashion with parallel-groups receiving 2.5mg, 5mg 10mg or 20mg of atorvastatin once daily after evening meals for 12 weeks. TG levels were not used as inclusion criteria. Two hundred six patients were included in the efficacy analysis. The percentage change of TC and LDL-C was -20.0±8.5% and -25.0±8.8%; -30.2±9.0% and -33.8±8.6%; –29.1±9.6% and -32.0±11.3%; and -39.6±16.0% and -49.5±11.4% in the 2.5mg, 5mg, 10mg and 20mg groups, respectively. The percentage change of TG was –6.2±31.6%, -19.7±33.7%, -16.7±43.3% and -12.0±48.8% in the 2.5mg, 5mg, 10mg and 20mg groups, respectively. However, the numerical changes were 156.4±107.8→141.1±112.9mg/dL, 204.4±112.5→150.3 ±83.4mg/dL, 184.6±141.9→131.9±85.5mg/dL and 134.7±85.2→100.0±45.5mg/dL, respectively. The incidence of adverse events excluding abnormal changes in lab test values in patients included in safety analysis was 5.0% (3/60), 12.1% (7/58), 7.0% (4/57) and 10.3% (6/58), in the 2.5mg, 5mg, 10mg and 20mg groups, respectively. Abnormal changes in lab test values were seen in 36.7% (22/60) of patients in the 2.5mg group, 34.5% (20/58) of the 5mg group, 33.3% (19/57) of the 10mg group and 46.6% (27/58) of the 20mg group.

A phase III study targeted 263 hyperlipidemia patients with TC levels of 220mg/dL or over and LDL-C levels of 140mg/dL or over in all measurements which were taken more than twice in the predose observation period. It was a 12-week double blind comparative study of 10mg atorvastatin with a control drug of 10mg pravastatin. Two hundred twelve patients were included in the efficacy analysis. In the atorvastatin group, TC levels were 278.6±41.6mg/dL predose and 196.0±36.2mg/dL postdose, showing a change of -29.4±9.6%, whereas in the control group, they were 285.4±44.8mg/dL predose and 243.2±45.3mg/dL postdose, showing a change of -14.5±10.0%. The atorvastatin group showed a significant decrease in TC levels. Similarly with LDL-C, LDL-C levels in the atorvastatin group were 190.7±41.6mg/dL predose and 110.4±33.5mg/dL postdose, showing a change of -41.9±12.5%, whereas in the control group, they were 195.5±44.3mg/dL predose and 152.8±43.9mg/dL postdose, showing a change of -21.5±13.7%. The atorvastatin group showed a significant decrease in LDL-C levels. With regard to TG, TG levels in the atorvastatin group were 166.1±78.3mg/dL predose and 118.8 ±53.6mg/dL post dose, showing a change of -21.0±34.2%, whereas

in the control drug group, they were 177.5±90.4mg/dL predose and 151.8±75.0mg/dL postdose, showing a change of -5.4±42.0%. The atorvastatin group showed a significant decrease in TG levels. Increases in HDL-C levels were seen in both groups, which were 7.5±8.7mg/dL and 5.9±7.9mg/dL higher than the predose levels respectively, but there was no difference between the groups. The incidence of adverse events excluding abnormal changes in lab test values in the each group of patients included in the safety analysis was 5.2% (6/116) in the atorvastatin groups and 9.1% (11/121) in the control group. Abnormal changes in lab test values which may be relevant to the study drugs were 37.1% (43/116) in the atorvastatin groups and 27.3% (33/121) in the control group. The common events with atorvastatin were increased liver enzyme levels including GOT, GPT and γ-GTP, elevated CPK, elevated glucose, elevated TSH and reduced testosterone. One patient in the atorvastatin group who had elevated liver enzyme levels was unable to continue with the study treatment and withdrawn from the study. The rate of patients who scored "no issues" in the overall safety assessment was 79.3% (92/116) in the atorvastatin groups and 80.2% (97/121) in the control group, showing no differences.

Other clinical trials implemented included a 12-week phase IIa study in 29 hyperlipidemia patients, a 52-week long-term study in 311 patients and a geriatric study in 57 elderly subjects. In the 12-week study, two patients were withdrawn due to raised liver enzyme levels. In the long-term study, two patients were withdrawn due to raised liver enzyme levels and one patient was withdrawn due to raised biliary enzyme levels, etc.

In an open study in 24 heterozygotic familial hypercholesterolemia patients, a dose amount of atorvastatin was increased every eight weeks starting from 10mg up to 40mg. In line with the increasing dose, a trend of TC reductions was observed, but safety was reduced as the dose increased. In the safety assessment, one patient in the 10mg group with an adverse drug reaction of "weakness/lassitude of the back and lower extremities", one patient in the 10mg group with raised liver enzyme levels, two patients in the 20mg group with raised liver enzyme levels and three patients in the 40mg group with raised liver enzyme levels were regarded to have had "concerns" over safety.

In a dose escalation open study in nine homozygotic familial hypercholesterolemia patients, a dose amount of atorvastatin was escalated from 10mg to up to 40mg. Three homozygotic patients showed a reduction in TC and LDL-C levels of over 10% compared with predose levels. However, other six cases showed deterioration; in particular some negative type patients whose LDL receptor activities were minimumal, showed deterioration of over 10%.

Three clinical pharmacological studies were implemented investigating 1) effect on bile lipids, 2) effect on the blood coagulation and fibrinolytic system and 3) effect on the glucose metabolisms (placebo controlled). In the study investigating the glucose metabolisms, one sudden cardiac death was reported but the subject was in the placebo group. No other serious adverse drug reactions were reported.

Overseas clinical study results

In overseas clinical studies, which were mainly carried out in the West, 4,271 subjects received atorvastatin (some were at more than one dose levels). The incidences of over threefold increases from the normal upper limit of transaminase in more than two successive tests were 0.2% (3/1843), 0.2% (2/892), 0.6% (5/811) and 2.3% (20/888) at a dose level of 10mg, 20mg, 40mg and 80mg, respectively. Although data on transaminase elevations with other HMG-CoA reductase inhibitors published in the Physician's Desk Reference were not necessarily suitable for a direct comparison because 1) approved doses were different and 2) incidences listed were not necessarily frequencies of over threefold increases from the normal upper limit of transaminase in "more than two successive tests", the data showed that the incidences were 1.3% for pravastatin (approved dose in Japan: 10 to 20mg, approved dose in the US: 10 to 40mg), 1.0% for simvastatin (Japan: 5 to 10mg, US: 5 to 40mg), 1.1% fluvastatin (Japan: 20 to 60mg, US: 20 to 80mg) and less than 1.0% for cerivastatin (Japan: 0.15 to 0.3mg, US: 0.3mg). The Applicant argued, therefore, that the incidence of liver function impairments with atorvastatin was not high compared with other similar drugs. However, some patients in the clinical studies of atorvastatin were withdrawn from the study due to liver function impairment. Furthermore, in overseas countries, when

subjects with normal liver function and cirrhosis patients received oral repeated dose of 10mg of atorvastatin once daily for 14 days, patients with mild cirrhosis in the category A of Child-Pugh Classification showed a 5.5 times increase in C_{max} and a 4.4 times increase in $AUC_{0\text{-}24hr}$ and patients with moderate cirrhosis in the category B of Child-Pugh Classification showed a 14.4 times increase in C_{max} and a 9.8 times increase in $AUC_{0\text{-}24hr}$ (it has been reported that AUC of the control drug pravastatin in cirrhosis patients with unknown severities was 1.34 times of normal subjects). Therefore, the Evaluation Centre instructed the Applicant to make a modification of the Precautions for Use in patients with hepatic impairments. We would like to hear from the Subcommittee whether the narratives in the Precautions for Use are satisfactory.

Indications, Dosage and Administration Method:

The cholesterol lowering effect of atorvastatin was demonstrated in clinical studies in hypercholesterolemia patients excluding homozygotic familial hypercholesterolemia patients. The efficacy of 10mg atorvastatin was supported by significant decreases in TC and LDL-C compared with the control drug of 10mg pravastatin. However, TC and LDL-C lowering effects were observed at a dose level of 2.5mg and the incidence of adverse events seemed to be correlated with the dosed amount. Therefore, we would like to hear the Subcommittee's opinion on appropriateness of selecting 10mg as the optimum dose. We also would like to hear the Subcommittee's opinion on appropriateness of the maximum dose, 40mg.

In the atorvastatin clinical program, hyperlipidemia patients were recruited, but the inclusion criteria did not specify TG levels, though it specified TC levels. In the clinical program, nine patients in the phase IIa studies, 12 patients in the phase IIb study and 26 patients in phase III study had fluctuations of TG levels within ±10% and over 150mg/dL during the observation period. As well as hypertriglyceridemia patients, many patients who only had raised TC were included in the placebo-controlled phase IIa study. However, the active drug groups showed a significant lowering effect than the placebo, though there was no difference in the 5mg, 10mg and 50mg groups and no clear dose-response was observed. In the phase III study, stratified analysis was carried out in

hypertriglyceridemia patients and atorvastatin's TG lowering effect was observed in comparison with the control drug. Therefore, the TG lowering effect was thought to be present, even though the mode of action was unknown. Nevertheless, the reduction rate was lower than fibrates. We would like to hear the Subcommittee's opinion on approvability with an indication for hyperlipidemia including hypertriglyceridemia.

3. RESULTS FROM A RELIABILITY CHECK BY THE *KIKO* AND INTERPRETATION BY THE EVALUATION CENTER

1) Interpretation of the reliability check result by the Evaluation Centre

The *Kiko* (Organization for Pharmaceutical Safety and Research) carried out an audit on documents as stipulated in the last paragraph of Section 4, Article 14 of the Pharmaceutical Affairs Law. There were some incompatibilities (e.g. there were some protocol violations in clinical results, expressions used in the approval application document did not reflect the source document correctly). However, the Evaluation Centre considered that the audit result would not cause an impediment in carrying out an evaluation based on the approval evaluation data.

2) Interpretation of the GCP audit result by the Evaluation Centre

In the GCP audit, it had come to light that patients included in a late phase IIb study were also included in a phase III study. The patients were excluded from the evaluation data. There were no other issues and the Evaluation Centre considered that the audit result would not cause an impediment in carrying out an evaluation based on the approval evaluation data.

4. OVERALL ASSESSMENT OF THE EVALUATION CENTRE

Subject to confirmation of the following points with the Subcommittee, the Evaluation Centre has no objection in approving the filed drug.

5) Indication: should it be hyperlipidemia including hypertriglyceridemia?
6) Appropriateness of the optimum dose of 10mg and the maximum dose of 40mg
7) Confirmation of Precautions for Use for hepatic impaired patients

4th October 1999

SUMMARY OF SUBCOMMITTEE DISCUSSION

The Second Subcommittee on New Drugs

1. DISCUSSION

Date of Subcommittee Meetings: 7th June 1999 (first meeting)
4th October 1999 (second meeting)

Conclusion by the Subcommittee

Based on the document submitted, we do not have objections in approving the drug, as long as the indications are amended and the chairperson verifies responses to the instructions for the Evaluation Centre.

2. REPORT FROM THE SUBCOMMITTEE

Regarding toxicity studies, the Subcommittee requested the Evaluation Centre for details of a mechanism of "hepatocellular variations" which were observed in the 52-week oral dose toxicity study in rats. Hepatocyte hypertrophy was a typical hepatocellular variation and it was considered to be a morphological change due to enzyme inductions. Unlike in rats, HMG-CoA reductase inhibitors did not induce these enzymes in humans and the Evaluation Centre believed such a change would not happen in humans. The hepatocellular variations observed with administration of atorvastatin were not progressive and the degree was reduced with time. Furthermore, as atorvastatin carcinogenicity studies in rats showed all negative oncogenecity, the Evaluation Centre explained that the hepatocellular variations were not associated with formation of neoplasia. The response was accepted.

The Evaluation Centre was asked to review liver toxicity of atorvastatin using a rat liver disease model. The Evaluation Centre argued that a toxicity assessment using a rat liver disease model was not widely accepted as a method of predicting undesirable effect of a drug in humans with hepatopathy. They also stated that the incidence of GOT and GPT elevations above fivefold of the normal value was 0.1% in the Japanese clinical studies and there was no significant difference in reports of hepatopathy with atorvastatin compared with other agents. The responses were accepted. To address this matter, the Important Basic Precautions in the Precautions for Use refers to a need for regular liver function tests.

The Evaluation Centre had argued that the hepatocarcinogenicity in mice was a result of a promoter activity of atorvastatin. The Subcommittee asked for the rationale of the argument. The Evaluation Centre replied that even though they mentioned the promoter actions as a mode of mechanism of carcinogenicity, no findings supported this theory. The Evaluation Centre explained that the mechanisms of the increase in hepatocellular tumour was unknown because atorvastatin did not show genotoxicity and there was no difference in cell proliferation activities compared with the control group when PCNA was used as index. However, the dose at which carcinogenicity was seen in mice differed largely from the clinical dose. Also, there was no report suggesting tumour inductions in the clinical use of HMG-CoA reductase inhibitors. Therefore, the Evaluation Centre believed that the atorvastatin had a low carcinogenic potential. The Subcommittee accepted the response.

The Subcommittee requested a review on the reduction of spermatid in the testis, which was observed in the 100mg/kg group of the rat oral feed-mix reproductive study. The Evaluation Centre replied that, in a gavage oral dose reproductive study, no effect on the reproductive function, male reproductive organs and sperm parameters was observed. The Subcommittee requested the Evaluation Centre to re-examine the reduction of spermatid in the testis, which might be an effect of atorvastatin. The Evaluation Centre replied that no effect on the spermatid count in the testis was observed in the gavage oral dose study. In addition, the Evaluation Centre submitted results of an already implemented 104-week oral dose toxicity study in beagles because the effect of some

HMG-CoA reductase inhibitors on the testis were observed in repeat-dose studies in dogs. They explained that test results from Week 52 to Week 91 did not show significant changes due to atorvastatin. Also abnormalities in sperm test data observed with 104 weeks administration of 120mg/kg, which reduced blood cholesterol levels to about 50% of the control group, were not considered to be biologically significant changes. However, the Subcommittee insisted on the study to be repeated because the existing study did not evaluate the effect of reduced blood cholesterol levels on reproduction and development.

With regard to malformation and mutation observed in the oral dose organogenesis study in rabbits, the Subcommittee asked for a justification of the no toxicity dose in dams and foetuses because one of the rationales for ruling out a relevancy to atorvastatin was not acceptable (malformation and mutation were limited to dams with poor foetal growth). The Evaluation Centre amended the no toxicity dose for dams and foetuses to 10mg/kg because death, body weight gain suppression, abortion in dams and foetal bodyweight reduction and an increase in the embryonic death rate after nidation were observed at 50mg/kg or over.

The Subcommittee also asked the Evaluation Centre to provide a discussion on a trend of increase in the incidence of pyelectasis in the 225mg/kg group, which was observed in the organogenesis, peri- and postnatal oral study in rats. The Evaluation Centre explained that this was associated with atorvastatin because it was higher than the control group, although within a range of background data for the rats used in the study. Descriptions in the Contraindications in the Precautions for Use and the Administration to Pregnant, Parturient and Nursing Women were amended to address this matter.

With regard to absorption, distribution, metabolism and excretion, the Subcommittee requested the Evaluation Centre to describe causes of the low (around 10%) atorvastatin bioavailability (BA) in human and experimental animals. The Evaluation Centre was instructed to explain absorption processes at the digestive tract and the first pass effect separately. They replied that the absorption rate of atorvastatin at the digestive tract was considered to be about 60 to 70% in both humans and animals and the differences from

BA were due to the first pass effect. Even though atorvastatin was mainly eliminated via the liver, a presence of metabolism in the digestive tract was qualitatively demonstrated in a metabolism experiment with human enterocyte microsome. The Evaluation Centre explained that metabolisms in the digestive tract as well as in the liver were involved because atorvastatin was metabolised by CYP3A4. The Subcommittee accepted the explanations. Furthermore, the Subcommittee asked for an explanation of a tendency of AUC to increase more than the dose ratio when the dose was increased in a human repeated oral dose study. The Evaluation Centre explained that this was due to one subject in 20mg who showed high AUC by chance and they demonstrated that the average increase without this subject was roughly proportional to the dosed amount.

With regard to the TC lowering effect of atorvastatin, the Subcommittee asked for a justification of the indication of hyperlipidemia, considering the fact that TG was not a primary endpoint in the atorvastatin clinical studies and the number of patients in the efficacy evaluation (with TG levels of above 150mg/dL as well as the TG fluctuations within ±10% in more than two serum lipids measurements during the observation period) was extremely low. The Evaluation Centre argued that various lipid parameters including TG levels were the primary endpoints in studies with an exception of the phase III comparative study. A significant TG Lowering effect compared with placebo was observed in the phase IIa study. They also indicated that TG was assessed as a secondly endpoint in the phase III comparative study and the study showed a trend of TG reduction by atorvastatin compared with pravastatin, although it varied. Furthermore, they expressed their opinion that dose dependent TG lowering effect was confirmed in overseas studies in hypertriglyceridaemia patients and the atorvastatin should be indicated for hyperlipidemia. However, the Subcommittee instructed that the indication should be “hypercholesterolemia” because they believed that insufficient data for demonstrating clinical usefulness were available.

The Subcommittee requested the Evaluation Centre to compare the LDL lowering effect and the inhibitory effect on VLDL secretion of atorvastatin with similar drugs and give a logical discussion using data from studies which directly supported a pharmacokinetic justification and findings from past papers. The Evaluation Centre expressed their

opinion that the lipid lowering effect was associated with 1) more selective and durable up-take to the liver, 2) stronger activities of the main metabolite with comparable plasma metabolite AUC to the parent-form, 3) a more durable effect due to longer plasma half-life of the parent-form and the main metabolite, compared with other drugs. With regard to the inhibitory effect on VLDL secretion, they suggested that because the half-life of atorvastatin was longer than other drugs, cholesterol synthesis activities were inhibited for longer, which led to a more pronounced inhibitory effect on VLDL secretion and expression of the serum TG lowering effect. They also argued that, at the same time that the LDL supply was reduced as expected from the inhibitory effect on VLDL secretion, the LDL lowering effect was enhanced by the induction of the LDL receptor activities, which led to the stronger blood LDL lowering effect. The Subcommittee accepted the replies. With regard to the clinical significance of TG reduction, the Evaluation Centre explained that a direct proof of the clinical significance had not been obtained, though suppression of development of ischemic heart diseases and arteriosclerotic diseases, which were reported in fibrates, would be expected considering the TG lowering effect of atorvastatin.

With regard to the high incidences of abnormal changes in lab test results, the Subcommittee requested a description of possible drug interactions with concomitant drugs. The Evaluation Centre replied that direct effect from concomitant drugs was relatively small compared with effect from concurrent disorder, etc. The Subcommittee accepted the response. The Evaluation Centre explained the higher incidence of testosterone reductions in females was not a sex difference due to the pharmacological actions of atorvastatin. There was no effect on serum testosterone concentrations in general pharmacology studies and there was no finding that suggested the presence of direct inhibitions of testosterone biosynthesis in the repeated oral dose studies. Therefore, the Evaluation Centre argued that the possibilities of atorvastatin to directly inhibit testosterone biosynthesis within the clinical dose range were low. Furthermore, with regard to a possibility of interactions via CYP, the Evaluation Centre stated that a possibility of enzyme inductions leading to the acceleration of testosterone metabolism was minimal because the main drug metabolising P450 in humans were not included in

testosterone biosynthesis enzymes and atorvastatin did not induce the atorvastatin metabolising enzyme CYP3A4. The Subcommittee accepted those responses.

The Evaluation Centre was instructed to provide an explanation on drug interactions of atorvastatin with SU preparations and oral contraceptives. They replied that they were unable to pinpoint obvious interactions with SU preparations. When oral estradiol or estriol were used concomitantly with atorvastatin, there was a possibility of their plasma concentrations increasing, involving metabolism inhibition by atorvastatin at the digestive tract. Also, a main component of bonding oestrogen was converted into estrone and metabolised by CYP3A4, hence estrone plasma concentrations might increase. Therefore, oral contraceptives were also added in the Drug Interactions of the Precautions for Use.

Results up to 52 weeks of the long-term study were submitted, integrating already submitted results up to 28 weeks.

In 311 hypercholesterolemia patients, changes in various serum lipid levels during a 52-week administration of 10mg of atorvastatin once daily after evening meals were almost constant after Week 4 till Week 52. The rates of normalisation of TC and LDL-C were 82.9% and 86.6% respectively. The incidences of adverse drug reactions and clinical test abnormal changes that may be relevant to atorvastatin based on data up to Week 26 were 9.4% and 40.1% and those based on data up to Week 52 were 11.8% and 41.5%, respectively. Common events were raised liver enzymes, CPK, glucose and HbAlc and reduced testosterone. These results were the same as the results obtained in other clinical studies of atorvastatin. No doubt over efficacy and safety was suggested in long-term administration for 52 weeks.

Discussion items which were pointed out by the Evaluation Centre:

1) Appropriateness of indication of hyperlipidemia including hypertriglyceridemia: The indication should be hypercholesterolemia because hypercholesterolemia patients were targeted in the clinical program and the number of TG patients

included in the efficacy analysis was minimal and data obtained were insufficient for demonstrating clinical usefulness.

2) Appropriateness of the optimum dose of 10mg and the maximum dose of 40mg: 10mg is appropriate as a dose level which is safe and provides maximum effect. In familial hypercholesterolemia patients, a reduction in cholesterol outweighs minor adverse drug reactions. Therefore, it is necessary to use the maximum dose of 40mg.
3) Precautions for Use for hepatic impaired patients are appropriate.

As a consequence of the above discussions, the Subcommittee reached a conclusion that the filed drug was approvable. Therefore, the articles are going to be brought forward to the Special Committee.

The drug substance and the drug products are not classified as Powerful Drug.

16th December 1999

EVALUATION SUMMARY (PART 2)

Pharmaceuticals and Medical Device Evaluation Centre

1. SUMMARY OF EVALUATION FOLLOWING THE FIRST SUBCOMMITTEE MEETING

With regard to stability, additional results of long-term storage studies were submitted.

In the long-term storage study (36 months), no changes in the drug substance were observed after storage and the drug substance was stable for three years at the ambient temperature.

In the long-term storage study (24 months), few changes in the drug products were observed and the drug products were stable for 24 months at the ambient temperature. The long-term storage study of the drug products is still on-going.

In relation to the effect of atorvastatin on the reduction of the testis sperm cell counts in the feed-mix reproductive study, the effect of low blood cholesterol levels caused by the efficacy of atorvastatin on the reproductive potentials of male animals, etc., was not assessed. The Applicant promised that they would investigate its effect on male reproductive potential using animal species that had blood cholesterol reductions.

The Evaluation Centre requested the Applicant to supply a justification on the use of rats in the female fertility study because, in general, HMG-CoA reductase inhibitors were known not to lower blood cholesterol concentrations of rats. The Applicant responded that a female fertility study was usually carried out in rats or mice and these animals were used in female fertility studies of other HMG-CoA reductase inhibitors. The applicant believed that they had completed assessment of reproductive and developmental

toxicities of atorvastatin and the metabolites, except for the issues related to blood cholesterol reductions. They explained that the biggest concern with regard to blood cholesterol reduction and reproductive and developmental toxicities was teratogenicity, but the organogenesis study in rabbits with any of the HMG-CoA reductase inhibitors did not show an induction of holoprosencephaly. The Applicant believed that HMG-CoA reductase inhibitors including atorvastatin would not reduce human blood cholesterol levels to the levels observed in patients with Smith-Lemli-Opitz Syndromes and a possibility of inducing malformation associated with hypocholesterolemia in clinical practice was minimal. Although atorvastatin was not likely to induce malformations due to hypocholesterolemia in clinical practice, the Applicant suggested implementing a study in order to investigate the effect of induced hypocholesterol on reproductive potential in male and female animals and development of early embryo. The Evaluation Centre accepted the responses.

Referring to the international prescribing information and the US labels, atorvastatin was contraindicated to breast-feeding women. Narratives of reductions in a number of offspring and effect on their survival and development, which were observed in animal experiments, and occurrences of congenital malformations with other HMG-CoA reductase inhibitors were added to the prescribing information under the section of Administration to Pregnant, Childbearing and Breastfeeding Women. The Evaluation Centre considered the amendments appropriate.

The Evaluation Centre believes the amendment of indication from “hyperlipidemia” to “hypercholesterolemia” is appropriate.

2. CONCLUSION OF EVALUATION

In conclusion of evaluation carried out at the Evaluation Centre and the Second Subcommittee Meeting on New Drug, the Evaluation Centre has no objection in granting approval of the filed articles.

24th December 1999

EVALUATION SUMMARY (PART 3)

Pharmaceuticals and Medical Device Evaluation Centre

The phrase “if further effect is required” in relation to a dose increase in the Dosage and Administration Method was not appropriate. The Evaluation Centre believed that this should be replaced with “in severe cases” and instructed the Applicant to amend the phrase.

27th January 2000
The Evaluation and Licensing Division,
Pharmaceutical and Medical Safety Bureau

EVALUATION REPORT (PART 2)

[Articles] Product Name: Lipitor, Lipitor 5mg Tablet, Lipitor 10mg Tablet
Generic Name: Atorvastatin calcium hydrate

[Submission Date] 24th August 1998 (Import approval of the drug substance, manufacturing approval of the drug product)

[Applicant] Drug substance: Warner-Lambert
Drug product: Yamanouchi Pharmaceutical Co., Ltd

During the discussion in the First Special Committee Meeting on Drugs of the Pharmaceutical Affairs Council, the committee pointed out that the calculated numeric data in the pharmacological investigation of the clinical dose against the effective dose were estimates and they should not have been used in a comparison. Therefore, relevant sentences concerning pharmacological actions in the *Gaiyo* (Part 1, page 5, lines 15 to 36) were deleted.

This amendment will not affect the conclusion of the evaluation.