SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PARMODIA tablets 0.1 mg.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 0.1 mg of pemafibrate.
For a full list of excipients see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
White round film-coated tablets printed 'Kowa 217' on one face and a score line on the reverse.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

PARMODIA is indicated as adjunctive therapy to diet to reduce TG in patients with dyslipidemia, including familial hyperlipidemia.

4.2 Posology and method of administration

Patients should be on a lipid-lowering diet before the initiation of PARMODIA, 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

The usual adult dose is 0.1 mg twice daily. The dose may be individualized according to the patient's age and symptoms. The maximum dose is 0.2 mg twice daily.

Elderly

Since elderly patients often have reduced physiological function, PARMODIA should be carefully administered with close monitoring for signs of adverse reactions and clinical status of the patient.

Pediatric population

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

Patients with renal impairment

PARMODIA should be used with caution in patients with renal impairment defined as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2. A lower starting dose or prolonged dosing intervals should be considered. The maximum dose is 0.2 mg daily (see section 5.2).

Patients with hepatic impairment

PARMODIA should be used with caution in patients with hepatic disorder (Child-Pugh grade A cirrhosis, etc.) or a history of hepatic disorder. Dose reduction should be considered as necessary (see section 5.2).
PARMODIA 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 should be taken orally twice daily in the morning and evening. PARMODIA can be taken without regard to meals.
The tablet can be divided into equal halves.

4.3 Contraindications

PARMODIA 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 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 should be used with caution in patients receiving statins.

Liver effects

In common with other lipid-lowering agents, PARMODIA 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 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. If eGFR is <30 mL/min/1.73 m^2, dose reduction or prolonged dosing intervals should be considered. The maximum dose is 0.2 mg daily.

Cholelithiasis

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

LDL-cholesterol

Since increases in LDL-cholesterol levels may occur, LDL-cholesterol levels should be monitored periodically during treatment.

Pediatric population

The safety of PARMODIA 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 is metabolized mainly by cytochrome P450 (CYP) 2C8, CYP2C9, and CYP3A. PARMODIA 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 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 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 should be stopped.	Risk factor: patients with pre-existing muscular disease
Clopidogrel sulfate	Concomitant administration of clopidogrel sulfate or clarithromycin with PARMODIA resulted in an increase in the plasma concentration of pemafibrate (see section 5.2). Dose reduction of PARMODIA should be considered as necessary when used concomitantly with PARMODIA.	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 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 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 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.	The strong induction of CYP3A by these drugs may accelerate the metabolism of pemafibrate.

4.6 Fertility, pregnancy and lactation

Pregnancy

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

Breast-feeding
The use of PARMODIA should be avoided in breast-feeding women. If the administration of PARMODIA is unavoidable, breast-feeding should be discontinued. An animal study (rat) has shown that PARMODIA 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 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 the safety profile
In clinical studies conducted by the time of approval in Japan, adverse reactions were observed in 206 of 1,418 patients (14.5%). The most commonly reported adverse reactions included cholelithiasis observed in 20 patients (1.4%), diabetes mellitus in 20 patients (1.4%), and blood creatine phosphokinase increased in 12 patients (0.8%).

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.

	≥1%	≥0.1% to <1%
Liver	Cholelithiasis	Hepatic function abnormal, Aspartate aminotransferase increased, Alanine aminotransferase increased
Muscle		Blood creatine phosphokinase increased, Myoglobin blood increased, Myalgia
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].
The incidences of pulmonary embolism and deep vein thrombosis were higher in the pemafibrate group, but no events 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
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 2/3 Comparative Confirmatory Study with Fenofibrate
In patients with dyslipidemia who had high TG and low HDL-cholesterol levels, placebo, 0.2 mg/day or 0.4 mg/day of PARMODIA (twice daily after breakfast and dinner), or micronized fenofibrate capsules of 100 mg/day or 200 mg/day (once daily after breakfast) was administered for 12 weeks. The percent change in fasting serum TG was as presented in the following table, which shows the superiority of PARMODIA groups over the placebo group, and non-inferiority of PARMODIA 0.2 mg/day and 0.4 mg/day groups over the micronized fenofibrate capsule 200 mg/day group.

Table 1. Percent change in fasting serum TG in placebo group and PARMODIA groups

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]	
	Percent change from baseline[c] (%)	Difference from placebo in percent change[d] (%)
Placebo 346.1±130.9, n=43	-2.775 [-11.783, 6.233]	-
PARMODIA 0.2 mg/day 367.2±153.6, n=128	-46.766 [-49.985, -43.547]	-43.991** [-55.455, -32.528]
PARMODIA 0.4 mg/day 362.6±158.5, n=84	-51.902 [-55.841, -47.963]	-49.127** [-60.922, -37.333]

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Repeated measures analysis of covariance for all treatment groups, with Weeks 8, 10, and 12 as repeated time points and baseline value as a covariate (The results of the PARMODIA 0.1 mg/day group are omitted.)
c) Least square mean [95% CI]
d) Least square mean [Adjusted 95% CI] **: p ≤0.01 (Dunnett's test)

Table 2. Percent change in fasting serum TG in PARMODIA groups and micronized fenofibrate capsule groups

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]	
	Percent change from baseline (%)	Difference from micronized fenofibrate capsule 200 mg/day group in percent change (%)
PARMODIA 0.2 mg/day 367.2±153.6, n=128	-46.690 [-49.904, -43.477]	4.844 [0.388, 9.299]
PARMODIA 0.4 mg/day 362.6±158.5, n=84	-51.836 [-55.768, -47.903]	-0.302 [-5.300, 4.696]
Micronized fenofibrate capsule 100 mg/day[c] 362.0±135.1, n=85	-38.261 [-42.230, -34.291]	-
Micronized fenofibrate capsule 200 mg/day[c] 347.3±123.8, n=140	-51.534 [-54.616, -48.452]	-

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Repeated measures analysis of covariance for all treatment groups, with Weeks 8, 10, and 12 as repeated time points and baseline value as a covariate (The results of the PARMODIA 0.1 mg/day group are omitted.)
Least square mean [95% CI] Non-inferiority margin: 10%

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

Table 3. Change over time in LDL-cholesterol by group

	Placebo group	PARMODIA group		Micronized fenofibrate capsule group	
		0.2 mg/day	0.4 mg/day	100 mg/day	200 mg/day
Baseline	133.8±33.9 (43)	131.4±35.5 (128)	125.9±33.5 (84)	133.8±35.9 (85)	133.8±36.1 (140)
Week 4	130.2±32.0 (43)	143.2±33.0 (127)	139.5±29.6 (83)	142.2±34.1 (83)	136.5±30.5 (139)
Week 8	137.8±32.3 (43)	147.8±35.7 (124)	141.7±30.6 (83)	148.2±32.6 (81)	135.8±30.9 (136)
Week 12	131.8±33.3 (43)	149.1±33.3 (122)	144.8±32.2 (80)	148.8±32.5 (79)	137.0±32.3 (128)

Mean ± SD (mg/dL) To convert LDL-C from mg/dL to mmol/L, multiply by 0.0259
(number of subjects)

Phase 3 Comparative Confirmatory Study with Fenofibrate

In patients with dyslipidemia who had high TG and low HDL-cholesterol levels, placebo, 0.2 mg/day or 0.4 mg/day of PARMODIA (twice daily after breakfast and dinner), or fenofibrate tablets of 106.6 mg/day (once daily after breakfast) was administered for 24 weeks. The fenofibrate tablets (solid dispersion) of 106.6 mg are equivalent to micronized fenofibrate capsules of 134 mg. The percent change in fasting serum TG was as presented in the following table, which shows the non-inferiority of all PARMODIA groups over the fenofibrate tablet 106.6 mg/day group.

Table 4. Percent change in fasting serum TG in PARMODIA groups and fenofibrate tablet group

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]	
	Percent change from baseline (%)	Difference from fenofibrate tablet 106.6 mg/day group[c] in percent change
PARMODIA 0.2 mg/day 242.4±53.3, n=73	-46.226 [-50.122, -42.329]	-6.541 [-12.004, -1.078]
PARMODIA 0.4 mg/day 233.3±60.8, n=74	-45.850 [-49.678, -42.023]	-6.166 [-11.576, -0.755]
Fenofibrate tablet 106.6mg/day 235.6±71.7, n=76	-39.685 [-43.511, -35.858]	-

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Repeated measures analysis of covariance with Weeks 8, 12, 16, 20, and 24 as repeated time points and baseline value as a covariate
Least square mean [95% CI] Non-inferiority margin: 10%
c) Fenofibrate tablets (solid dispersion) of 106.6 mg are equivalent to micronized fenofibrate capsules of 134 mg.

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

Table 5. Change over time in LDL-cholesterol by group

	PARMODIA group		Fenofibrate tablet 106.6 mg/day group
	0.2 mg/day	0.4 mg/day	
Baseline	157.8±29.2 (73)	154.0±27.4 (74)	152.6±26.1 (76)
Week 4	145.4±23.0 (73)	144.2±30.6 (74)	142.8±27.2 (76)
Week 8	145.4±24.6 (72)	145.7±32.3 (74)	139.7±28.8 (76)
Week 12	146.3±23.9 (71)	144.0±33.4 (74)	143.6±27.9 (72)
Week 16	144.4±25.0 (71)	142.0±33.0 (74)	138.8±30.0 (71)
Week 20	145.1±21.5 (70)	143.1±31.5 (74)	139.0±29.4 (70)
Week 24	144.6±26.5 (69)	147.0±32.2 (73)	141.4±31.7 (68)
Week 24 (LOCF)	144.7±25.8 (73)	146.7±32.0 (74)	142.2±31.5 (76)

Mean ± SD (mg/dL) To convert LDL-C from mg/dL to mmol/L, multiply by 0.0259
(number of subjects)
LOCF: Last observation carried forward

Phase 3 Long-term Administration Study in Dyslipidemia Patients with High TG Levels

In patients with dyslipidemia who had high TG levels, PARMODIA 0.2 mg/day (a dose increase to PARMODIA 0.4 mg/day was allowed as necessary in subjects with inadequate response to PARMODIA 0.2 mg/day at Week 12 and after) was administered twice daily before or after breakfast and dinner for 52 weeks. The percent change from the baseline fasting serum TG of 249.7±77.5 mg/dL (2.82±0.88 mmol/L) (Mean ± SD [the same applies hereinafter], n=189) at Week 24 and Week 52 were -48.77±20.47% and -45.93±21.84%, respectively (Last observation carried forward [LOCF] method was used). LDL-cholesterol value was 119.3±31.7 mg/dL (3.09±0.82 mmol/L) at baseline, and 116.6±29.1 mg/dL (3.02±0.75 mmol/L) at Week 52 (n=189).

Phase 3 Long-term Administration Study in Patients with Dyslipidemia and Type 2 Diabetes Mellitus

In patients with dyslipidemia and type 2 diabetes mellitus, placebo/PARMODIA 0.2 mg/day (starting from Week 24, the treatment was switched from placebo to PARMODIA 0.2 mg/day), PARMODIA 0.2 mg/day, or PARMODIA 0.4 mg/day was administered twice daily before or after breakfast and dinner for 52 weeks. The percent change in fasting serum TG at Week 24 and Week 52 (LOCF) was as presented in the following table.

Table 6. Percent change in fasting serum TG in Placebo/PARMODIA 0.2 mg/day group and PARMODIA groups (at Weeks 24 and 52)

Treatment group and Baseline fasting serum TG[a] (mg/dL)	Percent change in fasting serum TG[b]		
	Time point	Percent change from baseline[c] (%)	Difference from placebo in percent change[d] (%)
Placebo (up to Week 24) PARMODIA 0.2 mg/day (from Week 24) 284.3±117.6, n=57	Week 24	-10.814 [-17.933, -3.694]	-
	Week 52	-46.835 [-52.967, -40.704]	-
PARMODIA 0.2 mg/day 240.3±93.5, n=54	Week 24	-44.347 [-51.656, -37.038]	-33.534 [-45.154,-21.914]
	Week 52	-43.629 [-49.924, -37.334]	-
PARMODIA 0.4 mg/day 260.4±95.9, n=55	Week 24	-45.093 [-52.283, -37.904]	-34.280 [-45.723,-22.836]
	Week 52	-46.552 [-52.744, -40.360]	-

a) Mean ± SD To convert TG from mg/dL to mmol/L, multiply by 0.0113
b) Analysis of covariance with baseline value as a covariate
Last observation carried forward (LOCF) method was used.
c) Least square mean [95% CI]
d) Least square mean [Adjusted 95% CI]

5.2 Pharmacokinetic properties

Plasma pemafibrate concentration

(1) Single dose administration

When a single dose of PARMODIA 0.1 mg was orally administered under fasted conditions to healthy Japanese adult males (16 subjects), the plasma concentration versus time and pharmacokinetic parameters are as presented in the following figure.

Mean + SD (n=16)

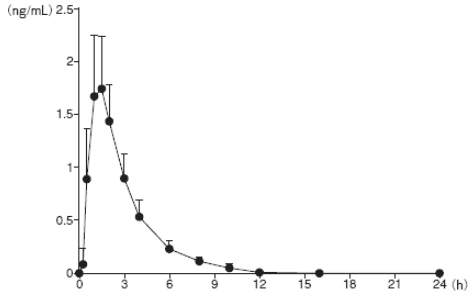

Figure. The plasma concentration versus time after a single oral dose in fasted healthy adult males.

Table 7. Pharmacokinetic parameters after a single oral dose in fasted healthy adult males.

C_{max} (ng/mL)	$AUC_{0\text{-}inf}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
1.82±0.54	5.75±1.50	1.50 (1.00, 2.00)	1.88±0.31

C_{max}, $AUC_{0\text{-}inf}$, $t_{1/2}$: Mean ± SD
t_{max}: Median (Minimum, Maximum)
n=16

(2) Repeated dose administration

When PARMODIA 0.2 mg/day or 0.4 mg/day was orally administered twice daily after breakfast and dinner for 7 days to healthy Japanese adult males (8 subjects), the pharmacokinetic parameters on Day 1 and Day 7 are as presented in the following table. The plasma concentration reached a steady state on Day 2. The accumulation ratio based on $AUC_{0\text{-}\tau}$ (repeated dosing/initial dosing, Mean ± SD) were 1.0997±0.0688 and 1.1169±0.1814, respectively.

Table 8. Pharmacokinetic parameters after repeated oral doses in healthy adult males

Dose of PARMODIA	Time point	C_{max} (ng/mL)	$AUC_{0\text{-}\tau}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
0.2 mg/day Twice daily	Day 1	1.401±0.249	4.884±1.201	2.000 (1.00, 3.00)	-
	Day 7	1.593±0.366	5.404±1.515	2.000 (1.00, 3.00)	1.528±0.402
0.4 mg/day Twice daily	Day 1	2.968±0.905	10.975±2.335	2.000 (1.00, 3.00)	-
	Day 7	3.572±1.021	12.207±2.900	2.000 (1.00, 3.00)	1.708±0.158

C_{max}, $AUC_{0\text{-}\tau}$, $t_{1/2}$: Mean ± SD, -: Not calculated
t_{max}: Median (Minimum, Maximum)
n=8

(3) Food effect

When a single dose of PARMODIA 0.1 mg was orally administered to healthy Japanese adult males (16 subjects), the ratio [90% CI] of geometric means of fasted state to fed state for C_{max} and $AUC_{0\text{-}t}$ were 0.873 [0.803, 0.950] and 0.911 [0.863, 0.961].

Absorption

The absolute bioavailability of pemafibrate 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 PARMODIA 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 9. Effect of co-administration of PARMODIA and each drug on pharmacokinetic parameters (data for non-Japanese subjects)

Co-administrated drug	Dose of Co-administrated drug	Dose of PARMODIA	Analyte	Ratio of geometric means [90% CI] (Combination therapy/ monotherapy)	
				C_{max}	$AUC_{0\text{-}inf}$
Cyclosporine	600 mg Single-dose	0.4 mg Single-dose	PARMODIA	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	PARMODIA	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	PARMODIA	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	PARMODIA	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	PARMODIA	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	PARMODIA	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	PARMODIA	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 PARMODIA monotherapy after repeated administration of rifampicin to PARMODIA monotherapy before repeated administration of rifampicin for C_{max} and $AUC_{0\text{-}inf}$.

b) $AUC_{0\text{-}\tau}$

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 PARMODIA 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 PARMODIA is an oral dose of 0.1 mg twice daily, and the maximum dosage is an oral dose of 0.2 mg twice daily (see section 4.2).

(2) Co-administration with HMG-CoA reductase inhibitors

When PARMODIA 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 10. Effect of co-administration of PARMODIA and each drug on pharmacokinetic parameters (data for Japanese and non-Japanese subjects)

Co-administrated drug	Dose of co-administrated drug	Dose of PARMODIA	Analyte	Ratio of geometric means [90% CI] (Combination therapy/ monotherapy)	
				C_{max}	$AUC_{0\text{-}\tau}$
Atorvastatin	20 mg/day Once daily 7 days	0.4 mg/day Twice daily 7 days	PARMODIA (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	PARMODIA (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	PARMODIA (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	PARMODIA (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	PARMODIA (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	PARMODIA (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 PARMODIA 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 11. Ratios [90% CI] of geometric means 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 PARMODIA 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 12. Ratios [90% CI] of geometric means 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]

PARMODIA 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 13. Ratio [90% CI] of geometric means of $AUC_{0-\tau}$ 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 14. Pharmacokinetic parameters after repeated oral administration 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

Tablet core

Lactose hydrate, Croscarmellose sodium, Microcrystalline cellulose, Hydroxypropylcellulose, Magnesium stearate

Film coating

Hypromellose, Triethyl citrate, Light anhydrous silicic acid, Titanium 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.

After the tablet is divided, store away from humidity, and use within 4 months.

6.5 Nature and contents of container

PVC/Aluminium blisters in a carton of 100 tablets (10 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. IMPORTER

Imported by: Kowa (Thailand) Co., Ltd.
175 Sathorn City Tower 17th floor, South Sathorn Road, Thungmahamek, Sathorn, Bangkok 10120
Under license from: Kowa Company, Ltd.

8. MANUFACTURER AND/OR PACKAGER

Manufactured and Packed by: Kowa Company, Ltd., Nagoya Factory
18-57, Hatooka 2-chome, Kita-ku, Nagoya, Aichi, JAPAN

9. MARKETING AUTHORISATION NUMBER(S)

Reg.No. 1C 15105/65 (NC)

10. DATE OF FIRST AUTHORISATION

10 August 2022

11. DATE OF REVISION OF THE TEXT

2 September 2024