Report on Investigation Results

September 13, 2018

Pharmaceuticals and Medical Devices Agency

I. Summary of drug

[Non-proprietary name]	See Appendix 1
[Branded name]	See Appendix 1
[Approval holder]	See Appendix 1
[Indications]	See Appendix 1
[Dosage and administration]	See Appendix 1
[Remarks]	Nothing noteworthy
[Investigating office]	Office of Safety II

II. Investigation background

Hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) are approved for marketing under the indication of hypercholesterolemia/familial hypercholesterolemia or hyperlipidemia/familial hyperlipidemia, whereas fibrates are approved under the indication of hyperlipidemia (including familial hyperlipidemia).

The Relative Contraindications sections of the current package inserts of these products state that these 2 classes of drugs “should be co-administered in patients with abnormal renal function values only when such use is deemed absolutely necessary for treatment [rhabdomyolysis tends to occur]".

The background regarding such statement is as follows;

Since May 1994, the Careful Administration section in the bezafibrate package insert has included the language “patients receiving HMG-CoA reductase inhibitors (pravastatin sodium, simvastatin)” and the Interactions section has warned that “Caution should be exercised when this drug is co-administered with HMG-CoA reductase inhibitors (pravastatin sodium,

Pharmaceuticals and Medical Devices Agency
Office of Safety I
3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

simvastatin) because rhabdomyolysis tends to occur with such combinations.[1)]" However, adverse drug reactions involving rhabdomyolysis have been intermittently reported.

During the re-examination of bezafibrate (March 1999), "patients receiving HMG-CoA reductase inhibitors whose serum creatinine levels exceed 1.5 mg/dL" were specified in the Contraindications and the Contraindications for Co-administration sections while considering that, together with other revisions based on the re-examination results, pre-dose serum creatinine levels above 1.5 mg/dL were frequently detected in cases of rhabdomyolysis in patients receiving bezafibrate co-administered with statins during the re-examination period.

After the revision based on the decision made during the re-examination of bezafibrate, the language concerning co-administration of bezafibrate with statins was moved from the Contraindications and the Contraindications for Co-administration sections to the Relative Contraindications and the Relative Contraindications for Co-administration sections. This language was also revised to "This drug should be co-administered with HMG-CoA reductase inhibitors in patients with abnormal renal function values only when such use is deemed absolutely necessary for treatment". This revision was made in consideration of the finding that bezafibrate was actually co-administered with statins in clinical practice to patients with abnormal renal function as well as the understanding the associated risks of elevated serum concentration and onset of rhabdomyolysis. Precautions for statins and other fibrates were also revised in line with the precautions for bezafibrate (Notification No.61 by the Director of Pharmaceutical Safety Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare (MHLW), dated June 16, 1999)

On April 11, 2018, the Japan Atherosclerosis Society (hereinafter, the "Society") submitted a "Written Request for Revision of Package Inserts concerning Co-administration of HMG-CoA Reductase Inhibitors (Statins) and Fibrates" to the Pharmaceutical Safety Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW (hereinafter, "Safety Division").

The Society cited the long-standing clinical practice in the US and Europe of co-administering statins and fibrates without restrictions under the Relative Contraindications section of the prescribing information, together with the needs of such co-administration also

[1)] The language in the Interactions section was revised in May 1995 to "Careful co-administration: HMG-CoA reductase inhibitors (pravastatin sodium, simvastatin) [rhabdomyolysis may occur]".

identified in Japan as the basis of its request for the revision of the package inserts related to the co-administration of statins and fibrates in patients with abnormal renal function values.

On July 30, 2018, Safety Division requested that the Pharmaceuticals and Medical Devices Agency (PMDA) conduct an investigation of the safety of co-administration of statins and fibrates in patients with abnormal renal function values (appropriateness of removing from the Relative Contraindications section). PMDA considered the revision of package inserts accordingly.

PMDA held an Expert Discussion as part of its investigation. The expert advisors present at the Expert Discussion were nominated based on their conflict of interest declarations concerning the relevant products (See Appendix 1), pursuant to the Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

III. PMDA Investigation

1. Description of content concerning concomitant administration of statins and fibrates in overseas prescribing information

Current precautions regarding concomitant administration of statins and fibrates in the US and EU prescribing information for individual statin and fibrate drug products

1.1 The United States package insert (USPI)

1.1.1 Current US Prescribing Information for statins

Contraindications

- Concomitant administration of gemfibrozil (not currently approved in Japan) is contraindicated. (simvastatin)

Dosage and Administration

- The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution. (atorvastatin)
- Avoid concomitant use of rosuvastatin with gemfibrozil. If concomitant use cannot be avoided, initiate rosuvastatin at 5 mg once daily. The dose of rosuvastatin should not exceed 10 mg once daily. (rosuvastatin)

Warnings and Precautions

● The risk of myopathy is increased with concurrent administration of fibric acid derivatives. Physicians considering combined therapy with fibric acid derivatives should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly with fibric acid derivatives. Periodic creatine phosphokinase (CPK[2)]) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. (atorvastatin)

● The combined use of simvastatin with gemfibrozil is contraindicated. Caution should be used when prescribing other fibrates with simvastatin, as these agents can cause myopathy when given alone and the risk is increased when they are co-administered. The benefits of the combined use of simvastatin with other fibrates should be carefully weighed against the potential risks of combinations. (simvastatin)

● The risk of myopathy may be increased with concurrent administration of fibrates. Pitavastatin should be administered with caution when used concomitantly with fibrates. (pitavastatin)

● The risk of myopathy during treatment with statins is increased with concurrent therapy with fibrates. The use of fibrates alone may occasionally be associated with myopathy. The benefit by the combined use with fibrates should be carefully weighed against the potential risks of this combination. (pravastatin)

● The risk of myopathy and/or rhabdomyolysis with statins is increased with concurrent therapy with fibrates. (fluvastatin)

● The risk of myopathy may be increased with concurrent administration of fibrates or gemfibrozil. (rosuvastatin)

Drug Interactions

● Concomitant administration of simvastatin and gemfibrozil is contraindicated. (simvastatin)

2) Creatine phosphokinase (CK or CPK)

● Due to an increased risk of myopathy/rhabdomyolysis when co-administered with gemfibrozil, the concomitant administration should be avoided. (atorvastatin, pitavastatin, pravastatin, fluvastatin)

● Because it is known that the risk of myopathy during treatment with statins is increased with concurrent administration of other fibrates, this drug should be administered with caution when used concomitantly with other fibrates. (atorvastatin, pitavastatin, pravastatin, fluvastatin)

● Caution should be used when prescribing other fibrates with simvastatin. (simvastatin)

● Gemfibrozil significantly increased rosuvastatin exposure. Due to an observed increased risk of myopathy/rhabdomyolysis, combination therapy with gemfibrozil should be avoided. If used together, the dose of rosuvastatin should not exceed 10 mg once daily. When rosuvastatin was co-administered with fenofibrate, no clinically significant increase in the AUC[3)] of rosuvastatin or fenofibrate was observed. Because it is known that the risk of myopathy during treatment with statins is increased with concomitant use of fenofibrates, caution should be used when prescribing fenofibrates with rosuvastatin. (rosuvastatin)

1.1.2 Current US Prescribing Information for fibrates

Warnings and Precautions

● Data from observational studies indicate that the risk for rhabdomyolysis is increased when fibrates, in particular gemfibrozil, are co-administered with a statin. The combination should be avoided unless the benefit of further alterations in lipid levels is likely to outweigh the increased risk of this drug combination. (fenofibrate)

1.2 The European package inserts (SPC)

1.2.1 Current EU Summary of Product Characteristics for statins

Posology and method of administration

● The dose of simvastatin should not exceed 10 mg daily in patients taking simvastatin with fibrates, other than gemfibrozil or fenofibrate. (simvastatin)

[3)] Area under the concentration-time curve of the analyte in plasma

● In case where co-administration with a fibrate is necessary, the benefit and the risk of concurrent treatment should be carefully considered. (fluvastatin)

Contraindications

● Concomitant administration of gemfibrozil is contraindicated. (simvastatin)

● The 40 mg dose of rosuvastatin is contraindicated in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include concomitant use of a fibrate. (rosuvastatin)

Special warnings and precautions for use

● The risk of myopathy may be increased with the concomitant use of gemfibrozil and other fibric acid derivates. If possible, alternative therapies should be considered. In case where co-administration of these medicinal products with atorvastatin is necessary, the benefit and the risk of concurrent treatment should be carefully considered. (atorvastatin)

● The use of simvastatin with gemfibrozil is contraindicated. Due to the increased risk of myopathy and rhabdomyolysis, the dose of simvastatin should not exceed 10 mg daily in patients taking simvastatin with other fibrates, expect fenofibrate. Caution should be used when prescribing fenofibrate with simvastatin, as either agent can cause myopathy when given alone. (simvastatin)

● Pitavastatin should be used with caution in patients taking drugs known to cause myopathy (e.g. fibrates). (pitavastatin)

● As for other statins, combination of pravastatin with fibrates is not recommended. The use of fibrates alone is occasionally associated with myopathy. The combined use of a statin and fibrates should generally be avoided. (pravastatin)

● The risk of myopathy has been reported to be increased in patients receiving fibrates. Fluvastatin should be used with caution in patients receiving such concomitant medicine. (fluvastatin)

● Rosuvastatin, as with other statins, should be prescribed with caution in patients with pre-disposing factors for myopathy/rhabdomyolysis. Such factors include concomitant use of fibrates. In clinical trials there was no evidence of increased skeletal muscle effects in the small number of patients dosed with rosuvastatin and concomitant

therapy. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other statins together with fibric acid derivatives including gemfibrozil. Gemfibrozil increases the risk of myopathy when given concomitantly with statins. Therefore, the combination of rosuvastatin and gemfibrozil is not recommended. The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates should be carefully weighed against the potential risks of such combinations. The 40 mg dose is contraindicated with concomitant use of fibrate. (rosuvastatin)

Interaction with other medicinal products and other forms of interaction

- The risk might be increased at concomitant administration of atorvastatin with other medicinal products that have a potential to induce myopathy, such as fibric acid derivates. The use of fibrates alone is occasionally associated with muscle related events, including rhabdomyolysis. The risk of these events may be increased with the concomitant use of fibric acid derivatives and atorvastatin. If concomitant administration cannot be avoided, the lowest dose of atorvastatin to achieve the therapeutic objective should be used and the patients should be appropriately monitored. (atorvastatin)
- The risk of myopathy, including rhabdomyolysis, is increased during concomitant administration with fibrates. Additionally, there is a pharmacokinetic interaction with gemfibrozil resulting in increased simvastatin plasma levels. When simvastatin and fenofibrate are given concomitantly, there is no evidence that the risk of myopathy exceeds the sum of the individual risks of each agent. (simvastatin)
- Gemfibrozil increases the AUC of simvastatin acid by 1.9-fold, possibly due to inhibition of the glucuronidation pathway and/or OATP[4)] 1B1. Concomitant administration with gemfibrozil is contraindicated. (simvastatin)
- The use of fibrates alone is occasionally associated with myopathy. Co-administration of fibrates with statins has been associated with increased myopathy and rhabdomyolysis. Pitavastatin should be administered with caution when used concomitantly with fibrates. In pharmacokinetic studies co-administration of pitavastatin with gemfibrozil resulted in a 1.4-fold increase in pitavastatin AUC; with fenofibrate AUC, increased 1.2-fold. (pitavastatin)

[4)] Organic anion transporting polypeptide

● The use of fibrates alone is occasionally associated with myopathy. An increased risk of muscle related adverse events, including rhabdomyolysis, have been reported when fibrates are co-administered with other statins. These adverse events with pravastatin cannot be excluded, therefore the combined use of pravastatin and fibrates (e.g. gemfibrozil, fenofibrate) should generally be avoided. If this combination is considered necessary, careful clinical and CK monitoring of patients on such regimen is required. (pravastatin)

● Concomitant administration of fluvastatin with bezafibrate or gemfibrozil has no clinically relevant effect on the bioavailability of fluvastatin or the other lipid-lowering agent. Since an increased risk of myopathy and/or rhabdomyolysis has been observed in patients receiving fibrates and statins, the benefit and the risk of concurrent treatment should be carefully weighed and these combinations should only be used with caution. (fluvastatin)

● Concomitant use of rosuvastatin and gemfibrozil resulted in a 2-fold increase in rosuvastatin Cmax[5)] and AUC. Based on data from specific interaction studies no pharmacokinetic relevant interaction with fenofibrate is expected, however a pharmacodynamics interaction may occur. Gemfibrozil, fenofibrate, and other fibrates increase the risk of myopathy when given concomitantly with rosuvastatin, probably because they can produce myopathy when given alone. The 40 mg dose of rosuvastatin is contraindicated with concomitant use of a fibrate. These patients should also start with the 5 mg dose. (rosuvastatin)

● When it is necessary to co-administer rosuvastatin with other medicinal products known to increase exposure to rosuvastatin, doses of rosuvastatin should be adjusted. Start with a 5 mg once daily dose of rosuvastatin if the expected increase in exposure (AUC) is approximately 2-fold or higher. The maximum daily dose of rosuvastatin should be adjusted so that the expected rosuvastatin exposure would not likely exceed that of a 40 mg daily dose of rosuvastatin taken without interacting medicinal products, for example a 20 mg dose of rosuvastatin with gemfibrozil (1.9-fold increase). (rosuvastatin)

5) Maximum concentration of analyte in plasma

1.2.2 Current EU SPC for fibrates

Contraindications

- Combination therapy of bezafibrate with statins in patients with predisposing factors for myopathy is contraindicated. (bezafibrate)

Special warnings and precautions for use

- The risk of muscle toxicity may be increased if the drug is administered with another fibrate or statin, especially in case of pre-existing muscular disease. Consequently, the co-prescription of fenofibrate with statin or another fibrate should be reserved to patients with severe combined dyslipidaemia and high cardiovascular risk without any history of muscular disease and a close monitoring of potential muscle toxicity. (fenofibrate)
- Reversible elevation in serum creatinine have been reported in patients receiving fenofibrate monotherapy or co-administered with statins. Elevations in serum creatinine were generally stable over time with no evidence for continued increases in serum creatinine with long term therapy and tended to return to baseline following discontinuation of treatment. During clinical trials, 10% of patients had a creatinine increase from baseline greater than 30 µmol/L with co-administered fenofibrate and simvastatin versus 4.4% with statin monotherapy. 0.3% of patients receiving co-administration had clinically relevant increases in creatinine to values > 200 µmol/L. Treatment should be interrupted when creatinine level is 50% above the upper limit of normal. It is recommended that creatinine is measured during the first 3 months after initiation of treatment and periodically thereafter. (fenofibrate)
- Bezafibrate should be used with caution in combination with statins as the combination of statins and fibrates has been shown to increase the incidence and severity of myopathy. Patients should be informed of symptoms and monitored for signs of myopathy and increased CPK activity and combination therapy discontinued if signs of myopathy develop. Combination therapy should not be used in patients with predisposing factors for myopathy. (bezafibrate)

Interaction with other medical products and other forms of interaction

- The risk of serious muscle toxicity is increased if a fibrate is used concomitantly with statins or other fibrates. Such combination therapy should be used with caution and patients monitored closely for signs of muscle toxicity. There is currently no evidence to suggest that fenofibrate affects the pharmacokinetics of simvastatin. (fenofibrate)
- Interaction between statins and fibrates may vary in nature and intensity depending on the combination of the administered drugs. A pharmacodynamics interaction between these two classes of drugs may, in some cases, also contribute to an increase in the risk of myopathy for specific dose recommendations of statins refer also to the SPC[6] of the relevant product. (bezafibrate)

2. Japanese and overseas guidelines

Japanese and overseas guidelines state as follows concerning co-administration of statins and fibrates:

2.1 Guidelines for Prevention of Arteriosclerosis Disease 2017[7]

Statins are indicated for cases of dyslipidaemia with a high LDL-C[8] level and are currently one of the most effective medications for lowering the LDL-C level. Myopathy-like symptoms, such as hepatic disorders, an increased creatinine kinase (CK) level, and muscular weakness, have been reported as adverse reactions to statins as well as, although very rare, rhabdomyolysis characterized by and increased myoglobin level in the blood and urine. The risk of these signs and symptoms can be increased by co-administration with fibrates, nicotine derivatives, cyclosporine, erythromycin or others.

Fibrates are the most effective medications for hypertriglyceridemia[9]. Fibrates are particularly effective for type III hyperlipidemia because they enhance the catabolism of remnant lipoproteins. They are also highly effective in increasing the HDL-C[10] level. The main adverse drug reaction is rhabdomyolysis, which is likely to occur in patients with renal dysfunction, so caution should be taken.

Co-administration of fibrates with statins is effective in reducing the risk of arteriosclerotic

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6) Summary of Product Characteristics
7) Japan Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerotic Cardiovacular Diseases 2017 Japan Atherosclerosis Society (JAS) 2017
8) Low density lipoprotein-cholesterol
9) Triglyceride
10) High density lipoprotein-cholesterol

diseases (Evidence level: 2[11], recommendation level: B[12]). The subanalysis in the ACCORD-LIPID trial conducted overseas involving type 2 diabetes subjects (primary prevention and secondary prevention) suggested that fibrate administration in addition to statins could prevent atherosclerotic disease incidence in the group with a TG level of > 204 mg/dL and an HDL-C level of <34 mg/dL.

2.2 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (the US)[13]

Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. (NHLBI Grade B[14], NHLBI Evidence Statements 46[15], ACC/AHA COR III Harm・ACC/AHA LOE B[16]).

Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD[17] risk reduction or triglyceride lowering when triglycerides are ≥500 mg/dL are judged to outweigh the potential risk for adverse effects. (NHLBI Grade E[18], ACC/AHA COR IIb・ACC/AHA LOE C[19]).

2.3 AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE (the US)[20]

Fibric acid derivatives (gemfibrozil, fenofibrate, fenofibric acid) have been associated with

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11) Classification of Evidence Levels in Relation treatment and Diagnosis (Evidence level: 2) Prospective cohort studies and meta analysis of them/systematic reviews, subgroup analyses of (prespecified) randomized case control studies
12) Recommendation level: B Weak recommendation
13) Neil J. Stone et al, 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. Circulation. 2014; 129[suppl 2]: S1-S45.
14) Grade B: Moderate Recommendation
15) Most RCTs of moderate-intensity statin therapy and all RCTs of high-intensity statin therapy excluded subjects with serious comorbidities and other conditions or concomitant drug therapy predisposing to adverse events from statin therapy.
16) Recommendation that procedure or treatment is not useful/effective and may be harmful. Evidence from single randomized trial or nonrandomized studies.
17) Atherosclerotic cardiovascular disease
18) Grade E: Expert Opinion
19) Recommendation's usefulness/efficacy less well established. Only diverging expert opinion, case studies, or standard of care.
20) Paul S. Jellinger et al. AACE 2017 Guidelines AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS AND AMERICAN COLLEGE OF ENDOCRINOLOGY GUIDELINES FOR MANAGEMENT OF DYSLIPIDEMIA AND PREVENTION OF CARDIOVASCULAR DISEASE.; Endocr Pract 2017: Suppl2; 23; 1-87

myopathy/rhabdomyolysis when used with statin (uncommon with gemfibrozil, but increased risk with all statins except fluvastatin). Interaction is less likely with fenofibrate or fenofibric acid with no apparent difference by statin.

Although rare, fibrate use has been associated with myositis, myalgia/myopathy, or rhabdomyolysis; this risk increases with concomitant statin therapy (EL 4; NE[21)]).

Although rhabdomyolysis is rare (reported rates are 0.44 per 10,000 person-years for statin monotherapy and 5.98 per 10,000 person-years for statin/fibrate combination therapy), any reported symptoms require close attention due to the high case fatality rate associated with this condition (EL 1; MRCT; EL 1; RCT)[22)]).

Elevated TG can often be effectively treated through lifestyle changes; however, fibrates in combination with statins may be appropriate options for many individuals with hypertriglyceridemia and associated low HDL-C (EL 1; RCT).

2.4 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias (EU)[23)]

Combinations of statins with fibrates may enhance the risk for myopathy. This risk is highest for gemfibrozil, and the association of gemfibrozil with statins should be avoided. The increased risk for myopathy when combining statins with other fibrates such as fenofibrate, bezafibrate or ciprofibrate seems to be small.

In high-risk patients with TG >2.3 mmol/L (200 mg/dL) despite statin treatment, fenofibrate may be considered in combination with statins (Class IIb[24)], Level C[25)]).

The risk of myopathy has been reported to be 5.5-fold greater with fibrate use as a monotherapy compared with statin use. The risk of myopathy is greater in patients with CKD, and it varies with different fibrates and statins used in combination. This is explained by the pharmacological interaction between different fibrates and statins. This effect differs in the glucuronidation of statins depending on the different fibrates. Gemfibrozil inhibits the metabolism of statins via the glucuronidation pathway, which leads to highly increased plasma concentrations of statins. As fenofibrate does not share the same pharmacokinetic

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21) No evidence
22) Strong evidence. Meta-analysis of randomized controlled trials (MRCT), Randomized controlled trial (RCT).
23) Alberico L et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias.; European Heart Journal 2016: 37; 2999-3058
24) Usefulness/efficacy is less well established by evidence/opinion. May be considered.
25) Consensus of Opinion of the experts and/or small studies, retrospective studies, registries.

pathways as gemfibrozil, the risk of myopathy is much less with this combination therapy.

A combination of statins with fibrates can also be considered while monitoring for myopathy, but the combination with gemfibrozil should be avoided.

3. Published literature

Search for Japanese and overseas literature on the co-administration of fibrates with statins in patients with abnormal renal function values found the following 1 study.

Intern Med.2011; 50; 845-53

A retrospective analysis was conducted on a total of 8,610 drug-associated rhabdomyolysis cases reported to the U.S. Food and Drug Administration (FDA) between January 2004 and December 2009 collected from the FDA Adverse Event Reporting System (AERS) database.

There were 2,523 cases of statin-associated rhabdomyolysis, of which 220 cases (8.7%) were co-administered fibric acid derivatives with statins. Proportion of fatal outcome for statin was 9.7% (95%CI; 8.5-11.0) without, and 5.5% (95%CI; 2.8, 9.3) with co-administration of fibric acid derivatives, respectively (odds ratio 0.54, 95% CI; 0.28-1.01). The p-value calculated using Fisher's exact test was 0.0392.

Out of 2,523 statin-associated rhabdomyolysis cases, 996 (39.5%) were reported coexistence of renal dysfunction. The proportion for fatal outcome with or without coexistence of renal dysfunction was 13.5% (95% CI; 11.4-15.8) and 6.6 % (95% CI; 5.4-8.0), respectively. The odds ratio for fatal outcome was 2.19 (95% CI; 1.66-2.91). The P-value calculated using Fisher's exact test was less than 0.0001.

Among the 220 co-administered cases, 114 were complicated with renal dysfunction and 106 were not. The proportion for fatal outcome with or without coexistence of renal dysfunction was 10.5% (95% CI; 5.6-17.7) and 0.0% (95% CI; 0.0-3.4), respectively. The odds ratio for fatal outcome was 0.00 (95% CI; 0.00-0.43). The p-value calculated using Fisher's exact test was 0.0006.

4. Post-marketing surveillance, etc.

Data on the safety of co-administration of statins and fibrates was reported as below based on the post-marketing surveillance conducted by the marketing authorization holders (MAHs) of the products found in the attached list of drugs investigated.

4.1 Atorvastatin

1) Use-results survey

Survey period: 1 June 2000 to 31 May 2003

Among 4805 cases subjected to safety analysis, adverse drug reactions occurred in 576 (12.0%) cases.

Rhabdomyolysis-related events were identified in 109 cases and blood creatine phosphokinase increased was observed in 109 cases. Of these, 2 (0.04%) cases were serious, and 107 (2.2%) cases were non-serious. Outcomes were reported as: recovered: 46 cases (1.0%); recovering/resolving: 19 cases (0.4%); not recovered: 19 cases (0.4%); unknown: 25 cases (0.5%).

Among the rhabdomyolysis-related events, 1 case (0.9%) co-administered with fibrates was reported. Non-serious blood creatine phosphokinase increased was observed and the outcome was reported as recovered. This case was not considered to be subject to the Relative Contraindications for Co-administration (abnormal renal functions values are observed).

2) Specified use-results survey (long-term use)

Survey period: 1 October 2000 to 30 September 2004

Among 667 cases subjected to safety analysis, adverse drug reactions occurred in 114 (17.1%) cases.

Rhabdomyolysis-related events were identified in 28 cases: rhabdomyolysis was observed in 1 (0.1%) case, and blood creatine phosphokinase increased was observed in 27 (4.0%) cases. Of these, 1 (0.1%) case was serious, and 27 (4.0%) cases were non-serious. Outcomes were reported as follows: recovered: 12 cases (1.8%); recovering/resolving: 5 cases (0.7%); not recovered: 3 cases (0.4%); unknown: 8 cases (1.2%).

No cases of co-administration with fibrates were identified in association with these events.

3) Post-marketing clinical study (retraction effect to yellow plaques in a coronary artery)

Study period: 4 July 2003 to 28 September 2005

Among 57 cases subjected to safety analysis, adverse drug reactions occurred in 6 (10.5%) cases.

No rhabdomyolysis-related events were identified in these cases.

Fibrates were specified as prohibited concomitant medications in this study and there were no cases of co-administration with fibrates.

4) Specified use-results survey (ALWAYS)

Survey period: September 2010 to March 2012

Among 22921 cases subjected to safety analysis, adverse drug reactions occurred in 722 (3.1%) cases.

Rhabdomyolysis-related events were identified in 79 cases: rhabdomyolysis was observed in 4 (0.02%) cases, and blood creatine phosphokinase increased was observed in 75 (0.3%) cases. Of these, 4 (0.02%) cases were serious, and 75 (0.3%) cases were non-serious. Outcomes were reported as follows: recovered: 57 cases (0.2%); recovering/resolving: 11 cases (0.05%); not recovered: 6 cases (0.03%), unknown: 5 cases (0.02%).

Among 108 cases of co-administration with fibrates, adverse drug reactions occurred in 4 (3.7%) cases. No rhabdomyolysis-related events were identified in these cases.

4.2 Simvastatin

1) Use-results survey

Survey period: 11 September 1991 to October 1995

Among 8123 cases subjected to safety analysis, adverse drug reactions occurred in 219 (2.7%) cases.

Rhabdomyolysis-related events were identified in 64 cases: rhabdomyolysis was observed in 1 (0.01%) case, and blood creatine phosphokinase increased was observed in 63 (0.8%) cases. All cases were non-serious. Outcomes were reported as follows: recovered: 22 cases (0.3%); recovered with sequelae: 1 case (0.01%); recovering/resolving: 9 cases (0.1%); unknown: 19 cases (0.2%); not recovered: 13 cases (0.2%).

Among the adverse drug reaction events, 1 case (0.5%) co-administered with fibrates was reported. A non-serious case of rhabdomyolysis was identified and the outcome was reported as recovered. This case was considered to be subject to the Relative Contraindications for Co-administration (abnormal renal function values are observed, or having complications considered to be renal impairment).

2) Special survey (Japan Lipid Intervention Trial (J-LIT))

Survey period: November 1991 to June 1999

Among 51321 cases subjected to safety analysis, adverse drug reactions occurred in 1670 (3.3%) cases.

Rhabdomyolysis-related events were identified in 439 cases (492 events) of musculoskeletal disorder: increase in serum creatine phosphokinase levels (344), myalgia (97), muscle spasticity (36), arthralgia (8), myopathy (4), myoglobin increased (2), and muscle atrophy (1). Although 4 cases of myopathy with increased creatine phosphokinase were reported, no cases of rhabdomyolysis (an event that was pre-defined in the protocol as associated with creatine phosphokinase exceeding 10000 IU/L and muscular symptom) were reported.

Among the musculoskeletal disorder cases, 21 cases (4.8%) co-administered with fibrates were reported. Incidences of musculoskeletal disorder in the non-fibrate co-administration and fibrate co-administration groups were 0.85% (418/49043) and 0.92% (21/2278) respectively. Outcomes in the non-fibrate co-administration group were reported as follows: recovered: 199 cases (47.6%); recovering/resolving: 67 cases (16.0%); not recovered: 62 cases (14.8%), and unknown: 90 cases (21.5%). Outcomes in the fibrate co-administration group were reported as follows: recovered: 13 cases (61.9%); recovering/resolving: 1 case (4.8%); not recovered: 4 cases (19.0%); and unknown: 3 cases (14.3%).

No information concerning the seriousness of observed adverse drug reactions, patient outcomes, or cases considered to be subject to the Relative Contraindications was included.

3) Special survey (East Japan CAG Study (A study to verify the effect of hyperlipidemia treatment on the progression or regression of coronary arteriosclerosis))

Survey period: 22 March 1994 to December 2000

Among 155 cases subjected to safety analysis, adverse drug reactions occurred in 19 (12.3%) cases.

Rhabdomyolysis-related events were identified in 5 (3.2%) cases and blood creatine phosphokinase increased was observed in 5 cases. All cases were non-serious. Outcomes were reported as follows: recovered: 2 cases (1.3%); and not recovered: 3 cases (1.9%).

No cases of co-administration with fibrates were identified among the observed rhabdomyolysis-related events.

4.3 Pitavastatin

Use-results survey and special survey on long-term use

Survey period: 1 December 2003 to 31 March 2007

Among 19925 cases subjected to safety analysis, adverse drug reactions occurred in 2070 (10.4%) cases.

Rhabdomyolysis-related events were identified in 565 (2.8%) cases: rhabdomyolysis was observed in 9 cases (0.05%), myopathy in 7 cases (0.04%), blood creatine phosphokinase increased in 542 cases (2.7%), myoglobin blood increased in 6 cases (0.03%), myoglobin urine present in 1 case (0.01%). Of these, 2 (0.01%) cases were serious, and 563 (2.8%) cases were non-serious. Outcomes were reported as follows: recovered: 341 cases (1.7%); recovering/resolving: 75 cases (0.4%); not recovered: 67 cases (0.3%); recovered with sequela: 1 case (0.01%); unknown: 81 cases (0.4%).

Among 225 (1.1%) cases of co-administration with fibrates, adverse drug reactions occurred in 18 (8.0%) cases. Rhabdomyolysis-related events were identified in 4 (1.8%) cases and blood creatine phosphokinase increased was observed in 4 cases. All cases were non-serious. Outcomes were reported as follows: recovered: 3 cases (1.3%); not recovered: 1 case (0.4%).

Of these, 43 cases were considered to be subject to the Relative Contraindications for Co-administration (abnormal renal function values are observed) and adverse drug reactions occurred in 5 (11%) cases. Rhabdomyolysis-related events were identified in 2 (4.7%) cases and blood creatine phosphokinase increased was observed in 2 cases. All cases were non-serious. Outcomes were reported as follows: recovered: 1 case (2.3%); not recovered: 1 case (2.3%).

4.4 Pravastatin

Specified use-results survey (long-term use in the high risk group for primary prevention)

Survey period: February 2008 to January 2011

Among 6053 cases subjected to safety analysis, adverse drug reactions occurred in 175 (2.9%) cases.

Rhabdomyolysis-related events were identified in 42 (0.7%) cases: rhabdomyolysis was observed in 1 case (0.02%), blood creatine phosphokinase increased in 41 cases (0.7%), and myoglobin blood increased in 1 case (blood creatine phosphokinase increased and myoglobin blood increased occurred in the same patient). All cases were non-serious. Outcomes were reported as follows: recovered: 28 cases; recovering/resolving: 3 cases; not recovered: 9 cases; unknown: 3 cases.

Among 79 (1.3%) cases of co-administration with fibrates, adverse drug reactions occurred in 2 (2.5%) cases. A rhabdomyolysis-related event was identified in 1 (1.3%) case as a non-serious blood creatine phosphokinase increased, and the outcome was reported as recovered.

Among the cases of co-administration with fibrates, 9 cases were considered to be subject to the Relative Contraindications for Co-administration (serum creatinine clearance <60 mL/min). No cases of drug adverse reactions were identified.

4.5 Fluvastatin

1) Use-results survey

Survey period: 1 October 1998 to 22 February 2003

Among 4903 cases subjected to safety analysis, adverse drug reactions occurred in 556 (11.3%) cases.

78 rhabdomyolysis-related events were identified including rhabdomyolysis (2) and blood creatine phosphokinase increased (76). All events were non-serious. Outcomes were reported as follows: recovered: 29 events; recovering/resolving: 10 events; not recovered: 13 events; death: 0 events; unknown: 26 events.

No information of co-administration with fibrates was included.

2) Special survey (long-term use)

Survey period: 1 April 1999 to 31 March 2002

Among 591 cases subjected to safety analysis, adverse drug reactions occurred in 90 (15.2%) cases.

Rhabdomyolysis-related events were identified in 26 (4.4%) cases and blood creatine phosphokinase increased was observed in 26 cases. Of these, 1 (0.2%) case was serious, and 25 (4.2%) cases were non-serious. Outcomes were reported as follows: recovered: 16 cases (2.7%); recovering/resolving: 4 cases (0.7%); not recovered: 3 cases (0.5%); unknown: 3 cases (0.5%).

7 cases (1.2%) co-administered with fibrates were reported. No information of adverse drug reactions onset among the cases of co-administration with fibrates was included.

3) Special survey (long-term event survey)

Survey period: 1 April 2000 to 29 June 2004

Among 17358 cases subjected to safety analysis, adverse drug reactions occurred in 1195 (6.9%) cases.

111 rhabdomyolysis-related events were identified including rhabdomyolysis (3), blood creatine phosphokinase increased (105), and myoglobin blood increased (3). Seriousness of observed adverse drug reactions and patient outcomes were unknown.

No information of co-administration with fibrates was included.

4) Post-marketing clinical study (dose-confirmation study in patients with hypercholesterolemia)

Study period: 15 June 2000 to 15 March 2002

Among 232 cases subjected to safety analysis, adverse drug reactions occurred in 37 (15.9%) cases.

Rhabdomyolysis-related events were identified in 3 (1.3%) cases and blood creatine phosphokinase increased was observed in 3 cases. All cases were non-serious. Outcomes were reported as follows: recovered: 2 cases (0.9%); not recovered: 1 case (0.4%).

Fibrates were specified as prohibited concomitant medications in this study and there were no cases of co-administration with fibrates.

4.6 Rosuvastatin

Use-results survey

Survey period: May 2005 to May 2007

Among 8700 cases subjected to safety analysis, adverse drug reactions occurred in 974 (11.2%) cases.

Rhabdomyolysis-related events were identified in 202 (2.3%) cases: rhabdomyolysis was observed in 1 (0.01%) case, blood creatine phosphokinase increased in 199[26)] (2.3%) cases, myoglobinuria in 1 (0.01%) case, and myoglobin urine present in 1 (0.01%) case. Of these, 6 (0.07%) cases were serious, and 196 (2.3%) cases were non-serious. Outcomes were reported as follows: recovered: 117 cases (1.3%), recovering/resolving: 22 cases (0.3%); not recovered: 43 cases (0.5%); unknown: 21 cases (0.2%).

89 (1.0%) cases co-administered with fibrates were reported and of these, adverse drug reactions occurred in 7 (7.9%) cases. Rhabdomyolysis-related events were identified in 2 (2.2%) cases, and blood creatine phosphokinase increased was observed in 2 cases. 1 (1.1%) case was serious, and 1 (1.1%) case was non-serious. Outcomes were reported as follows: recovered: 1 case (1.1%); not recovered: 1 case (1.1%).

Among the cases of co-administration with fibrates, 13 cases were considered to be subject to the Relative Contraindications for Co-administration (abnormal renal function values are observed) and adverse drug reactions occurred in 1 (1.1%) case. No rhabdomyolysis-related events were identified in these cases.

4.7 Clinofibrate

Use-results survey was conducted but since statins were not yet launched, no data regarding co-administration with statins are available.

4.8 Clofibrate

No information concerning the data of post-marketing surveillance etc. was included.

[26)] 2 events of blood creatine phosphokinase increased occurred in one patient and the outcomes were reported as recovered and not recovered respectively.

4.9 Fenofibrate

1) Use-results survey

Survey period: 1 June 1999 to 31 May 2002

Among 3431 cases subjected to safety analysis, adverse drug reactions occurred in 553 (16.1%) cases.

Rhabdomyolysis-related events were identified in 51 (1.5%) cases: rhabdomyolysis was observed in 2 cases, and blood creatine phosphokinase increased was observed in 49 cases. Of these, 1 (0.03%) case was serious, and 50 (1.5%) cases were non-serious. Outcomes were reported as follows: recovered: 27 cases (0.8%); recovering/resolving 14 cases (0.4%); not recovered: 5 cases (0.1%); unknown: 5 cases (0.1%).

Among 115 (3.4%) cases of co-administration with statins, adverse drug reactions occurred in 22 (19.1%（22/115）) cases. Rhabdomyolysis-related events were identified in 7 (6.1%) cases: rhabdomyolysis was observed in 1 (0.9%) case, and blood creatine phosphokinase increased was observed in 6 (5.2%) cases. All cases were non-serious. Outcomes were reported as follows: recovered: 3 cases (2.6%); recovering/resolving: 4 cases (3.5%).

Of these, no cases were considered to be subject to the Relative Contraindications for Co-administration (abnormal renal function values are observed).

2) Special survey (long-term use)

Survey period: 1 June 1999 to 31 May 2004

Among 594 cases subjected to safety analysis, adverse drug reactions occurred in 102 (17.2%) cases.

Rhabdomyolysis-related events were identified in 13 (2.2%) cases: rhabdomyolysis was observed in 1 (0.2%) case, and blood creatine phosphokinase increased was observed in 12 (2.0%) cases. Of these, 2 (0.3%) cases were serious, and 11 (1.9%) cases were non-serious. Outcomes were reported as follows: recovered: 12 cases (2.0%); recovering/resolving: 1 case (0.2%).

32 (5.4%) cases co-administered with Statins was reported and of these, adverse drug reactions occurred in 5 (0.8%) cases. Rhabdomyolysis-related events were identified in 1

(3.1%) case. Non-serious blood creatine phosphokinase increased was observed and the outcome was reported as recovered.

No cases were considered to be subject to the Relative contraindications for co-administration (abnormal renal function values are observed).

4.10 Bezafibrate

1) Use-results survey of Bezatol SR Tab on previous system

Survey period: 18 January 1991 to 17 January 1996

Among 7347 cases subjected to safety analysis, adverse drug reactions occurred in 210 (2.9%) cases.

69 Rhabdomyolysis-related events were identified including rhabdomyolysis (1), myalgia (5), feelings of weakness (1), and creatine phosphokinase increased (62). No information concerning the seriousness of observed adverse drug reactions, patient outcomes, and co-administration with statins was included.

2) Use-results surveys of Bezatol SR Tab and Bezalip tablets on new system (Integrated the data from the two surveys)

Survey period: 1 April 1995 to 17 January 1997

Among 1675 cases subjected to safety analysis, adverse drug reactions occurred in 123 (7.3%) cases.

27 rhabdomyolysis-related events were identified including rhabdomyolysis (1), myalgia (1), blood myoglobin increased (1), and creatine phosphokinase increased (24).

107 cases co-administered with Statins and of these, adverse drug reactions occurred in 10 cases. Rhabdomyolysis-related events were identified as creatine phosphokinase increased (3). No information concerning the seriousness of observed adverse drug reactions and patient outcomes was included.

4.11 Pemafibrate

No post-marketing surveillance data have been obtained.

5. Accumulation status of adverse reaction reports in Japan

Details of the serious adverse drug reactions identified in the reported events related to rhabdomyolysis[27] (hereinafter "rhabdomyolysis-related events") obtained by the MAHs of the products found in the attached list of drugs investigated from April 1, 2004 through April 30, 2018 are as follows[28] .

5.1 Adverse drug reactions reports in Japan associated with statins

5.1.1 Atorvastatin

Rhabdomyolysis-related events were identified in 609 monotherapy cases and in 5 co-administration cases with fibrates (4 cases with fenofibrate, 1 case with bezafibrate). Adverse drug reactions associated with co-administration were: rhabdomyolysis: 4 cases with fenofibrate; 1 case with bezafibrate. Outcomes were reported as follows: recovered: 3 cases; recovering/resolving: 2 cases. 1 case was considered to be subject to the Relative Contraindications with the outcome was reported as recovered.

5.1.2 Simvastatin

Rhabdomyolysis-related events were identified in 108 monotherapy cases and in 1 co-administration case with fibrates (with bezafibrate). Rhabdomyolysis and blood creatine phosphokinase increased were reported in the co-administration case. Outcomes of the events were reported as recovered and recovering/resolving respectively. This case was considered to be subject to the Relative Contraindications.

5.1.3 Pitavastatin

Rhabdomyolysis-related events were identified in 202 monotherapy cases and in 2 co-administration cases with fibrates (all were with bezafibrate). As adverse drug reactions associated with co-administration rhabdomyolysis was identified in 2 cases. Outcomes were reported as recovered in 2 cases. 1 case was considered to be subject to the Relative Contraindications.

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[27] Events corresponding to Rhabdomyolysis/Myopathy (narrow area) categorized as Standardized MedDRA Query (SMQ), and to Blood creatine phosphokinase MM increased, Blood creatine phosphokinase abnormal, Blood creatine phosphokinase increased categorized as Preferred Terms (PT) in the Medical Dictionary for Regulatory Activities (MedDRA)

[28] Including duplicate reports.

5.1.4 Pravastatin

Rhabdomyolysis-related events were identified in 177 monotherapy cases and in 6 co-administration cases with fibrates (1 case with fenofibrate, 5 cases with bezafibrate). Adverse drug reactions associated with co-administration were: rhabdomyolysis: 1 case with fenofibrate; 4 cases with bezafibrate; blood creatine phosphokinase increased: 1 case with bezafibrate. Outcomes were reported as follows: recovered: 1 case; recovering/resolving: 4 cases; unknown: 1 case. 1 case was considered to be subject to the Relative Contraindications with the outcome as recovering/resolving.

5.1.5 Fluvastatin

Rhabdomyolysis-related events were identified in 115 monotherapy cases. No co-administration cases with fibrates were identified.

5.1.6 Rosuvastatin

Rhabdomyolysis-related events were identified in 418 monotherapy cases and in 13 co-administration cases with fibrates (10 case with bezafibrate, 3 cases with fenofibrate,). Adverse drug reactions associated with co-administration were: rhabdomyolysis: 4 cases with bezafibrate; 1 case with fenofibrate; myopathy: 2 cases with bezafibrate; 1 case with fenofibrate; blood creatine phosphokinase increased: 4 cases with bezafibrate; 1 case with fenofibrate. Outcomes were reported as follows: recovered: 10 cases; recovering/resolving: 2 cases; recovered with sequelae: 1 case. 5 cases were considered to be subject to the Relative Contraindications with the patient outcomes reported as follows: recovered: 3 cases; recovering/resolving: 2 cases.

5.2 Adverse drug reactions reports in Japan associated with combination drug containing statins

5.2.1 Amlodipine/atorvastatin

Rhabdomyolysis-related events were identified in 21 monotherapy cases. No co-administration cases with fibrates were identified.

5.2.2 Ezetimibe/atorvastatin

No rhabdomyolysis-related events were reported.

5.3 Adverse drug reactions reports in Japan associated with fibrates

5.3.1 Clinofibrate

Rhabdomyolysis-related events were identified in 1 case of monotherapy.

5.3.2 Fenofibrate

Rhabdomyolysis-related events were identified in 42 monotherapy cases and in 9 co-administration cases (4 cases with atorvastatin, 2 cases with pravastatin, 3 cases with rosuvastatin). Adverse drug reactions associated with co-administration were: rhabdomyolysis: 4 cases with atorvastatin; 2 cases with pravastatin; 1 case with rosuvastatin; myopathy: 1 case with rosuvastatin; blood creatine phosphokinase increased: 1 case with rosuvastatin. Outcomes were reported as follows: recovered: 4 cases; recovering/resolving: 2 cases; not recovered: 1 case; unknown: 2 cases. 1 case was considered to be subject to the Relative Contraindications with the outcome unknown.

5.3.3 Bezafibrate

Rhabdomyolysis-related events were identified in 139 monotherapy cases and in 15 co-administration cases (3 cases with atorvastatin, 1 case with simvastatin, 2 cases with pitavastatin, 6 cases with pravastatin, 3 cases with rosuvastatin). Adverse drug reactions associated with co-administration were: rhabdomyolysis: 3 cases with atorvastatin; 2 cases with pitavastatin; 5 cases with pravastatin; 3 cases with rosuvastatin; blood creatine phosphokinase increased: 1 case with simvastatin; 2 cases with pravastatin. Outcomes were reported as follows: recovered: 8 cases; recovering/resolving: 5 cases; not recovered: 1 case; unknown: 1 case. 2 cases were considered to be subject to the Relative Contraindications and the outcome was reported as recovered for the both patients.

5.3.4 Clofibrate, pemafibrate

No rhabdomyolysis-related events were reported.

6. Summary of PMDA Investigation

Current US package inserts and EU SPC do not specifically contraindicate co-administration of statins and fibrates concerning the use in patients with abnormal renal function values.

The US package inserts and EU SPC specify the combination of simvastatin and gemfibrozil as a contraindicated co-administration of statins and fibrates. However, gemfibrozil is not currently approved in Japan. While the EU SPC lists the combination of rosuvastatin 40 mg and fibrates in the Contraindications section, this combination is not listed in the corresponding section in the US package insert. Although the EU SPC includes the combination therapy of bezafibrate with statins in patients with predisposing factors for myopathy in the Contraindications section, the Japanese package insert includes no restrictions concerning the co-administration of fibrates with statins in patients with predisposing factors for myopathy. It was considered that the current situation also does not warrant new regulatory measures in this respect.

With regard to the drugs of the classes and associated dosage and administration currently approved in Japan, co-administration of statins and fibrates in patients with abnormal renal function values is currently not contraindicated in Japanese or overseas guidelines.

Safety information of co-administration of statins and fibrates in patients with abnormal renal function values was limited, due to the fact that cases associated with co-administration of statins and fibrates were rarely reported during the post-marketing surveillance or in the adverse drug reaction reports. In addition, considering the repeal of the Relative Contraindications section and reassignment of the majority of language under the section to the Precautions Concerning Patients with Specific Backgrounds section expected in line with the enforcement on April 1, 2019 of the revised Instructions for Package Inserts of Prescription Drugs (PSEHB Notification No.0608-1, by the Directory-General of the Pharmaceutical Safety and Environmental Health Bureau, MHLW, dated June 8, 2017), PMDA concluded that the language under the Relative Contraindications and the Relative Contraindications of Co-administration sections may be removed from the package insert while continued precaution regarding rhabdomyolysis in patients with abnormal renal function values associated with co-administration of statins and fibrates was considered necessary.

PMDA's conclusions above were supported by its expert advisors based on the opinions expressed by them as follows.

・Co-administration of statins and fibrates is required in a certain proportion of cases because statin therapy alone is not sufficient to control the relevant risks in such patients. The potential benefit of co-administration outweighs the risk of adverse reactions in some cases.

・Removal of the language under the Relative Contraindications and the Relative Contraindications for Co-administration sections should be appropriate if precaution against rhabdomyolysis with co-administration of statins and fibrates is maintained.

・Co-administration of statins and fibrates without careful consideration in patients with renal function abnormalities is a concern due to the removal of the language under the Relative Contraindications and the Relative Contraindications for Co-administration sections. Taking ongoing precautions with respect to co-administration in patients with abnormal renal function is critical.

IV. Overall Evaluation

PMDA concluded that the Precautions in the package insert may be appropriately revised as follows: See Appendix 2 for the proposed revisions (Appendix 2 is not included. See the Detailed information on revisions of PRECAUTIONS).

Appendix 1

List of drugs investigated

Drugs containing HMG-CoA reductase inhibitors

Nonproprietary name	Branded name	Marketing authorization holder	Indications	Dosage and administration
Atorvastatin calcium hydrate	Lipitor Tablets 5 mg, 10 mg, and others	Astellas Pharma Inc., and others	Hypercholesterolemia Familial hypercholesterolemia	Hypercholesterolemia The usual adult dosage is 10 mg of atorvastatin administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. The dose may be increased to a maximum of 20 mg/day in severe cases. Familial hypercholesterolemia The usual adult dosage is 10 mg of atorvastatin administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. The dose may be increased to a maximum of 40 mg/day in severe cases.
Simvastatin	Lipovas Tablets 5, 10, 20, and others	MSD K.K., and others	Hyperlipidemia Familial hypercholesterolemia	The usual adult dosage is 5 mg of simvastatin administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is

				insufficient, the dose may be increased to a maximum of 20 mg/day.
Pitavastatin calcium hydrate	Livalo Tab. 1 mg, 2 mg, 4 mg, Livalo OD Tab. 1 mg, 2 mg, 4 mg	Kowa Company, Ltd., and others	Hypercholesterolemia Familial hypercholesterolemia	Hypercholesterolemia The usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day. Familial hypercholesterolemia Adults: the usual adult dosage is 1 or 2 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. If lowering of LDL cholesterol is insufficient, the dose may be increased to a maximum of 4 mg/day. Pediatric patients: The usual dosage in pediatric patients aged ≥10 years is 1 mg of pitavastatin calcium administered orally once daily. The dose may be adjusted according to the patient's condition. If lowering of LDL cholesterol is insufficient, the

				dose may be increased to a maximum of 2 mg/day.
Pravastatin sodium	Mevalotin Tablets 5, 10, Mevalotin Fine Granules 0.5%, 1%, and others	Daiichi Sankyo Propharma Co., Ltd.	Hyperlipidemia Familial hypercholesterolemia	The usual adult dosage is 10 mg of pravastatin sodium administered orally once or in two divided doses daily. The dose may be adjusted according to the patient's age and symptoms. The dose may be increased to a maximum of 20 mg/day in severe cases.
Fluvastatin sodium	Lochol Tablets 10 mg, 20 mg, 30 mg, and others	Sun Pharma Japan Limited, and others	Hypercholesterolemia Familial hypercholesterolemia	The usual adult dosage is 20 to 30 mg of fluvastatin administered orally once daily after dinner. The dose starts from 20 mg, and it may be adjusted according to the patient's age or symptoms. The dose may be increased to a maximum of 60 mg/day in severe cases.
Rosuvastatin calcium	Crestor Tablets 2.5 mg, 5 mg, Crestor OD Tablets 2.5 mg, 5 mg, and others	AstraZeneca K.K., and others	Hypercholesterolemia Familial hypercholesterolemia	The usual adult dosage starts from 2.5 mg of rosuvastatin once daily, but the dosage can start from 5 mg when early lowering of LDL-cholesterol is required. The dose may be adjusted according to the patient's age and symptoms. The dose may be increased gradually to a maximum of 10 mg if lowering of LDL-cholesterol is insufficient after

				week 4 of administration or dose increment. Only for the patients with severe symptoms such as familial hypercholesterolemia and with insufficient lowering of LDL-cholesterol even after administering 10 mg, the dose may be increased further to a maximum of 20 mg/day.
Amlodipine basilate/atorvastatin calcium hydrate	Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban, and others	Pfizer Japan Inc., and others	Use this drug (amlodipine/atorvastatin combination) in the following patients for whom treatment with both amlodipine and atorvastatin is appropriate: Patients with hypertension or angina, hypercholesterolemia or familial hypercholesterolemia Each amlodipine and atorvastatin are indicated	This drug (amlodipine/atorvastatin combination) is administered orally once daily. The dose should be decided tailored to individual patients based on the dosage and administration of amlodipine and atorvastatin as follows: Amlodipine ·Hypertension The usual adult dosage is 2.5 to 5 mg of amlodipine administered orally once daily. The dose may be adjusted according to the patient's symptoms. The dose may be increased to a maximum of 10 mg/day if patients are not adequately responsive. ·Angina The usual adult dosage is 5 mg of amlodipine administered orally once daily. The dose may be

			for treatment of the following disorders: Amlodipine ·Hypertension ·Angina Atorvastatin ·Hypercholesterolemia ·Familial hypercholesterolemia	adjusted according to the patient's age and symptoms. Atorvastatin ·Hypercholesterolemia The usual adult dosage is 10 mg of atorvastatin administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. The dose may be increased to a maximum of 20 mg/day in severe cases. ·Familial hypercholesterolemia The usual adult dosage is 10 mg of atorvastatin administered orally once daily. The dose may be adjusted according to the patient's age and symptoms. The dose may be increased to a maximum of 40 mg/day in severe cases.
Ezetimibe/atorvastatin calcium hydrate	Atozet Combination Tablets LD, HD	MSD K.K.	Hypercholesterolemia Familial hypercholesterolemia	The usual adult dosage is a tablet (10/10 mg or 10/20 mg of ezetimibe/atorvastatin) administered orally once daily after a meal.

Fibrates

Nonproprietary name	Branded name	Marketing authorization holder	Indications	Dosage and administration
Clinofibrate	Lipoclin Tablets 200	Sumitomo Dainippon Pharma Co., Ltd.	Hyperlipidemia	The usual adult dosage is 600 mg of clinofibrate administered orally in three divided doses daily. The dose may be adjusted according to the patient's age and symptoms.
Clofibrate	Clofibrate Capsules 250 mg [Tsuruhara]	Tsuruhara Pharmaceutical Co., Ltd.	Hyperlipidemia	The usual adult dosage is 750 to 1500 mg of clofibrate administered orally in two or three divided doses daily. The dose may be adjusted according to the patient's age and symptoms.
Fenofibrate	Tricor Tablets 53.3 mg, 80 mg, and others	Mylan EPD G.K.	Hyperlipidemia (including familial)	The usual adult dosage is 106.6 to 160 mg of fenofibrate administered orally once daily after a meal. The dose may be adjusted according to the patient's age and symptoms. The daily dose should not exceed 160 mg.
	Lipidil Tablets 53.3 mg, 80 mg, and others	Aska Pharmaceutical. Co., Ltd., and others		

Bezafibrate	Bezatol SR Tab. 100 mg, 200 mg, and others	Kissei Pharmaceutical Co., Ltd.	Hyperlipidemia (including familial)	The usual adult dosage is 400 mg of bezafibrate administered orally in two divided doses daily after breakfast and dinner. The dose should be adjusted for patients with renal impairment and for elderlies.
Pemafibrate	Parmodia Tab. 0.1mg	Kowa Company, Ltd.	Hyperlipidemia (including familial)	The usual adult dosage is 0.1 mg of pemafibrate administered orally twice daily in the morning and evening. The dose may be adjusted according to the patient's age and symptoms. The maximum daily dose should be 0.2 mg administered twice daily.