This English version is intended to be a reference material to provide convenience for users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

Summary of Investigation Results

Preparations containing HMG-CoA reductase inhibitor

July 20, 2023

Non-proprietary name

a. Atorvastatin calcium hydrate
b. Simvastatin
c. Pitavastatin calcium hydrate
d. Pravastatin sodium
e. Fluvastatin sodium
f. Rosuvastatin calcium
g. Amlodipine besilate/atorvastatin calcium hydrate
h. Ezetimibe/atorvastatin calcium hydrate
i. Ezetimibe/rosuvastatin calcium
j. Pitavastatin calcium hydrate/ezetimibe

Brand name (marketing authorization holder)

a. Lipitor Tablets 5 mg, 10 mg (Viatris Pharmaceuticals Japan Inc.), and the others
b. Lipovas Tablets 5, 10, 20 (Organon K.K.), and the others
c. Livalo Tablets 1 mg, 2 mg, 4 mg, Livalo OD Tablets 1 mg, 2 mg, 4 mg (Kowa Company, Ltd.), and the others
d. Mevalotin Tablets 5, 10, Mevalotin Fine Granules 0.5%, 1% (Daiichi Sankyo Co., Ltd.), and the others
e. Lochol Tablets 10 mg, 20 mg, 30 mg (Sun Pharma Japan Limited), and the others
f. Crestor Tablets 2.5 mg, 5 mg, Crestor OD Tablets 2.5 mg, 5 mg (AstraZeneca K.K.), and the others
g. Caduet Combination Tablets 1ban, 2ban, 3ban, 4ban (Viatris Pharmaceuticals Japan Inc.), and the others

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

h. Atozet Combination Tablets LD, HD (Organon K.K.), and the others
i. Rosuzet Combination Tablets LD, HD (Organon K.K.)
j. Livazebe Combination Tablets LD, HD (Kowa Company, Ltd.)

Japanese market launch

a. May 2000
b. Tablets 5: December 1991, Tablets 10, 20: June 2002
c. Tablets 1 mg, 2 mg: September 2003, Tablets 4 mg: June 2012, OD Tablets 1 mg, 2 mg: July 2013, OD Tablets 4 mg: December 2013
d. Tablets 5, Fine Granules 0.5%: October 1989, Tablets 10, Fine Granules 1%: December 1991
e. September 1998 (Japanese market launch of “Lochol Capsules 10mg, 20 mg, 30mg”)
f. Tablets 2.5 mg, 5 mg: April 2005, OD Tablets 2.5 mg, 5 mg: June 2016
g. December 2009
h. April 2018
i. May 2019
j. December 2022

Indications

a., c., e., f., h.-j. Hypercholesterolaemia, familial hypercholesterolaemia
b., d. Hyperlipidaemia, familial hypercholesterolaemia
g. This drug (amlodipine/atorvastatin combination drug) should be used in the following patients for whom treatment with both amlodipine and atorvastatin is appropriate:
Patients with hypertension or angina pectoris, hypercholesterolaemia or familial hypercholesterolaemia
The indications for amlodipine and atorvastatin are as follows:
Amlodipine
•Hypertension
•Angina pectoris
Atorvastatin
•Hypercholesterolaemia

•Familial hypercholesterolaemia

Summary of revisions

1. “Patients with myasthenia gravis or a history of it” should be added to the PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS section (new instructions) or the Careful Administration section (old instructions).
2. “Myasthenia gravis” should be added to the Clinically Significant Adverse Reactions section.

Investigation results and background of the revision

Cases involving myasthenia gravis reported in Japan and overseas, published literature, and Japanese and overseas guidelines were evaluated. As a result of consultation with expert advisors, the MHLW/PMDA concluded that revision of PRECAUTIONS was necessary, taking into consideration the following:

•Cases [note 1] of myasthenia gravis for which a causal relationship with HMG-CoA reductase inhibitor (hereinafter referred to as “statins”) was reasonably possible have been reported as adverse reactions in Japan.

•Cases indicating a reasonably possible causal relationship between statins and myasthenia gravis, such as cases in which symptoms of myasthenia gravis relapsed following readministration of statins or in which they disappeared by discontinuing statins, have been reported [note 2] in the published literature.

•It has been reported [note 4, note 5] in the published literature that a disproportionality analysis using the WHO Individual Case Safety Reports (ICSRs) Global Database (VigiBase) [note 3] statistically showed higher numbers (reporting odds ratio 2.66 [95% CI 2.28−3.10]) of adverse reaction of myasthenia gravis reported for statins than would be expected for the entire database. In addition, a disproportionality analysis performed by the PMDA using the dataset of VigiBase as of May 23, 2023 showed similar results (myasthenia gravis: IC_{025} [note 6] 0.9, ocular myasthenia: IC_{025} 1.7) [note 4] (see appendix).

•In Japanese and overseas guidelines [note 7], statins are described as drugs that require cautions when they are used in patients with myasthenia gravis.

Reference: Number of cases note 8 **and patient mortalities involving myasthenia gravis, ocular myasthenia reported in Japan**

<Myasthenia gravis>

a. A total of 4 cases have been reported to date (including 1 case for which a causal relationship between the drug and event was reasonably possible).

No patient mortalities have been reported to date.

f. One case has been reported to date. (A causal relationship between the drug and event could not be established for this case.)

No patient mortalities have been reported to date.

b.-e., g.-j. No cases have been reported to date.

<Ocular myasthenia>

a.-j. No cases have been reported to date.

Note 1: Medicine. 2015;94:e416

Note 2: Eur J Neurol. 2008;15:e92-3、J Med Assoc Thai. 2011;94:256-8

Note 3: VigiBase is the World Health Organization (WHO) global database of reported potential adverse reactions of medicinal products, developed and maintained by Uppsala Monitoring Center (UMC). The information comes from a variety of sources, and the probability that the suspected adverse reaction is drug-related is not the same in all cases.

Note 4: The information does not represent the opinion of the WHO or UMC.

Note 5: Muscle & Nerve. 2019;60:382-6

Note 6: Lower limit of 95% confidence interval for information component (IC)

Note 7: Practical Guideline for Myasthenia Gravis (MG) and Lambert-Eaton Myasthenic Syndrome (LEMS) 2022 (supervised by Japanese Society of Neurology), International Consensus Guidance for Management of Myasthenia Gravis 2020 (Neurology. 2021;96:114-122)

Note 8: Cases collected in the PMDA's database for adverse drug reactions, etc. reports

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, 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).

Pharmaceuticals and Medical Devices Agency

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp