1. NAME OF THE MEDICINAL PRODUCT

PARMODIA XR Film-coated Tablets 0.2 mg
PARMODIA XR Film-coated Tablets 0.4 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each PARMODIA XR (extended release) tablet contains 0.2 mg or 0.4 mg of pemafibrate.
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

PARMODIA XR Film-coated Tablets 0.2 mg: Light yellow, round film-coated tablet. The tablet is printed with “Kowa XR 0.2” on both sides.
PARMODIA XR Film-coated Tablets 0.4 mg: Light yellow, round film-coated tablet. The tablet is printed with “Kowa XR 0.4” on both sides.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARMODIA XR is indicated as adjunctive therapy to diet or other nonpharmacological treatment (e.g. exercise) to reduce TG and to increase HDL-C in patients with dyslipidemia characterised by high TG ≥150 mg/dL, particularly when there is evidence of associated risk such as hypertension and smoking.

4.2 Posology and method of administration

Patients should be on a lipid-lowering diet before the initiation of PARMODIA XR, and should continue dietary control during treatment. Serum lipid levels should be monitored periodically. If an adequate response has not been achieved, complementary or different therapeutic measures should be considered.

Posology
Adult
Normally in adults, 0.2 mg as pemafibrate is orally administered once daily. However, the dose may be increased up to 0.4 mg once daily depending on the degree of high triglyceride levels.

Elderly
No dose adjustment is necessary.
Since elderly patients often have reduced physiological function, PARMODIA XR should be carefully administered with close monitoring for signs of adverse reactions and clinical status of the patient.

Pediatric population
The safety of PARMODIA XR in low birth weight infants, newborns, infants, and children has not been established. No data are available.

Patients with renal impairment
PARMODIA XR should be used with caution in patients with renal impairment defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. When administered, PARMODIA XR should be administered at a dose of 0.2 mg once daily (see section 5.2).

Patients with hepatic impairment
PARMODIA XR should be used with caution in patients with hepatic disorder (Child- Pugh grade A cirrhosis, etc.) or a history of hepatic disorder.
PARMODIA XR is contraindicated in patients with severe hepatic disorder, Child-Pugh grade B or C cirrhosis, or biliary obstruction (see section 4.3 and section 5.2).

Method of administration
- PARMODIA XR should be taken orally once daily.
- PARMODIA XR can be taken without regard to meals.
- Patients should be informed that PARMODIA XR should not be chewed or crushed, and should be swallowed whole.

4.3 Contraindications

PARMODIA XR is contraindicated:
- in patients with known hypersensitivity to pemafibrate or to any of the excipients
- in patients with severe hepatic disorder, Child-Pugh grade B or C cirrhosis, or biliary obstruction
- in patients with cholelithiasis
- in pregnant or possibly pregnant women
- in patients receiving concomitant cyclosporine or rifampicin

4.4 Special warnings and precautions for use

Muscle effects
Muscle toxicity, including very rare cases of rhabdomyolysis (with and without acute renal failure), has been reported with other lipid-lowering agents.

Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscle cramps and weakness and/or marked increases in CK (>5 times the upper limit of normal range [ULN]). In such cases, treatment with PARMODIA XR should be stopped.
An increased risk of rhabdomyolysis has been reported with other fibrates when co-administered with an HMG-CoA reductase inhibitor (statin), especially in cases of pre-existing muscular disease. PARMODIA XR should be used with caution in patients receiving statins.

Liver effects
In common with other lipid-lowering agents, PARMODIA XR should be used with caution in patients with hepatic disorder or those with a history of hepatic disorder. Abnormal liver function tests may occur. The plasma concentration of PARMODIA XR may increase in patients with hepatic disorder (Child-Pugh grade A cirrhosis, etc.) (see section 5.2). Liver function should be monitored periodically during treatment.

Renal effects
In patients with renal impairment, renal function should be monitored periodically during treatment with PARMODIA XR. If eGFR is <30 mL/min/1.73 m^2, the appropriateness of administration of PARMODIA XR should be carefully evaluated. When administered, PARMODIA XR should be administered at a dose of 0.2 mg once daily.

Cholelithiasis
Since cholelithiasis has been reported, PARMODIA XR should be used with caution in patients with a history of cholelithiasis.

Pediatric population
The safety of PARMODIA XR in low birth weight infants, newborns, infants, and children has not been established. No data are available.

4.5 Interaction with other medicinal products and other forms of interaction

PARMODIA XR is metabolized mainly by cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A. PARMODIA XR is a substrate of organic anion transporting polypeptide (OATP) 1B1 and OATP1B3.

Contraindications for co-administration (Do not co-administer with the following drugs.)

Drug	Clinical symptoms/Treatment	Mechanism/Risk factors
Cyclosporine	Concomitant administration of cyclosporine or rifampicin with PARMODIA XR resulted in an increase in the plasma concentration of pemafibrate (see section 5.2).	Presumably due to inhibition of OATP1B1, OATP1B3, CYP2C8, CYP2C9, and CYP3A by cyclosporine.
Rifampicin		Presumably due to inhibition of OATP1B1 and OATP1B3 by rifampicin.

Precautions for co-administration (PARMODIA XR should be administered with caution when co-administered with the following drugs.)

Drug	Clinical symptoms/Treatment	Mechanism/Risk factors
HMG-CoA reductase inhibitors Pravastatin sodium Simvastatin Fluvastatin sodium, etc.	Muscle toxicity should be suspected in patients presenting diffuse myalgia, myositis, muscle cramps and weakness and/or marked increases in CK (>5 times ULN). In such cases, treatment with PARMODIA XR should be stopped.	Risk factor: patients with pre-existing muscular disease
Clopidogrel sulfate	Concomitant administration of clopidogrel sulfate or clarithromycin with PARMODIA XR resulted in an increase in the plasma concentration of pemafibrate (see section 5.2). Dose reduction of PARMODIA XR should be considered as necessary when used concomitantly with PARMODIA XR.	Presumably due to inhibition of CYP2C8 and OATP1B1 by clopidogrel sulfate.
Clarithromycin HIV protease inhibitors Ritonavir, etc.		Presumably due to inhibition of CYP3A, OATP1B1 and OATP1B3 by clarithromycin (or HIV protease inhibitors).
Fluconazole	Concomitant administration of fluconazole with PARMODIA XR resulted in an increase in the plasma concentration of pemafibrate (see section 5.2).	Presumably due to inhibition of CYP2C9 and CYP3A by fluconazole.
Anion exchange resins Cholestyramine Colestimide	PARMODIA XR should be administered with the longest interval possible after the intake of anion exchange resins because the plasma concentration of pemafibrate may be decreased.	PARMODIA XR may be absorbed onto anion exchange resins, and the absorption of pemafibrate may be reduced.
Strong CYP3A inducers Carbamazepine Phenobarbital Phenytoin Foods containing hypericum perforatum (St. John's wort), etc.	The plasma concentration of pemafibrate may be decreased, which may reduce the efficacy of PARMODIA XR.	The strong induction of CYP3A by these drugs may accelerate the metabolism of pemafibrate.

4.6 Fertility, pregnancy and lactation

Pregnancy
PARMODIA XR is contraindicated in pregnant or possibly pregnant women (see section 4.3). The safety of PARMODIA XR has not been established for use during pregnancy.

Breast-feeding
The use of PARMODIA XR should be avoided in breast-feeding women. If the administration of PARMODIA XR is unavoidable, breast-feeding should be discontinued. An animal study (rat) has shown that PARMODIA XR is excreted in rat milk.

Fertility
No current data.

4.7 Effects on ability to drive and use machines

No studies of the effects of PARMODIA XR on a patient's ability to drive, or to measure a reduced capacity to safely use machines have been performed.

4.8 Undesirable effects

Summary of adverse reactions
Clinical studies experience
Adverse reactions and frequencies observed in clinical studies conducted by the time of approval in Japan are listed below. If any of the following adverse reactions or similar is observed, the patients should be treated appropriately according to the symptoms.

	≥0.5%	≥0.1% to <0.5%	Frequency unknown
Liver	Alanine aminotransferase increased		Cholelithiasis, Hepatic function abnormal, Aspartate aminotransferase increased
Muscle	Blood creatine phosphokinase increased, Myalgia		Myoglobin blood increased
Skin	Rash		Itching
Others		Diabetes mellitus (including Diabetes mellitus aggravated)	Glycosylated haemoglobin increased, Low density lipoprotein increased, Blood uric acid increased

Post-marketing experience
The following adverse reactions have been reported, but the incidence of events cannot be calculated and are unknown because these events include the events reported as spontaneous reports.

	Incidence unknown
Liver	Hepatic function disorder, Jaundice

Description of adverse events from the PROMINENT study : Venous thromboembolism
In the PROMINENT study, a randomized placebo-controlled trial performed in 10,538 patients with type 2 diabetes, moderate hypertriglyceridemia and low levels of high-density lipoprotein cholesterol, higher incidences of pulmonary embolism and deep vein thrombosis were observed in the pemafibrate group compared to the placebo group [0.7% (37/5,264) in the pemafibrate group versus 0.3% (16/5,274) in the placebo group, 0.7% (36/5,264) in the pemafibrate group versus 0.2% (13/5,274) in the placebo group, respectively].
No events of pulmonary embolism or deep vein thrombosis were assessed as related to pemafibrate by the investigator.

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. Since pemafibrate is highly bound to plasma proteins, hemodialysis is unlikely to be of benefit.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid Modifying Agents, Plain
ATC Code: C10AB12

Mechanism of action
Pemafibrate activates PPARα by binding to this receptor and regulates the target gene expression, leading to decreased plasma triglyceride (TG) concentration, decreased triglyceride-rich lipoprotein, decreased apolipoprotein (Apo) C-3, and increased HDL-cholesterol.
(1) The activation of PPARα by pemafibrate was more potent than the activation of PPARγ or PPARδ, indicating the selectivity of pemafibrate to PPARα (*in vitro*).
(2) Pemafibrate inhibited TG synthesis in the liver (rats).
(3) Pemafibrate significantly reduced TG secretory rate (rats).
(4) Pemafibrate increased LPL activity (rats).
(5) Pemafibrate significantly reduced plasma concentrations of ApoC-3 and Angiopoietin-like Protein 3, which negatively regulate LPL activity; moreover, pemafibrate inhibited the gene expression (*Apoc3, Angptl3*) in the liver. In addition, pemafibrate upregulated the expression of genes (*Aco, Cpt1a*) involved in β-oxidation of free fatty acids that inhibits LPL activity (rats).
(6) Pemafibrate facilitated plasma TG clearance (rats).
(7) Pemafibrate increased plasma concentration of fibroblast growth factor 21 (FGF21), a protein that reduces TG concentration and increases HDL-cholesterol concentration (rats).

Pharmacodynamic effects
Pharmacological action
(1) Effect of reducing plasma lipid
When pemafibrate was orally administered to rats with high fructose-induced hypertriglyceridemia, plasma TG concentration was decreased in a dose-dependent manner.
(2) Effect of increasing HDL-cholesterol
When pemafibrate was orally administered to human ApoA-1 transgenic mice, plasma concentration of HDL-cholesterol and concentration of human ApoA-1 were increased.
(3) Anti-arteriosclerotic effect
When pemafibrate was orally administered to LDL-receptor deficient mice under high fat/high cholesterol diet, the area of lipid deposition area in the aortic sinus was decreased.

Clinical efficacy
Phase 3 Confirmatory Study
When PARMODIA XR 0.2 mg/day or 0.4 mg/day once daily and IR tablets (immediate release formulation of pemafibrate; PARMODIA Film-coated Tablets 0.1 mg) 0.2 mg/day twice daily was administered to dyslipidemia patients with high TG levels for 12 weeks, the percent change from baseline in fasting serum TG, as presented in the following table, showing the non-inferiority of the PARMODIA XR 0.2 mg/day group and 0.4 mg/day group to the IR tablets 0.2 mg/day group.

Table 1 Percent Change from Baseline in Fasting Serum TG

	PARMODIA XR 0.2 mg/day (once daily)	PARMODIA XR 0.4 mg/day (once daily)	IR tablets 0.2 mg/day (twice daily)
Baseline [a)]	338.6 ± 117.0 (117)	355.0 ± 157.5 (119)	354.2 ± 142.3 (117)
Week 4 [a)]	186.6 ± 97.4 (116)	177.1 ± 103.4 (119)	168.3 ± 70.4 (116)
Week 8 [a)]	180.2 ± 76.0 (116)	170.6 ± 75.9 (119)	179.2 ± 102.5 (117)
Week 12 [a)]	192.1 ± 90.6 (115)	166.5 ± 81.6 (118)	173.5 ± 80.7 (116)
Percent change (%) [b)]	-43.80 [-47.20, -40.39]	-48.00 [-51.37, -44.63]	-48.00 [-51.40, -44.60]
Difference from the IR tablets 0.2 mg/day group (%) [b)]	4.20 [-0.62, 9.02]	0.00 [-4.79, 4.79]	-

a) Mean ± SD (mg/dL) (number of subjects)
b) Least square mean [95% CI] non-inferiority margin: 10%
Repeated measures ANOVA with baseline value, sex, timing of study drug administration (before or after meals), presence or absence of concomitant use of statins , and study site as covariates, and Weeks 4, 8, and 12 in the treatment period as repeated time points

The change over time in LDL-cholesterol at time points was as presented in the following table.

Table 2 Change over Time in LDL-cholesterol (Direct Method) in Each Group

	PARMODIA XR 0.2 mg/day	PARMODIA XR 0.4 mg/day	IR tablets 0.2 mg/day
Baseline	139.0 ± 43.6 (117)	132.3 ± 35.5 (119)	137.3 ± 42.2 (117)
Week 4	139.4 ± 34.9 (116)	140.0 ± 36.2 (119)	141.1 ± 39.3 (116)
Week 8	139.4 ± 39.1 (116)	140.7 ± 37.8 (119)	140.8 ± 40.7 (117)
Week 12	142.3 ± 33.4 (115)	142.3 ± 34.4 (118)	140.9 ± 38.5 (116)

Mean ± SD (mg/dL) (number of subjects)

The incidence rates of adverse drug reactions to PARMODIA XR were 2.5% (3/118 subjects) and 5.9% (7/119 subjects) in the PARMODIA XR 0.2 mg/day and 0.4 mg/day groups, respectively. The most common adverse drug reactions were increased ALT (1.7% [2/118 subjects] in the 0.2 mg/day group) and increased blood ketone body (1.7% [2/119 subjects] in the 0.4 mg/day group).

Phase 3 Long-term Administration Study
When PARMODIA XR 0.2 mg/day (increased to 0.4 mg/day at Week 12 if ineffective) was administered to dyslipidemia patients with high TG levels once daily in the morning or evening for 52 weeks, the mean percent change [95% CI] in fasting serum TG from baseline (264.0 ± 109.2 mg/dL [mean ± SD], n=121) at and immediately before the final evaluation (at Week 52 or at discontinuation) was -44.82% [-49.70, -39.94] for the morning group (n=61) and -46.61% [-51.34, -41.88] for the evening group (n = 60). The difference of the least square mean [95% CI] in the morning group compared to the evening group was 3.03% [-3.55, 9.62].
The change over time in LDL-cholesterol at time points was as presented in the following table.

Table 3 Change over Time in LDL-cholesterol (Direct Method) in Each Group

	PARMODIA XR	
	Morning group	Evening group
Baseline	120.4 ± 30.7 (61)	130.1 ± 40.9 (60)
Week 4	122.2 ± 28.2 (61)	123.7 ± 41.0 (59)
Week 16	125.5 ± 24.3 (61)	121.4 ± 31.3 (56)
Week 28	123.4 ± 24.4 (61)	119.4 ± 31.9 (56)
Week 40	127.6 ± 30.6 (61)	122.0 ± 34.0 (56)
Week 52	121.2 ± 26.4 (59)	120.1 ± 35.9 (55)

Mean ± SD (mg/dL) (number of subjects)

The incidence rates of adverse drug reactions were 19.0% (23/121 subjects) in all subjects: 18.0% (11/61 subjects) and 20.0% (12/60 subjects) in the morning dose group and evening dose group, respectively. The most common adverse drug reactions were myalgia (5.0% [3/60 subjects] in the evening dose group), and increased blood creatine phosphokinase, muscle spasms, periarthritis, rash, and hypertension each in 1 patient in the morning dose and evening dose groups.

5.2 Pharmacokinetic properties

Plasma pemafibrate concentration
Repeated dose administration and Food effect

PARMODIA XR 0.4 mg/day once daily or IR tablets 0.2 mg/day twice daily was administered as repeated oral doses to dyslipidemia patients with high triglyceride (TG) levels before or after meals for 4 weeks (2-period crossover). The time course of plasma pemafibrate concentrations at Week 4 of administration of PARMODIA XR was as presented in the following figure, and the pharmacokinetic parameters were as presented in the following table. The geometric mean ratios [90% CI] of C_{max} and $AUC_{0-\tau}$ after postprandial administration to that after preprandial administration at Week 4 were 1.124 [0.840, 1.503] and 1.097 [0.879, 1.370], respectively.
The geometric mean ratio [90% CI] of $AUC_{0-\tau}$ after administration of PARMODIA XR 0.4 mg/day at Week 4 to that after administration of IR tablets 0.2 mg/day, for which the daily dose of pemafibrate was equally corrected, were 0.863 [0.797, 0.934] after preprandial administration and 0.870 [0.788, 0.960] after postprandial administration, respectively.

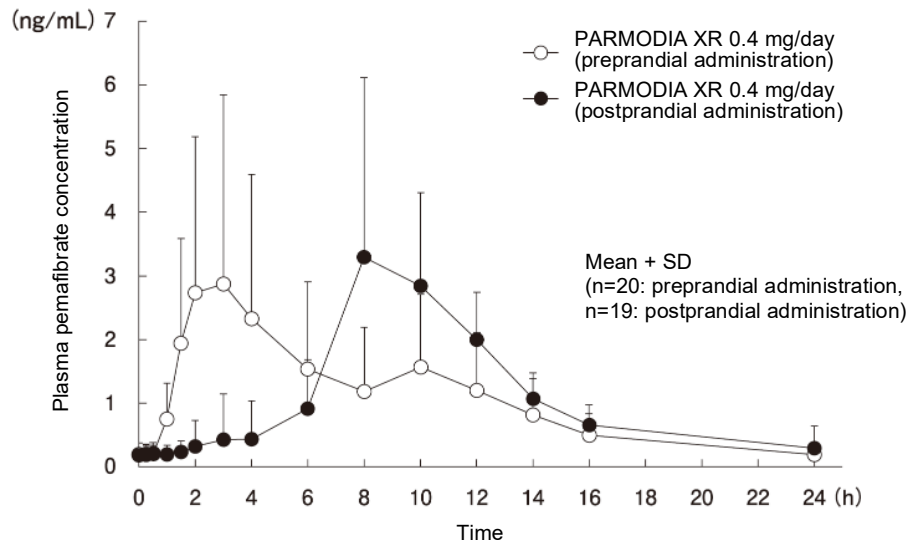

Figure 1 Time Course of Plasma Pemafibrate Concentrations at Week 4 of Repeated Oral Doses of PARMODIA XR 0.4 mg/day before or after meals in Dyslipidemia Patients with High TG Levels

Table 4 Pharmacokinetic Parameters at Week 4 of Repeated Oral Doses of PARMODIA XR 0.4 mg/day before or after meals in Dyslipidemia Patients with High TG Levels

	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
Preprandial administration	3.1283 [70.6] n = 20	22.7233 [61.8] n = 20	3.00 [1.5,14.0] n = 20	5.549 [43.6] n = 17
Postprandial administration	3.5149 [59.3] n = 19	24.9334 [37.7] n = 19	8.00 [3.0, 11.9] n = 19	4.185 [23.6] n = 17

C_{max}, $AUC_{0-\tau}$, $t_{1/2}$: Geometric mean [coefficient of variation (%)]
t_{max}: Median [min, max]

Absorption
The absolute bioavailability of IR tablets (pemafibrate 0.2 mg) was 61.5% (Data for non-Japanese subjects).

Plasma protein binding ratio
The human plasma protein binding ratio of pemafibrate was ≥99%.

Metabolism
(1) When a single dose of ^{14}C-pemafibrate was orally administered to healthy adult subjects, the main metabolites in plasma were an oxidized form at the benzyl position, and a mixture of glucuronide conjugate of dicarboxylated form and *N*-dealkylated form (Data for non-Japanese subjects).
(2) Pemafibrate is a substrate of CYP2C8, CYP2C9, CYP3A4, CYP3A7, UGT1A1, UGT1A3, and UGT1A8 (*in vitro*).

Excretion
(1) When a single dose of ^{14}C-pemafibrate was administered to healthy adult subjects, excretion of radioactivity in urine and feces up to 216 hours after administration was 14.53% and 73.29%, respectively (Data for non-Japanese subjects). Pemafibrate is excreted mainly in the feces.
(2) Pemafibrate is a substrate of P-gp, BCRP, OATP1A2, OATP1B1, OATP1B3, OCT2, and NTCP (*in vitro*).

Drug interactions
(1) Co-administration with cyclosporin, rifampicin, clopidogrel, clarithromycin, fluconazole, digoxin, or warfarin
When IR tablets was co-administered with each drug in healthy adult subjects (non-Japanese), the effect on the pharmacokinetic parameters was as presented in the following table.

Table 5 Effect of co-administration of IR tablets and each drug on pharmacokinetic parameters (data for non-Japanese subjects)

Co-administrated drug	Dose of Co-administrated drug	Dose of Pemafibrate	Analyte	Ratio of geometric means [90% CI] (Combination therapy/monotherapy)	
				C_{max}	AUC_{0-inf}
Cyclosporine	600 mg Single-dose	0.4 mg Single-dose	Pemafibrate	8.9644 [7.5151, 10.6931] n=14	13.9947 [12.6175,15.5223] n=12
Rifampicin	600 mg Single-dose	0.4 mg Single-dose	Pemafibrate	9.4336 [8.3626, 10.6419] n=20	10.9009 [9.9154, 11.9844] n=17
	600 mg/day Once daily 10 days Monotherapy	0.4 mg Monotherapy	Pemafibrate	0.3792[a)] [0.3378, 0.4257] n=20	0.2221[a)] [0.2065, 0.2389] n=16
Clopidogrel	300 mg Single dose Day 4	0.4 mg Single dose Day 4	Pemafibrate	1.4855 [1.3915, 1.5858] n=20	2.3728 [2.2473, 2.5052] n=20
	75 mg/day Once daily 5 days Days 5 to 9	0.4 mg Single-dose Day 7	Pemafibrate	1.3415 [1.2583, 1.4302] n=20	2.0876 [1.9811, 2.1998] n=20
Clarithromycin	1,000 mg/day Twice daily 8 days	0.4 mg Single-dose	Pemafibrate	2.4246 [2.1632, 2.7174] n=18	2.0975 [1.9158, 2.2964] n=17
Fluconazole	400 mg/day Once daily 11 days	0.4 mg Single-dose	Pemafibrate	1.4409 [1.2899, 1.6096] n=19	1.7891 [1.6638, 1.9239] n=17
Digoxin	0.5 mg/day Twice daily (Day 1), 0.25 mg/day Once daily 16 days	0.8 mg/day Twice daily 6 days Days 11 to 16	Digoxin	1.0325 [0.9511, 1.1210] n=19	0.9463[b)] [0.9090, 0.9850] n=19
Warfarin*	5 mg/day Once daily (Day 1 and Day 2), Maintenance dose[c)] Once daily 21 days	0.4 mg/day Twice daily 8 days Days 14 to 21	R-warfarin	1.004 [0.972, 1.037] n=19	1.029[b)] [1.004, 1.055] n=19
			S-warfarin	0.929 [0.889, 0.970] n=19	0.951[b)] [0.926, 0.976] n=19

a) Geometric mean ratios [90% CI] of IR tablets monotherapy after repeated administration of rifampicin to IR tablets monotherapy before repeated administration of rifampicin for C_{max} and AUC_{0-inf}.
b) $AUC_{0-\tau}$
c) On Day 3 through Day 9, the dosage was adjusted to achieve an international normalized ratio of prothrombin time (PT-INR) of 1.2 to 2.2. On Day 10 and thereafter, the maintenance dose that achieved PT-INR of 1.2 to 2.2 was administered.
* Least square mean ratios [90% CI] of repeated co-administration of warfarin with IR tablets to repeated warfarin monotherapy for PT-INR and PT were 1.0196 [0.9878, 1.0514] (n=19) and 1.0191 [0.9869, 1.0512] (n=19).
Note: The approved dosage and administration of IR tablets is an oral dose of 0.1 mg twice daily, and the maximum dosage is an oral dose of 0.2 mg twice daily.

(2) Co-administration with HMG-CoA reductase inhibitors
When IR tablets and HMG-CoA reductase inhibitors were co-administered to healthy adult males (Japanese and non-Japanese), the effect of co-administration on the pharmacokinetic parameters was as presented in the following table.

Table 6 Effect of co-administration of IR tablets and each drug on pharmacokinetic parameters (data for Japanese and non-Japanese subjects)

Co-administrated drug	Dose of co-administrated drug	Dose of Pemafibrate	Analyte	Ratio of geometric means [90% CI] (Combination therapy/monotherapy)	
				C_{max}	$AUC_{0-\tau}$
Atorvastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	Pemafibrate (n=18)	1.166 [1.069, 1.272]	1.098 [1.016, 1.187]
			Atorvastatin (n=18)	1.032 [0.960, 1.109]	0.934 [0.851, 1.024]
			o-hydroxyatorvastatin (n=18)	0.875 [0.826, 0.927]	0.784 [0.736, 0.836]
Simvastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	Pemafibrate (n=18)	1.230 [1.090, 1.388]	1.125 [0.997, 1.270]
			Simvastatin (n=19)	0.858 [0.660, 1.114]	0.846 [0.722, 0.992]
			Open acid form of simvastatin (n=19)	0.626 [0.541, 0.725]	0.405 [0.345, 0.475]
Pitavastatin	4 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	Pemafibrate (n=18)	1.061 [0.970, 1.160]	1.122 [1.041, 1.209]
			Pitavastatin (n=18)	1.011 [0.973, 1.050]	1.036 [1.007, 1.066]
Pravastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	Pemafibrate (n=18)	1.058 [0.964, 1.162]	1.057 [1.013, 1.102]
			Pravastatin (n=18)	1.107 [0.908, 1.351]	1.065 [0.922, 1.231]
Fluvastatin	60 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	Pemafibrate (n=18)	1.181 [1.080, 1.290]	1.207 [1.144, 1.274]
			Fluvastatin (n=18)	0.989 [0.790, 1.239]	1.151 [1.057, 1.253]
Rosuvastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	Pemafibrate (non-Japanese subjects, n=24)	1.106 [1.048, 1.167]	1.110 [1.046, 1.177]
			Rosuvastatin (non-Japanese subjects, n=24)	1.092 [1.016, 1.174]	1.025 [0.964, 1.091]

Special populations

Pharmacokinetics in Patients with Fatty Liver and Patients with Hepatic Cirrhosis

When a single dose of IR tablets (pemafibrate 0.2 mg) was orally administered to Japanese patients with fatty liver and patients with hepatic cirrhosis, the ratios of pharmacokinetic parameters (patients with fatty liver or with hepatic cirrhosis to subjects with normal hepatic function) were as presented in the following table. Compared with subjects with normal hepatic function, the exposure was higher in patients with fatty liver and patients with hepatic cirrhosis.

Table 7 Ratios [90% CI] of geometric means after single oral administration of IR tablets (pemafibrate 0.2 mg) of patients with fatty liver or hepatic cirrhosis to subjects with normal hepatic function (n=8) for C_{max} and AUC_{0-t}.

	C_{max}	AUC_{0-t}
Fatty liver group (n=10)	1.198 [0.819, 1.750]	1.194 [0.836, 1.707]
Mild hepatic cirrhosis Child-Pugh grade A group (n=8)	2.329 [1.561, 3.475]	2.076 [1.425, 3.026]
Moderate hepatic cirrhosis Child-Pugh grade B group (n=6)	3.882 [2.520, 5.980]	4.191 [2.790, 6.294]

Pharmacokinetics in Patients with Renal Impairment

When a single dose of IR tablets (pemafibrate 0.2 mg) was orally administered to Japanese patients with renal impairment (mild, moderate, severe, or end-stage renal failure), the ratios of pharmacokinetic parameters (patients with renal impairment to subjects with normal renal function) were as presented in the following table. Compared with subjects with normal renal function, the exposure was higher in patients with renal impairment; however, the exposure did not increase as the renal function reduced.

Table 8 Ratios [90% CI] of geometric means after single oral administration of IR tablets (pemafibrate 0.2 mg) of patients with renal impairment to subjects with normal renal function (n=8) for C_{max} and AUC_{0-t}

	C_{max}	AUC_{0-t}
Mild renal impairment group [50 ≤ Ccr < 80 mL/min] (n=8)	1.644 [1.155, 2.342]	1.629 [1.161, 2.287]
Moderate renal impairment group [30 ≤ Ccr < 50 mL/min] (n=8)	1.093 [0.767, 1.556]	1.154 [0.822, 1.620]
Severe renal impairment group [Ccr < 30 mL/min] (n=7)	1.545 [1.072, 2.228]	1.296 [0.913, 1.841]
End-stage renal failure group [Undergoing hemodialysis] (n=7)	1.258 [0.872, 1.813]	1.607 [1.131, 2.282]

IR tablets was orally administered at a dose of 0.1 mg twice daily in morning and evening for 12 weeks to patients with dyslipidemia accompanied by high TG value and renal impairment (severe renal impairment with eGFR <30 mL/min/1.73 m^2 or on dialysis and mild-to-moderate renal impairment with eGFR ≥30 and <60 mL/min/1.73 m^2). The ratio and 90% CI of geometric means of $AUC_{0-\tau}$ in patients with severe renal impairment compared to those with mild-to-moderate renal impairment (control group) at Week 12 were as presented in the following table. The level of exposure did not increase in patients with severe renal impairment.

Table 9 Ratio [90% CI] of geometric means of $AUC_{0-\tau}$ after repeated oral administration of IR tablets (pemafibrate 0.2 mg) in patients with severe renal impairment (n=8) compared to those with mild-to-moderate renal impairment (n=7)

	Ratio of geometric means of $AUC_{0-\tau}$ [90% CI]
Severe renal impairment group [eGFR <30 mL/min/1.73 m^2 or on dialysis]	0.9177 [0.6198,1.3587]

Pharmacokinetic parameters were presented in the following table.

Table 10 Pharmacokinetic parameters after repeated oral administration of IR tablets (pemafibrate 0.2 mg) in patients with dyslipidemia accompanied by high TG value and renal impairment

	C_{max} (ng/mL)	$AUC_{0-\tau}$ (ng·h/mL)
Mild-to-moderate renal impairment group [30≤ eGFR <60 mL/min/1.73 m^2] (n=7)	2.4483±0.9535	8.6994±4.0397
Severe renal impairment group [eGFR <30 mL/min/1.73 m^2] (n=4)	2.0508±0.6588	7.4130±3.9548
Severe renal impairment group [dialysis] (n=4)	1.8798±0.5728	8.4470±3.3054

Mean ± SD

5.3 Preclinical safety data

In a carcinogenicity study in mice (≥0.075 mg/kg/day), an increase in the incidence of hepatocellular carcinomas and hepatocellular adenomas was observed. In a carcinogenicity study in rats (≥0.3 mg/kg/day in male rats and ≥1 mg/kg/day in female rats), an increase in the incidence of hepatocellular carcinomas, hepatocellular adenomas, pancreatic acinar cell carcinomas, pancreatic acinar cell adenomas, testicular Leydig cell adenomas, and thyroidal follicular epithelial cell adenomas was observed. All of these findings are considered to be specific to rodents.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Film-coated tablets

Microcrystalline cellulose spheres, Hydrated silicon dioxide, Hypromellose, Methacrylic acid copolymer L, Ethylcellulose, D-Mannitol, Microcrystalline cellulose, Crospovidone, Hydroxypropylcellulose, Magnesium stearate, Titanium oxide, Triethyl citrate, Light anhydrous silicic acid, Yellow ferric oxide, Carnauba wax

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

PVC/PVDC/PE/Aluminum blisters in an aluminum-laminated bag, in a carton of 30 tablets (3 blisters x 10 tablets).

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Kowa Company, Ltd.
6-29, Nishiki 3-chome, Naka-ku, Nagoya, Aichi, JAPAN

8. MANUFACTURER'S NAME AND ADDRESS

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

9. DATE OF REVISION OF THE TEXT

5 June 2026