1. NAME OF THE MEDICINAL PRODUCT

LIVAZEBE® Film-coated Tablets 2 mg/10 mg
LIVAZEBE® Film-coated Tablets 4 mg/10 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LIVAZEBE Film-coated Tablets 2 mg/10 mg
Each film-coated tablet contains 2 mg pitavastatin (as pitavastatin calcium) and 10 mg ezetimibe.

LIVAZEBE Film-coated Tablets 4 mg/10 mg
Each film-coated tablet contains 4 mg pitavastatin (as pitavastatin calcium) and 10 mg ezetimibe.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet
LIVAZEBE 2 mg/10 mg: white, round, film-coated tablets with a diameter of approximately 8.1 mm, a thickness of approximately 4.4 mm and a weight of approximately 218 mg, debossed with “Kowa 221” on one side.
LIVAZEBE 4 mg/10 mg: light yellow, round, film-coated tablets with a diameter of approximately 8.1 mm, a thickness of approximately 4.4 mm and a weight of approximately 218 mg, debossed with “Kowa 222” on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Hypercholesterolemia/ Familial Hypercholesterolemia
LIVAZEBE is indicated as adjunct therapy to diet for treatment of primary hypercholesterolemia including heterozygous familial hypercholesterolemia.
LIVAZEBE is indicated as adjunct therapy to LDL apheresis as non-drug therapies for treatment of homozygous familial hypercholesterolemia or when such therapies are not feasible.

4.2 Posology and method of administration

Posology
In general for adult patients, 1 tablet (2 mg/10 mg or 4 mg/10 mg of pitavastatin calcium/ezetimibe) is orally administered once daily after a meal.

Application of LIVAZEBE should be considered for each patient based on the following dosage and administration of pitavastatin calcium hydrate and ezetimibe in adults:

- Pitavastatin calcium hydrate; In general for adult patients, 1 to 2 mg of pitavastatin calcium is orally administered once daily. The dosage may be adjusted according to the patient's age and symptoms. The dosage may be increased if the decrease in LDL-cholesterol level is insufficient, but the maximum dose should be 4 mg per day.
- Ezetimibe; In general for adult patients, 10 mg of ezetimibe is orally administered once daily. The dosage may be reduced according to the patient's age and symptoms.

LIVAZEBE should be used in patients where use of a fixed-dose combination is appropriate

- patients not appropriately controlled with pitavastatin alone
- patients already treated with pitavastatin and ezetimibe

In principle, application of LIVAZEBE Film-coated Tablets 2 mg/10 mg (pitavastatin calcium 2 mg/ezetimibe 10 mg) should be considered when pitavastatin calcium 2 mg and ezetimibe 10 mg are co-administered, or when pitavastatin calcium 2 mg is not sufficiently effective.
In principle, application of LIVAZEBE Film-coated Tablets 4 mg/10 mg (pitavastatin calcium 4 mg/ezetimibe 10 mg) should be considered when pitavastatin calcium 4 mg and ezetimibe 10 mg are co-administered, or when pitavastatin calcium 4 mg or pitavastatin calcium 2 mg/ezetimibe 10 mg are not sufficiently effective.

Patients should be on an appropriate lipid lowering diet and continue on this diet during treatment with LIVAZEBE. Exercise therapy and reduction of risk factors for ischemic heart disease, such as hypertension and smoking, should also be carefully considered.

LIVAZEBE should not be used as a first-line drug for the treatment of hypercholesterolemia or familial hypercholesterolemia.

Adequate tests should be performed to confirm that a patient has hypercholesterolemia or familial hypercholesterolemia before the initiation of LIVAZEBE.

A liver function test should be performed when switching from pitavastatin monotherapy to LIVAZEBE. In addition, it is recommended that liver function tests be performed before the initiation of LIVAZEBE and if signs or symptoms of liver injury occur (see sections 4.4 and 4.8). During treatment with LIVAZEBE, blood lipid levels should be examined periodically. If no response to the treatment is observed, the treatment should be discontinued.

If hyperlipidemia is caused by secondary factors, including complications of diseases such as hypothyroidism, obstructive gall bladder/biliary tract diseases, chronic renal failure, and pancreatitis, or use of drugs that adversely affect serum lipids, appropriate measures (e.g., treatment of the primary disease, switching of treatment) should be taken before the initiation of LIVAZEBE.

Rhabdomyolysis
Since adverse events related to rhabdomyolysis may occur as the dose of pitavastatin (systemic exposure) increases, caution should be exercised to prodromal symptoms of rhabdomyolysis, such as increased CK levels, myoglobinuria, myalgia and feelings of weakness, when the dosage is increased to 4 mg of pitavastatin calcium. In a clinical study of pitavastatin in adults, administration of pitavastatin calcium exceeding 8 mg was discontinued due to rhabdomyolysis and other related adverse events. (See sections 4.4 and 4.8)

Cholelithiasis
There is limited experience in the combined use of ezetimibe and fibrates. When co-administered, give attention to the onset of adverse reactions such as cholelithiasis. Fibrates may increase cholesterol excretion in the bile, leading to gallstone formation. Ezetimibe is reported to have increased cholesterol levels in the gallbladder bile in dogs. (See section 4.4)

Special population
Paediatrics
No clinical studies have been conducted to evaluate efficacy and safety in paediatric patients.

Elderly
If adverse reactions occur, measures such as dose reduction should be taken. Physiological function is generally decreased. Rhabdomyolysis is reported to be likely to occur. (See section 5.2)

Hepatic disorder
When LIVAZEBE is used in patients with liver disorders, periodical clinical monitoring is recommended because each monotherapy of active ingredients shown the influence on plasma concentration of the active ingredients. The maximum dose as pitavastatin calcium should be by 2mg for these patients. (See section 5.2)

Renal impairment
When LIVAZEBE is used in patients with renal impairments, periodical clinical monitoring is recommended because each monotherapy of active ingredients shown the influence on plasma concentration of the active ingredients. (See section 5.2)

4.3 Contraindications

- Patients with a history of hypersensitivity to any of the components of LIVAZEBE.
- Patients with severe hepatic impairment, active liver disease, unexplained persistent elevations in serum transaminases (exceeding 3 times the upper limit of normal), or biliary obstruction. (See sections 4.4 and 5.2)

- Patients receiving cyclosporine. (See section 4.5)
- Women who are or may be pregnant and breast-feeding women. (See section 4.6)

4.4 Special warnings and precautions for use

There have been reported that the risk of rhabdomyolysis may be increased in following patients:

- Patients with hypothyroidism
- Patients with hereditary muscular disease (e.g., muscular dystrophy) or with family history
- Patients with a history of drug-induced muscle disorders
- Patients with alcohol poisoning

Patients with myasthenia gravis/ocular myasthenia or a history of it:
Exacerbation or relapse of myasthenia gravis (ocular or systemic) may occur. (See section 4.8)

In few cases, statins have been reported to induce de novo or aggravate pre-existing myasthenia gravis or ocular myasthenia. LIVAZEBE should be discontinued in case of aggravation of symptoms. Recurrences when the same or a different statin was (re-) administered have been reported.

There have been very rare reports of an immune-mediated necrotizing myopathy (IMNM) during or after treatment with some statins. IMNM is clinically characterized by:

- persistent proximal muscle weakness and elevated serum creatine kinase, which persist despite discontinuation of statin treatment;
- muscle biopsy showing necrotizing myopathy without significant inflammation;
- improvement with immunosuppressive agents.
  (See section 4.8)

Patients with Renal Impairment
Patients with abnormal laboratory test values related to renal function:
LIVAZEBE and fibrates should be used concomitantly only when the co-administration is considered therapeutically essential. The risk of rhabdomyolysis may be increased, accompanied by rapid renal function decline. In cases where the co-administration is necessary and cannot be avoided, renal function tests should be performed periodically. If subjective symptoms (e.g., myalgia, feelings of weakness), increase in CK levels, increases in blood/urine myoglobin levels or any sign of renal function decline such as increase in serum creatinine levels are noted, the treatment should be immediately discontinued. (See sections 4.5 and 4.8)

Patients with renal disorders or its history:
Many of the reported cases of rhabdomyolysis associated with pitavastatin are observed in patients with renal impairment, and rapid renal function decline is seen in association with rhabdomyolysis. (See sections 4.5 and 4.8)

Patients with Hepatic Impairment
Patients with severe hepatic impairment, active liver disease, unexplained persistent elevations in serum transaminases (exceeding 3 times the upper limit of normal), or biliary obstruction:
Do not administer LIVAZEBE to these patients. Plasma pitavastatin concentrations may increase, leading to the increased incidence of adverse reactions. In addition, liver disorders may progress. (See section 5.2)

Patients with moderate hepatic impairment:
It is recommended not to administer LIVAZEBE to these patients. Plasma ezetimibe concentrations may increase. (See sections 4.2, 4.8 and 5.2)

Patients with other liver disorders or its history:
Since pitavastatin is largely distributed and activated in the liver, it may worsen liver disorders. The concentration of ezetimibe in plasma increases according to the severity of hepatic impairment. (See sections 4.2, 4.8 and 5.2)

Paediatric Use
No clinical studies have been conducted to evaluate efficacy and safety in paediatric patients.

Geriatric Use

If adverse reactions occur, measures such as dose reduction should be taken. Physiological function is generally decreased. Rhabdomyolysis is reported to be likely to occur. (See section 5.2)

Other Precautions

Information Based on Clinical Use

In an overseas multicenter, double-blind, placebo-controlled, study in patients with combined hyperlipidemia (involving 625 subjects receiving treatment within 12 weeks and 576 subjects within 1 year), the incidence of elevated serum transaminase levels (consecutive elevations ≥3 times the upper normal limits) (adjusted for duration of exposure) is 4.5% in the fenofibrate monotherapy group and 2.7% in the co-administration group receiving ezetimibe/fenofibrate. Similarly, the incidence of cholecystectomy is 0.6% in the fenofibrate monotherapy group and 1.7% in the co-administration group receiving ezetimibe/fenofibrate. Increased CK levels (≥10 times the upper normal limits) are not seen in either group in this study. In addition, one of the common adverse events associated with the co-administration of ezetimibe and fenofibrate is abdominal pain. This study is not designed to compare infrequent adverse events between groups.

4.5 Interaction with other medicinal products and other forms of interaction

Pitavastatin is hardly metabolized by hepatic cytochrome P450 (CYP) (metabolized slightly by CYP2C9).

Contraindicated Combinations

Drug name	Clinical symptoms/measures	Mechanism/risk factors
Cyclosporine (See section 4.3)	Serious adverse events, such as rhabdomyolysis, is likely to occur, accompanied by rapid renal function decline. In addition, the incidence of adverse reactions may increase.	Co-administration with pitavastatin increases the plasma pitavastatin concentration (by 6.6 times for Cmax and by 4.6 times for AUC). Additionally, co-administration with ezetimibe has been reported to have increased the blood concentrations of ezetimibe and cyclosporine.

Precautions for Combinations

Drug name	Clinical symptoms/measures	Mechanism/risk factors
Fibrates Bezafibrate, etc. (See sections 4.2, 4.4 and 4.8)	Concurrent use of fibrates may cause severe myositis and myoglobinuria. The risk of rhabdomyolysis may be increased, accompanied by rapid renal function decline. If subjective symptoms (myalgia, feelings of weakness), or renal function decline (e.g., increases in CK levels, urinary/blood myoglobin levels, or serum creatinine levels) are observed, treatment should be discontinued immediately	Rhabdomyolysis has been reported with fibrates, pitavastatin, and ezetimibe. Risk factor: Patients with abnormal laboratory test values related to renal function
Nicotinic acid (See section 4.8)		Risk factor: Renal disorders
Anion exchange resins Colestimide Cholestyramine, etc.	Blood pitavastatin concentration may decrease. Additionally, co-administration with ezetimibe has been reported to have decreased the blood ezetimibe concentration. LIVAZEBE should be administered 2 hours before or at least 4 hours after the administration of anion exchange resins.	Co-administration may decrease the absorption of pitavastatin. In addition, ezetimibe may bind to anion exchange resins, resulting in a delayed or reduced absorption.
Erythromycin (See sections 4.2 and 4.8)	The risk of rhabdomyolysis may be increased, accompanied by rapid renal function decline. If subjective symptoms (myalgia, feelings of weakness), or renal function decline (e.g., increases in CK levels, urinary/blood myoglobin levels, or serum creatinine levels) are observed, treatment should be discontinued immediately.	Erythromycin and rifampicin are considered to inhibit the uptake of pitavastatin in the liver.
Rifampicin	Co-administration with pitavastatin has been reported to have increased pitavastatin concentration by 2.0 times for Cmax and 1.3 times for AUC.	
Coumarin anticoagulants Warfarin, etc.	Co-administration with ezetimibe has been reported to have increased the prothrombin time International Normalized Ratio (INR). If co-administered, INR	Mechanism unknown

	test should be performed as necessary.	

Pitavastatin

Cyclosporine:

When multiple-dose of pitavastatin calcium 2 mg were orally administered once daily for 6 days to 6 healthy male adults, and single dose of cyclosporine 2 mg/kg was administered 1 hour prior to the dosing on Day 6, the concentration of pitavastatin in plasma increased by 6.6 times for Cmax and by 4.6 times for AUC. (See section 4.3)

Erythromycin:

When multiple-dose of erythromycin 500 mg were orally administered for 6 days to 18 healthy adults, and pitavastatin 4 mg was co-administered in the morning of Day 4, the concentration of pitavastatin in plasma increased by 3.6 times for Cmax and 2.8 times for AUC, as compared to pitavastatin monotherapy.

Rifampicin:

When multiple-dose of rifampicin 600 mg were orally administered for 15 days to 18 healthy adults, and pitavastatin 4 mg was co-administered on Days 11 to 15, the concentration of pitavastatin in plasma increased by 2.0 times for Cmax and 1.3 times for AUC, as compared to pitavastatin monotherapy.

Fibrates:

When multiple-dose of pitavastatin calcium 4 mg were orally administered for 6 days to 24 healthy adults, and fenofibrate or gemfibrozil were co-administered for 7 days from Day 8, the concentration (AUC) of pitavastatin in plasma increased by 1.2 times by fenofibrate and by 1.4 times by gemfibrozil.

In vitro studies:

In an inhibitory study of CYP molecular species on model substrates, pitavastatin had no effects on CYP2C9-mediated tolbutamide or CYP3A4 mediated testosterone. Additionally, the organic anion transporter OATP1B1 (OATP-C/OATP2) is involved in the uptake of pitavastatin in the liver, and the uptake was inhibited by cyclosporine, erythromycin, and rifampicin.

Ezetimibe

Effects on cytochrome P450 enzyme system:

When ezetimibe 20 mg* and probe drugs for indexing cytochrome P450 enzymes were co-administered to 12 healthy adults, activities of CYP1A2, CYP2C8/9, CYP2D6 and CYP3A4 or N-acetyltransferase activity were not affected.

*: The approved dosage of LIVAZEBE is 1 tablet (2 mg/10 mg or 4 mg/10 mg of pitavastatin calcium/ezetimibe) once daily.

Effects by cholestyramine:

When cholestyramine 4 g (twice daily) and ezetimibe 10 mg (once daily) were co-administered for 14 days to 8 adults (LDL-cholesterol level ≥130 mg/dL), the concentration (AUC) of total ezetimibe (unconjugated form and glucuronide conjugate) in plasma decreased. When ezetimibe monotherapy was compared to co-administration with cholestyramine, the relative bioavailability was 45%.

Interactions with fenofibrate:

When fenofibrate 200 mg (once daily) and ezetimibe 10 mg (once daily) were co-administered for 14 days to 8 adults (LDL-cholesterol level ≥130 mg/dL), the concentration of total ezetimibe (unconjugated form and glucuronide conjugate) in plasma increased by approximately 64% for Cmax and 48% for AUC, indicating no clinical significance. Ezetimibe did not affect the pharmacokinetics of fenofibrate.

Interactions with cyclosporine preparations:

When single dose of ezetimibe 10 mg was administered to 8 renal transplant recipients with creatinine clearance ≥50 mL/min who were receiving a stable dose (75 to 150 mg twice daily) of cyclosporine preparations, the concentration (AUC) of total ezetimibe (unconjugated form and glucuronide conjugate) in plasma was approximately 3.4 times higher than that of healthy adults. In another study, when single dose of ezetimibe 10 mg was orally administered to 1 patient who underwent renal transplant for severe renal impairment and took treatments with cyclosporine preparations, the concentration (AUC) of total ezetimibe in plasma increased by approximately 12 times, as compared

to that in healthy adults. When multiple-dose of ezetimibe 20 mg* were administered once daily for 8 days to 12 healthy adults, and single dose of cyclosporine preparation 100 mg was orally administered on Day 7, the blood cyclosporine concentration increased by 10% for Cmax and 15% for AUC, as compared to cyclosporine monotherapy. (See section 4.3)
*: The approved dosage of LIVAZEBE is 1 tablet (2 mg/10 mg or 4 mg/10 mg of pitavastatin calcium/ezetimibe) once daily.

Other pharmacokinetic interactions:
When ezetimibe 10 mg was co-administered with warfarin, digoxin or oral contraceptives (ethinyl estradiol or levonorgestrel) in a drug interaction study, there were no effects on the pharmacokinetics of these drugs. When cimetidine and ezetimibe 10 mg were co-administered, the bioavailability of ezetimibe was not affected. When an antacid (containing aluminum hydroxide and magnesium hydroxide) was co-administered with ezetimibe 10 mg, the concentration (AUC) of total ezetimibe (unconjugated form and glucuronide conjugate) in plasma was not affected; however, Cmax decreased from 55.9 ng/mL to 37.1 ng/mL.

4.6 Pregnancy, lactation and fertility

Pregnancy
Do not administer LIVAZEBE tablets to women who are or may be pregnant. In a study of pitavastatin during perinatal and lactation periods in animals (rats) (≥1 mg/kg), deaths of dams are observed before and after delivery. In addition, deaths of dams are observed in a study of administration during organogenesis in rabbits (≥0.3 mg/kg). Skeletal malformations have been reported in rats receiving large doses of other HMG-CoA reductase inhibitors. In humans, congenital malformations of the fetus are reported in the case of the administration of an HMG-CoA reductase inhibitor in women during the first 3 months of pregnancy.

Breast-feeding
Do not administer LIVAZEBE to these patients. In animal studies (rats), pitavastatin has been reported to be excreted in milk. It is not known whether ezetimibe is excreted in human milk. However, ezetimibe has been shown to be excreted in infants of rats born to mothers receiving the drug during the period from pregnancy to lactation.

Fertility
No current data

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability driving and using machines have been performed.
However, it should be taken into account that there are reports of dizziness and/or somnolence during treatment with pitavastatin or ezetimibe which are active ingredients of LIVAZEBE.

4.8 Undesirable effects

Summary of the safety profile
Adverse reactions of LIVAZEBE may be caused by the effect of each drug of pitavastatin and ezetimibe. Use of LIVAZEBE should be considered appropriately.
The safety evaluation of LIVAZEBE in the two clinical studies of Phase 3 demonstrated no new risks associated with LIVAZEBE compared with monotherapy with pitavastatin or ezetimibe.

The following adverse reactions may occur. Patients should be closely monitored, and if an abnormality is detected, appropriate measures such as discontinuing administration should be taken.

Tabulated list of adverse reactions
Adverse reactions observed in clinical studies conducted by the time of approval in Japan are listed. The frequencies of adverse reactions are ranked according to the following convention: common (≥1/100 to 1<1/10), uncommon (≥1/1,000 to 1<1/100). If any of the following adverse reactions or similar is observed, the patients should be treated appropriately according to the symptoms.

	Common	Uncommon	Incidence unknown[2)]
Skin			Rash, pruritus, urticaria, erythema, erythema multiforme, angioedema, alopecia, pain of skin
Gastrointestinal			Thirst, dry mouth, stomatitis, glossitis, queasy/nausea, vomiting, reflux oesophagitis, gastritis, stomach discomfort, dyspepsia, abdominal pain, bloating, amylase increased, pancreatitis, cholelithiasis, cholecystitis, flatulence/flatus, constipation, diarrhoea, inappetence
Hepatic	ALT increased	γ-GTP increased	AST increased, LDH increased, bilirubin increased, cholinesterase increased, AL-P increased, hepatitis
Renal		Proteinuria	Pollakiuria, BUN increased, serum creatinine increased
Cardiovascular			Extrasystoles, palpitations, blood pressure increased, chest pain, hot flush
Muscular [1)]		CK increased	Myalgia, back pain, pain in extremities, feelings of weakness, muscle spasms, muscular weakness, myoglobin increased
Psychiatric and nervous system			Headache/dull headache, numbness, dizziness, stiffness, sleepiness, insomnia, sciatica, depression, paraesthesia
Hematologic		Leukocytosis	Anaemia, platelets decreased, granulocytopenia, leukopenia, eosinophilia, globulin increased, Coombs test result turning positive
Endocrine			Testosterone decreased, aldosterone decreased, aldosterone increased, ACTH increased, cortisol increased, TSH increased
Other			Malaise, fatigue, asthenia, arthralgia, oedema, vision blurred, flickering vision, sensation of block in ear, taste abnormality, herpes zoster, herpes simplex, conjunctivitis, cough, pain, antinuclear antibody result turning positive, urinary occult blood, chromaturia, uric acid level increased, serum potassium increased, serum phosphorus increased

[1)] These symptoms may be an early sign of rhabdomyolysis. Patients should be closely monitored, and treatment should be discontinued if necessary.
[2)] These adverse reactions which were not observed in the clinical studies of LIVAZEBE, but are reported in patients with administration of pitavastatin or ezetimibe.

Clinically Significant Adverse Reactions (Frequency not known)

Hypersensitivity:
Hypersensitivity symptoms, including anaphylaxis, angioneurotic oedema, and rash, have been reported with ezetimibe.

Rhabdomyolysis:
Rhabdomyolysis, characterized by myalgia, feelings of weakness, and increases in CK levels and blood/urinary myoglobin levels, may occur and lead to serious renal disorders, such as acute kidney injury. In case such symptoms are noted, treatment should be discontinued. (See sections 4.2 and 4.4)

Myopathy:
In case widespread myalgia, muscle tenderness, or marked increase in CK levels are noted, treatment should be discontinued.

Immune-mediated necrotizing myopathy (IMNM):
IMNM is characterized by proximal muscle weakness, elevated CK levels, muscle fiber necrosis without inflammation, positive anti-HMG CoA reductase antibody, etc. and may occur with the use of HMG-CoA reductase inhibitors. In addition, there have been reports of cases in which IMNM persisted despite treatment discontinuation. Caution should be exercised by close monitoring of patient's condition. Furthermore, improvement with immunosuppressants have been reported. (See sections 4.4)

Hepatic function disorder, jaundice:
Since hepatic function disorder and jaundice associated with marked increases in AST and ALT levels may develop, patients should be closely monitored by periodic liver function tests, etc. (See sections 4.2,

4.4 and 5.2)

Thrombocytopenia:
Patients should be closely monitored by blood tests, etc.

Interstitial pneumonia:
Even for cases of long-term administration, if pyrexia, cough, dyspnoea, chest X-ray abnormal, etc. are noted, treatment should be discontinued, and appropriate measures such as administration of corticosteroids should be taken.

Myasthenia gravis:
Myasthenia gravis (ocular or systemic) may occur or worsen. (See section 4.4)

Statin class effects:
There have been rare post-marketing reports of cognitive impairment (e.g. memory loss, forgetfulness, amnesia, memory impairment, confusion) associated with statin use. These cognitive issues have been reported for all statins. The reports are generally non-serious and reversible upon statin discontinuation, with variable times to symptom onset (1 day to years) and symptom resolution (median 3 weeks).

Increases in HbA1c and fasting blood glucose have been reported with statins. The risk of hyperglycemia, however, is outweighed by the reduction in vascular risk with statins.

Musculoskeletal disorders:
Frequency not known: Immune-mediated necrotizing myopathy

Nervous system disorders:
Frequency not known: Myasthenia gravis

Eye disorders:
Frequency not known: Ocular myasthenia

4.9 Overdose

There is no specific treatment in the event of overdose. The patient should be treated symptomatically and supportive measures instituted as required. Liver function and CK levels should be monitored. Haemodialysis is unlikely to be of benefit.

In an clinical study of pitavastatin in adults, administration of pitavastatin calcium exceeding 8 mg was discontinued due to rhabdomyolysis and other related adverse events. (See sections 4.2 and 4.8)

In clinical studies, administration of ezetimibe, 50 mg/day, to 15 healthy subjects for up to 14 days, 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Combination of various lipid modifying agents
ATC Code: C10BA13

Pitavastatin
Mechanism of Action
Pitavastatin competitively inhibits HMG-CoA reductase, a rate-limiting enzyme for cholesterol biosynthesis, thereby inhibiting cholesterol synthesis in the liver. As a result, the expression of LDL-receptors followed by the uptake of LDL from blood to the liver is accelerated and then the plasma total cholesterol decreases. In addition, sustained inhibition of cholesterol synthesis in the liver reduces VLDL secretion into the blood, thereby the plasma triglyceride decreases.

LDL receptor expression promoting effect:
Pitavastatin promoted the expression of LDL receptor mRNA in human hepatoma-derived cells (HepG2 cells) and increased the binding to LDL, uptake volume, and degradation of apo B (*in vitro*). Moreover,

it promoted expression of LDL receptors in a dose-dependent manner after oral administration (guinea pigs).

VLDL secretion reducing effect:
Oral pitavastatin administration significantly reduced VLDL-triglyceride secretion (guinea pigs).

Pharmacodynamic Effects
HMG-CoA reductase inhibitory effect:
In a study using rat liver microsomes, pitavastatin competitively inhibited HMG-CoA reductase, and the IC50 for inhibition was 6.8 nM (*in vitro*).

Cholesterol synthesis inhibitory effect:
In a study using HepG2 cells, pitavastatin inhibited cholesterol synthesis in a concentration-dependent manner, (*in vitro*). The inhibitory effect on cholesterol synthesis after oral administration was liver selective (rats).

Plasma lipid-lowering effect:
Oral pitavastatin administration significantly reduced plasma total cholesterol and plasma triglyceride (guinea pigs, dogs).

Inhibitory effects on lipid accumulation and intimal thickening:
Pitavastatin inhibited accumulation of cholesterol ester in the macrophages loaded with oxidized LDL (mouse monocyte-derived cell line), (*in vitro*). In addition, oral administration significantly inhibited intimal thickening in the carotid artery injury model (rabbits).

Ezetimibe
Mechanism of Action
Ezetimibe inhibits absorption of dietary and biliary cholesterol. Ezetimibe acts on the small intestine. In animal studies using hamsters, etc., ezetimibe selectively inhibited absorption of cholesterol in the small intestine, resulting in cholesterol content reduction in the liver and blood cholesterol reduction. Ezetimibe inhibits absorption of cholesterol and phytosterol through protein (Niemann-Pick C1 Like 1) expressed in the small-intestinal wall cells. Therefore, the mechanism of action of ezetimibe differs from other antihyperlipidemic drugs (HMG-CoA reductase inhibitors, anion-exchange resins, fibrates, and phytosterols). In an overseas clinical pharmacology study in 18 patients with hypercholesterolemia, ezetimibe inhibited cholesterol absorption in the small intestine by 54% compared to the placebo group after administration for 2 weeks.
Ezetimibe reduces cholesterol contents in the liver by inhibiting cholesterol absorption in the small intestine, but there is a compensatory increase in cholesterol biosynthesis in the liver. A study in dogs and an overseas study in patients with hypercholesterolemia demonstrated that co-administration with an HMG-CoA reductase inhibitor, which suppresses cholesterol biosynthesis, decreased blood cholesterol in a complementary manner. Furthermore, a study in rats, etc. showed that ezetimibe selectively inhibited cholesterol absorption but had no effects on the absorptions of fatty acids, bile acids, progesterone, ethinyl estradiol, or fat-soluble vitamins A and D.

Pharmacodynamic Effects
Blood cholesterol-lowering effect:
The cholesterol-lowering effect of ezetimibe was investigated in high fat-fed dogs and rhesus monkeys. Repeated dietary administration with ezetimibe inhibited the increase in total plasma cholesterol.

Inhibitory effect on atherosclerotic lesion progression:
Repeated dietary administration with ezetimibe inhibited atherosclerotic lesion progression in the aorta or carotid artery of the atherosclerotic model (mice).

Clinical efficacy and safety
Japanese phase III verification study:
The results of a double-blind, active-controlled drug study in which 1 tablet of LIVAZEBE film-coated tablets 2 mg/10 mg or tablets 4 mg/10 mg, or of pitavastatin calcium 2 mg or 4 mg was administered once daily after meal for 12 weeks to patients with hypercholesterolemia are shown below.
In regard to the percentage change in LDL-cholesterol (Friedewald formula) from baseline to Week 12

of the treatment period, superiority of the group receiving LIVAZEBE film-coated tablets 4 mg/10 mg to the pitavastatin calcium 4 mg group, superiority of the group receiving LIVAZEBE film-coated tablets 2 mg/10 mg to the pitavastatin calcium 2 mg group, and the percentage change in LIVAZEBE film-coated tablets 4 mg/10 mg group to be lower than that in LIVAZEBE film-coated tablets 2 mg/10 mg group were verified by MMRM (mixed model for repeated measurements).

Table: Percentage change in LDL-cholesterol (Friedewald formula) from baseline to Week 12 of the treatment period

		PS 2 mg	PS 4 mg	LIVAZEBE LD	LIVAZEBE HD
Baseline (mg/dL)		166.18 ± 19.11 (n = 72)	162.14 ± 21.94 (n = 72)	168.92 ± 19.88 (n = 72)	167.01 ± 19.51 (n = 72)
Final assessment at Week 12 (mg/dL)		100.24 ± 15.61	88.73 ± 16.92	81.48 ± 21.18	69.99 ± 14.16
Percentage change (%)		-39.481 (-41.752, -37.209)	-45.152 (-47.439, -42.866)	-51.423 (-53.700, -49.146)	-57.843 (-60.130, -55.556)
Difference between groups	vs. PS 2 mg	-	-	-11.942**[a] (-15.159, -8.726)	-
	vs. PS 4 mg	-	-	-	-12.690**[a] (-15.932, -9.449)
	vs. LIVAZEBE LD	-	-	-	-6.420 (-9.642, -3.197)

PS: Pitavastatin calcium
LIVAZEBE LD: LIVAZEBE film-coated tablets 2 mg/10 mg
LIVAZEBE HD: LIVAZEBE film-coated tablets 4 mg/10 mg
Mean ± SD was used for the values at baseline and last assessment at Week 12, and least squares mean or least squares mean difference (95% confidence interval) was used for percentage changes.
a: Model (MMRM): Analysis model includes treatment group, time point, the interaction term of treatment group by time point, and risk category based on the Japan Atherosclerosis Society (JAS) Guidelines for prevention of Atherosclerotic Cardiovascular Diseases 2017 as fixed effects and LDL-C baseline value as a covariate. Data from 72 subjects in each group on Weeks 4 and 8, and 72 subjects each in PS 2 mg group, PS 4 mg group, and LIVAZEBE LD group on Week 12 and 70 subjects in LIVAZEBE HD group on Week 12 are included in the analysis model.
**: $p \leq 0.01$

The incidences of adverse reactions were 5.6% (4/72 subjects) in the group receiving LIVAZEBE film-coated tablets 2 mg/10 mg and 6.9% (5/72 subjects) in the group receiving LIVAZEBE film-coated tablets 4 mg/10 mg. The major adverse reactions included ALT increased (1.4% [1/72 subjects] in the group receiving LIVAZEBE film-coated tablets 2 mg/10 mg and 5.6% [4/72 subjects] in the group receiving LIVAZEBE film-coated tablets 4 mg/10 mg).

Japanese phase III long-term administration study:
When 1 tablet of LIVAZEBE film-coated tablets 2 mg/10 mg or 4 mg/10 mg was administered once daily for 52 weeks to hypercholesterolemia patients with inadequate response to pitavastatin calcium 2 mg or 4 mg, the percentage changes in LDL-cholesterol (Friedewald formula) from baseline to the last assessment (using the last observation carried forward [LOCF] method) were -30.28% ± 14.30% (mean ± SD [the same hereinafter], n = 109) in all subjects receiving LIVAZEBE, -29.50% ± 11.71% (n = 62) in the group receiving LIVAZEBE film-coated tablets 2 mg/10 mg, and -31.32% ± 17.20% (n = 47) in the group receiving LIVAZEBE film-coated tablets 4 mg/10 mg. Additionally, the percentage changes from Week 4 to Week 52 of the treatment period were -26.68% ± 15.52% to -30.38% ± 14.48% in all subjects receiving LIVAZEBE, -25.55% ± 14.45% to -30.62% ± 11.13% in the group receiving LIVAZEBE film-coated tablets 2 mg/10 mg, and -26.93% ± 15.16% to -31.33% ± 17.39% in the group receiving LIVAZEBE film-coated tablets 4 mg/10 mg, indicating a sustained effect of LIVAZEBE.
The incidence of adverse reactions was 0.9% (1/109 subjects) in all subjects receiving LIVAZEBE, which included blood creatine phosphokinase increased reported in the group receiving LIVAZEBE film-coated tablets 4 mg/10 mg (2.1%, 1/47 subjects).

5.2 Pharmacokinetic properties

Blood level

Pharmacokinetic parameters and changes in plasma concentrations after 1 tablet of LIVAZEBE film-coated tablets 4 mg/10 mg or 1 tablet each of pitavastatin calcium tablet 4 mg and ezetimibe tablet 10 mg (co-administration of monotherapies) as single dose to 55 healthy male adults in a fasted state in a crossover design are shown.

Table: Pharmacokinetic parameters after single dose oral administration in a fasted state (LIVAZEBE film-coated tablets 4 mg/10 mg or co-administration of monotherapies)

		AUC_{0-t} (ng・h/mL)	Cmax (ng/mL)	tmax (h)	t1/2 (h)
Pitavastatin (Unchanged form)	LIVAZEBE HD	140.745 ± 48.794 (55)	64.215 ± 29.056 (55)	1.000 [0.50, 2.00] (55)	12.227 ± 2.886 (38)
	Co-administration of monotherapies	143.664 ± 49.904 (54)	66.353 ± 31.811 (54)	1.000 [0.50, 2.00] (54)	14.061 ± 4.225 (45)
Ezetimibe (Unconjugated form)	LIVAZEBE HD	89.9823 ± 41.0849 (55)	5.7285 ± 3.4775 (55)	4.000 [0.50, 12.00] (55)	16.950 ± 6.663 (38)
	Co-administration of monotherapies	94.7826 ± 43.6560 (54)	6.6849 ± 4.6191 (54)	5.000 [0.50, 24.00] (54)	20.199 ± 12.952 (41)

AUC_{0-t}, Cmax, t1/2: mean ± SD (number of subjects)
tmax: median [minimum, maximum] (number of subjects)
LIVAZEBE HD: LIVAZEBE film-coated tablets 4 mg/10 mg

Figure: The plasma concentration of pitavastatin (in unchanged form) versus time after single dose oral administration in a fasted state (LIVAZEBE 4 mg/10 mg or co-administration of monotherapies)

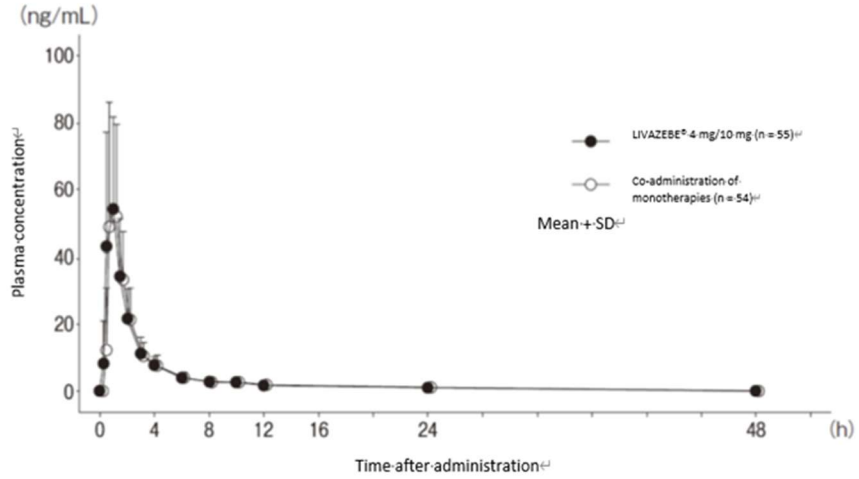
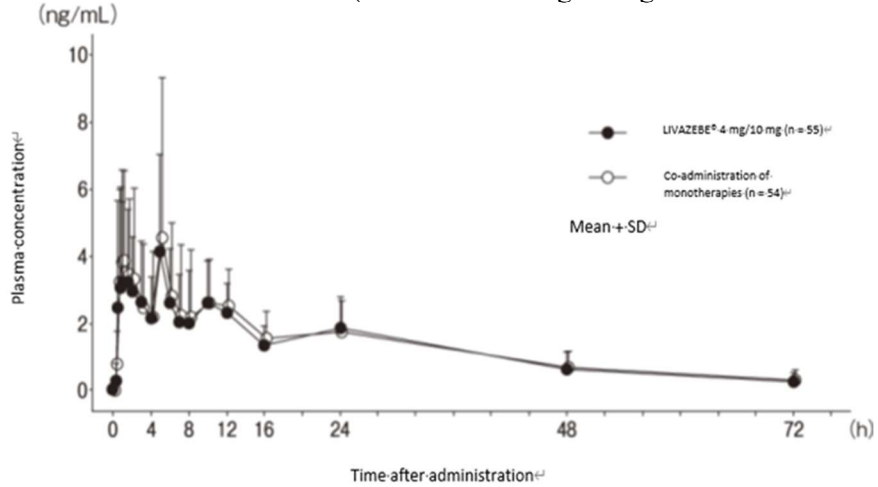


Figure: The plasma concentration of ezetimibe (unconjugated form) versus time after single dose oral administration in a fasted state (LIVAZEBE 4 mg/10 mg or co-administration of monotherapies)



Absorption (Dietary influences)

Pitavastatin

When 1 tablet of LIVAZEBE film-coated tablets 4 mg/10 mg was orally administered as single dose in 14 healthy male adults in a fasted state or after breakfast, the dietary influences on the pharmacokinetics of pitavastatin (in unchanged form) included a decrease in Cmax by 42.5% in a fed state compared to the fasted state, but no significant difference was observed in AUC.

Ezetimibe

When 1 tablet of LIVAZEBE film-coated tablets 4 mg/10 mg was orally administered as single dose in 14 healthy male adults in a fasted state or after breakfast, the dietary influences on the pharmacokinetics of ezetimibe (unconjugated form) included an increase in Cmax by 32.2% in a fed state compared to the fasted state, but no significant difference was observed in AUC.

Distribution (protein binding rate)

Pitavastatin

The each plasma protein binding rate of pitavastatin was high at 99.5% to 99.6% in human plasma and 4% human serum albumin, and 94.3% to 94.9% in 0.06% human α1-acid glycoprotein (*in vitro*).

Ezetimibe

When ezetimibe was added to human plasma, the each protein binding rate was 99.5% to 99.8% for ^{3}H-ezetimibe (unconjugated form) and 87.8% to 92.0% for ^{3}H-ezetimibe (glucuronide conjugate). Hepatic or renal impairment does not affect the plasma protein binding rate (*in vitro*).

Biotransformation

Pitavastatin

Metabolic pathway:

Pitavastatin was metabolized in the body by cyclization into the lactone form, β oxidation of the side chain, hydroxylation of the quinoline ring, and glucuronidation or taurine conjugation (rats, rabbits, and dogs).

Metabolites in blood and urine:

When pitavastatin was administered to healthy male adults, its unchanged form and the major metabolite (in lactone form) were observed in blood. As other metabolites, propanoic acid derivative and 8-hydroxylated form were slightly detected. In urine, the unchanged form, lactone form, dehydrolactone form, 8-hydroxylated form, and their conjugates were all slightly detected.

Metabolizing enzyme:

In a metabolism study using human liver microsomes, pitavastatin was slightly metabolized, producing the 8-hydroxylated form primarily by CYP2C9 (*in vitro*).

Ezetimibe

Ezetimibe is mainly metabolized in the small intestine with a first-pass effect to form a glucuronide conjugate, which is the major active metabolite of ezetimibe. When single dose of ^{14}C-ezetimibe capsule 20 mg* was orally administered to 8 healthy male adults, the percentages (AUC ratio) of ezetimibe (unconjugated form) and ezetimibe (glucuronide conjugate) were 11% and 82% of the total plasma radioactivity, respectively (93% in total).

*: The approved dosage of LIVAZEBE is 1 tablet (2 mg/10 mg or 4 mg/10 mg of pitavastatin calcium/ezetimibe) once daily.

Elimination

Pitavastatin

Excretory pathway:

The main excretory pathway of pitavastatin was through feces (rats, dogs).

Excretion rate:

When single dose of pitavastatin calcium 2 mg or 4 mg was orally administered to 6 healthy male adults at each dose, the urinary excretion rate was low at <0.6% in the unchanged form, <1.3% in the lactone form, and <2% in total. Additionally, when repeated doses of pitavastatin calcium 4 mg were orally

administered to 6 healthy male adults once daily for 7 days, the urinary excretion of the unchanged and lactone forms did not increase from baseline to the seventh dose and rapidly decreased after the administration was complete.

Ezetimibe
Urinary /fecal excretion:
When single dose of ^{14}C-ezetimibe capsule 20 mg* was orally administered to 8 healthy male adults, the radioactivity excretion rate by 240 hours after administration was 78% in the feces and 11% in the urine. When single doses of ezetimibe 10 mg, 20 mg*, and 40 mg* were orally administered to 6 healthy male adults at each dose, the urinary excretion rate as ezetimibe (unconjugated form) by 72 hours after administration was <0.05%, and the urinary excretion rate of total ezetimibe (unconjugated form and glucuronide conjugate) was 8.7% to 11%.
*: The approved dosage of LIVAZEBE is 1 tablet (2 mg/10 mg or 4mg/10 mg of pitavastatin calcium/ezetimibe) once daily.

Biliary excretion (enterohepatic circulation):
Ezetimibe (glucuronide conjugate) is excreted into the bile and then undergoes deconjugation by intestinal flora, some of which is reabsorbed as ezetimibe (unconjugated form) (enterohepatic circulation).

Special populations
Renal insufficiency:
Pitavastatin
When repeated doses of pitavastatin calcium 2 mg were orally administered once daily for 7 days to 6 patients with hypercholesterolemia and renal impairment (between 1.5 times and 3 times of the upper normal limit of serum creatinine standard value) and to 6 patients with hypercholesterolemia and normal renal functions, the plasma concentration on Day 7 was 1.7 times higher for Cmax and 1.9 times higher for AUC in patients with renal impairment than in patients with normal renal function.

Ezetimibe
When single dose of ezetimibe 10 mg was orally administered to 8 patients with severe chronic renal impairment (creatinine clearance 10 to 29 mL/min), the each concentration of ezetimibe (unconjugated form) and ezetimibe (glucuronide conjugate) in plasma showed increases by approximately 1.6 times and 1.5 times for AUC, respectively, compared to 9 healthy adults (creatinine clearance >80 mL/min).

Hepatic insufficiency:
Pitavastatin
When single dose of pitavastatin calcium 2 mg was orally administered to 12 patients with hepatic cirrhosis and 6 healthy adults, the plasma concentration was 1.3 times higher for Cmax and 1.6 times higher for AUC in the patients with Child-Pugh grade A than in healthy adults, and 2.7 times higher for Cmax and 3.9 times higher for AUC in the patients with Child-Pugh grade B than in healthy adult.
When repeated oral doses of pitavastatin calcium 2 mg were orally administered once daily for 7 days to 6 patients with hepatic impairment (hepatic steatosis) and 6 subjects with normal hepatic function, the pharmacokinetics were weakly affected. (See sections 4.2, 4.3, 4.4 and 4.8)

Ezetimibe
When single dose of ezetimibe 10 mg was orally administered to 4 each of patients with mild, moderate, and severe chronic hepatic impairment and 8 healthy adults, the plasma concentration of ezetimibe (unconjugated form) was 4.8 to 5.8 times higher for AUC in patients with moderate and severe hepatic impairment than in healthy adults, and the plasma concentration of ezetimibe (glucuronide conjugate) was 1.7 to 4 times higher for AUC depending on the severity of hepatic impairment. (See section 4.4)

Elderly:
Pitavastatin
When multiple-dose of pitavastatin calcium 2 mg were orally administered once daily for 5 days to 6 elderly men (aged 65 to 71 years) and 5 non-elderly men (aged 22 to 24 years), no differences were observed in the pharmacokinetic parameters between the groups.

Ezetimibe

When multiple-dose of ezetimibe 10 mg were orally administered once daily for 10 days to 12 elderly men (aged 65 to 75 years), the concentration of ezetimibe (glucuronide conjugate) in plasma showed an increase by approximately 2.4 times for AUC compared to that of 11 non-elderly men in the control group; however, no marked changes were observed in AUC of ezetimibe (unconjugated form).

5.3 Preclinical safety data

Pitavastatin
In an oral administration study of pitavastatin in dogs (≥3 mg/kg/day for 3 months, ≥1 mg/kg/day for 12 months), development of cataracts is observed. Cataracts are not observed in other animals (rats, monkeys).

Ezetimibe
In the administration of ezetimibe in dogs (≥0.03 mg/kg/day), the gallbladder bile cholesterol levels are increased by approximately 2 to 3 times after 1-month administration. However, gallstones or the hepatic/biliary system are not affected after 12-month administration in dogs at a dose of 300 mg/kg/day. Even 2-week administration in mice (5 mg/kg/day) does not affect gallbladder bile cholesterol levels.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

LIVAZEBE Film-coated Tablets 2 mg/10 mg:
Tablet core:
Lactose Hydrate, Crospovidone, Hypromellose, Magnesium Aluminometasilicate, Microcrystalline Cellulose, Povidone, Croscarmellose Sodium, Sodium Lauryl Sulfate, Magnesium Stearate

Coating layer:
Hypromellose, Titanium Oxide, Triethyl Citrate, Light Anhydrous Silicic Acid, Carnauba Wax

LIVAZEBE Film-coated Tablets 4 mg/10 mg:
Tablet core:
Lactose Hydrate, Crospovidone, Hypromellose, Magnesium Aluminometasilicate, Microcrystalline Cellulose, Povidone, Croscarmellose Sodium, Sodium Lauryl Sulfate, Magnesium Stearate

Coating layer:
Hypromellose, Titanium Oxide, Triethyl Citrate, Light Anhydrous Silicic Acid, Yellow Ferric Oxide, Carnauba Wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

24 months

6.4 Special precautions for storage

Store below 30 ºC in the original package.
Protect from moisture and light after opening the aluminium-laminated bag.

6.5 Nature and contents of container

Blister pack (film and aluminum), aluminum-laminated bag and paper box
Pack sizes: 30 film-coated tablets (3 blisters × 10 tablets)

6.6 Special precautions for disposal

Not applicable.

7. MANUFACTURER

Kowa Company, Ltd., Nagoya Factory
18-57, Hatooka 2-chome, Kita-ku, Nagoya, Aichi, JAPAN

8. PRODUCT REGISTRATION HOLDER

DKSH Malaysia Sdn Bhd

B-11-01, The Ascent, Paradigm
No. 1 Jalan SS 7/26A, Kelana Jaya
47301 Petaling Jaya, Selangor Darul Ehsan, Malaysia.

9. DATE OF REVISION OF THE TEXT

April 2026