Review Report

May 12, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Parmodia XR Tablets 0.2 mg Parmodia XR Tablets 0.4 mg
Non-proprietary Name	Pemafibrate (JAN*)
Applicant	Kowa Company, Ltd.
Date of Application	September 12, 2022
Dosage Form/Strength	Extended-release tablets: Each tablet contains 0.2 or 0.4 mg of Pemafibrate.
Application Classification	Prescription drugs (5) Drugs in new dosage forms
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug II

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of hyperlipidemia, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication
Hyperlipidemia (including familial hyperlipidemia)

Dosage and Administration
The usual adult dosage is 0.2 mg of pemafibrate orally administered once daily. The dose may be increased up to 0.4 mg once daily depending on the extent of the elevated triglyceride level.

Approval Condition
The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Attachment

Review Report (1)

March 29, 2023

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Parmodia ER Tablets 0.2 mg Parmodia ER Tablets 0.4 mg
Non-proprietary Name	Pemafibrate
Applicant	Kowa Company, Ltd.
Date of Application	September 12, 2022
Dosage Form/Strength	Extended-release tablets: Each tablet contains 0.2 or 0.4 mg of Pemafibrate.

Proposed Indication

Hyperlipidemia (including familial hyperlipidemia)

Proposed Dosage and Administration

The usual adult dosage is 0.2 mg of pemafibrate orally administered once daily. The dose may be adjusted according to the patient's age and symptoms. The maximum dose should be 0.4 mg once daily.

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Pemafibrate is a peroxisome proliferator-activated receptor (PPAR) α agonist developed as a fibrate agent by the applicant in Japan, and immediate release tablets "Parmodia Tab. 0.1 mg" containing pemafibrate as the active ingredient was approved in 2017 for the indication of "hyperlipidemia (including familial hyperlipidemia)" at the dosage of twice daily.

In 20[redacted], the applicant initiated clinical development of Parmodia XR Tablets (hereinafter referred to as Parmodia XR). Parmodia XR is an extended-release tablet of pemafibrate designed for once daily administration. The applicant has submitted the application for the marketing approval of Parmodia XR with the proposed indication of "hyperlipidemia (including familial hyperlipidemia)," based on the results of Japanese clinical studies as pivotal data. As of March 2023, the immediate release tablets of pemafibrate are approved in Singapore and Thailand, but Parmodia XR has yet to be approved in any country or region.

The applicant initially proposed the brand names of "Parmodia ER Tablets 0.2 mg" and "Parmodia ER Tablets 0.4 mg," but they were changed to "Parmodia XR Tablets 0.2 mg" and "Parmodia XR Tablets 0.4 mg," respectively, from a healthcare safety perspective.

In the sections below, "Parmodia Tab. 0.1 mg" is expressed as "the existing Parmodia" as indicated under Appendix, unless specified otherwise.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance pemafibrate is identical with the drug substance used for the manufacture of the existing Parmodia.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an extended-release, film-coated tablet,[1)] each containing 0.2 or 0.4 mg of pemafibrate. The drug product contains, as excipients, microcrystalline cellulose (granules), hydrated silicon dioxide, hypromellose, methacrylate copolymer L, ethyl cellulose, magnesium stearate, D-mannitol, microcrystalline cellulose, crospovidone, hydroxypropylcellulose, titanium dioxide, triethyl citrate, light anhydrous silicic acid, yellow ferric oxide, and carnauba wax.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], film-coating, filling/packaging/labeling, and storage/tests. [redacted] was identified as the critical step. In-process control parameters and control values were defined in the critical step and in [redacted], [redacted], [redacted], [redacted], and [redacted].

1) A change was made from tablets with a score line to tablets without a score line during the review process for the reason of healthcare safety.

The quality control strategy was designed based on the following investigations (Table 1).

- Identification of critical quality attributes (CQAs)

Table 1. Summary of quality control strategy of drug product

CQA	Control method
[redacted]	Manufacturing process
[redacted]	Manufacturing process
Dissolution characteristics of finished tablets	Manufacturing process, specifications
[redacted]	Manufacturing process

2.2.3 Control of drug product

The proposed specifications for the drug product include strength, description (appearance), identification (high performance liquid chromatography [HPLC] and ultraviolet-visible spectroscopy [UV/VIS]), purity (related substances [HPLC]), uniformity of dosage units (content uniformity [HPLC]), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of drug product

Table 2 shows main stability studies of the drug product. Results demonstrated the stability of the drug product. Photostability testing showed that the drug product is photostable.

Table 2. Main stability studies for drug product

Study	Primary batch	Temperature	Humidity	Storage container	Storage period
Long-term	Pilot scale batches 3 packaged batches each of 0.2 mg and 0.4 mg tablets	25°C	60% RH	Blister pack[a] + aluminum bag Bottle[b] container	12 months
Accelerated		40°C	75% RH		6 months

a Multilayered film consisting of PVC/PVDC/PE and aluminum foil
b HDPE bottle with PP cap

Based on the above, a shelf life of 24 months has been proposed for the drug product when packed in a multilayered film consisting of polyvinyl chloride (PVC)/polyvinylidene chloride (PVDC)/polyethylene (PE) plus an aluminum foil with a blister pack and placed in aluminum pouches and cardboard boxes or in a high-density polyethylene (HDPE) bottle with polypropylene (PP) cap and stored at room temperature in accordance with the Guideline on Evaluation of Stability Data (ICH Q1E Guideline). Long-term testing will be continued for 36 months.

2.R Outline of the review conducted by PMDA

On the basis of its review of the submitted data and the reviews outlined below, PMDA concluded that the quality of the drug substance and drug product was, for the most part, adequately controlled, but, as described in Section 2.R.1, concluded that the specifications for [redacted] of [redacted] should be further reviewed in Review Report (2).

2.R.1 Specifications for [redacted] of [redacted]

The applicant's explanation about [redacted] of [redacted]:

Since the drug product is a [redacted] extended-release formulation and the mechanism of dissolution control is [redacted], dissolution of [redacted] is affected by [redacted]. In order to prevent [redacted] during the formulation process, [redacted] was confirmed for the drug product [redacted] of

[redacted]grade. However, whether the difference in [redacted] of [redacted] affects the prevention of [redacted] has not been investigated. Accordingly, [redacted] will be added to the specifications for [redacted].

PMDA's view:
Given the explanation of the applicant, the applicant's proposal to add [redacted] to the specifications for [redacted] is appropriate. However, the appropriateness of the specifications for [redacted] of [redacted] should be evaluated based on the results of batch analysis to be submitted in the future. Therefore PMDA's conclusion on this issue will be described in the Review Report (2).

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA
Since this application relates to a new dosage form, no new study data have been submitted.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA
Although this application relates to a new dosage form, the active ingredient of Parmodia XR is identical with that of the existing Parmodia and the distribution, metabolism, and excretion of pemafibrate were evaluated during the review process for the approval of the existing Parmodia, and absorption of pemafibrate has been evaluated in human subjects, thus, no new have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA
Since this application relates to a new dosage form, no new study data have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA
Pharmacokinetics (PK) parameter values are expressed in geometric means (coefficient of variation in %), unless specified otherwise.

6.1 Summary of biopharmaceutic studies and associated analytical methods
The bioequivalence between the formulation (Parmodia XR 0.4 mg tablets) used in the phase II study (Study K-877-CR-01 [Study CR-01]) and the formulation (Parmodia XR 0.4 mg tablets) used in the confirmatory study (Study K-877-ER-02 [Study ER-02]) was demonstrated by a dissolution test conducted according to the Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (Bioequivalence [BE] Guidelines for Formulation Changes). Bioequivalence of Parmodia XR 0.2 mg tablets and Parmodia XR 0.4 mg tablets used in Study ER-02 was demonstrated by a dissolution test conducted according to the Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms (BE Guideline for Different Strengths).

During the review process, the to-be-marketed formulation was changed from tablets with a score line to tablets without a score line. The biological equivalence between the to-be-marketed formulation (Parmodia XR 0.2 mg tablets and 0.4 mg tablets) and the formulation used in Study ER-02 (Parmodia XR 0.2 mg tablets and 0.4 mg tablets) for each of different strengths has to be evaluated based on the dissolution test being conducted according to the BE Guidelines for Formulation Changes. Results of the test will be detailed and reviewed in the Review Report (2).

6.2 Clinical pharmacology

6.2.1 Studies in patients

6.2.1.1 Japanese phase II study (Study CR-01, CTD 5.3.1.1-1, September to December 2019)

A 12-treatment, 2-period cross-over study (no washout period) was conducted in 60 patients with dyslipidemia showing a high triglyceride (TG) level. The subjects orally received Parmodia XR 0.4 mg or 0.8 mg/day or the existing Parmodia 0.2 mg/day, repeatedly, for 4 weeks (Table 3). Table 4 shows the PK parameter values of pemafibrate at Week 4 after the start of administration in each group. In subjects receiving Parmodia XR 0.4 mg/day, the geometric mean ratio [90% confidence interval (CI)] of C_{max} and $AUC_{0\text{-}24h}$ of pemafibrate under fed conditions to those under fasted conditions were 1.124 [0.840, 1.503] and 1.097 [0.879, 1.370], respectively.

Table 3. Composition of treatment groups in Study CR-01

Treatment group	Period 1		Period 2	
	Dosage regimen	Timing of administration	Dosage regimen	Timing of administration
A	Parmodia 0.1 mg, twice a day	Fasted	Parmodia XR 0.4 mg, once a day	Fasted
B		Fed		Fed
C		Fasted	Parmodia XR 0.8 mg, once a day	Fasted
D		Fed		Fed
E	Parmodia XR 0.4 mg, once a day	Fasted	The existing Parmodia 0.1 mg, twice a day	Fasted
F		Fed		Fed
G		Fasted	Parmodia XR 0.8 mg, once a day	Fasted
H		Fed		Fed
I	Parmodia XR 0.8 mg, once a day	Fasted	The existing Parmodia 0.1 mg, twice a day	Fasted
J		Fed		Fed
K		Fasted	Parmodia XR 0.4 mg, once a day	Fasted
L		Fed		Fed

5 subjects/group

Table 4. PK parameter values of pemafibrate at Week 4 of repeated oral administration of Parmodia XR or the existing Parmodia

	Dose (mg/day)	Timing of administration	No. of subjects	C_{max} (ng/mL)	t_{max}[a] (h)	AUC[b] (ng·h/mL)	$t_{1/2}$ (h)
Parmodia XR	0.4	Fasted	20	3.1283 (70.6)	3.00	22.7233 (61.8)	5.549 (43.6)[c]
		Fed	19	3.5149 (59.3)	8.00	24.9334 (37.7)	4.185 (23.6)[c]
	0.8	Fasted	20	6.6871 (31.7)	3.00	47.9576 (32.4)	5.154 (50.0)[d]
		Fed	19	8.3458 (39.1)	10.00	61.0355 (45.1)	3.775 (21.3)[e]
Existing Parmodia	0.2	Fasted	20	2.0585 (37.9)	1.00	6.4507 (63.5)	2.001 (30.1)
		Fed	18	1.4603 (32.1)	3.00	7.7144 (38.2)	2.118 (25.7)

a Median
b $AUC_{0\text{-}24h}$ for Parmodia XR and $AUC_{0\text{-}12h}$ for the existing Parmodia
c n = 17
d n = 19
e n = 16

6.R Outline of the review conducted by PMDA

6.R.1 Appropriateness of dosage and administration

The applicant's explanation about the proposed dosage and administration for Parmodia XR:

Based on the PK data obtained from the phase II study (Study CR-01), the geometric mean ratio [95% CI] of $AUC_{0\text{-}24h}$ of pemafibrate after administration of Parmodia XR 0.4 mg/day or 0.8 mg/day to $AUC_{0\text{-}12h}$ of pemafibrate after administration of the existing Parmodia 0.2 mg/day was calculated, after

adjusting for the difference in daily dosing frequency and in each dose.[2)] For Parmodia XR 0.4 mg/day to the existing Parmodia 0.2 mg/day, the geometric mean ratio [95% CI] was 0.863 [0.797, 0.934] under fasted condition and 0.870 [0.788, 0.960] under fed condition. For Parmodia XR 0.8 mg/day to the existing Parmodia 0.2 mg/day, the geometric mean ratio [95% CI] was 0.879 [0.812, 0.952] under fasted condition and 1.035 [0.940, 1.139] under fed condition. Results showed no significant difference in the exposure to pemafibrate after administration of Parmodia XR or the existing Parmodia, at either dose.

The above results suggest that the exposure to pemafibrate after administration of Parmodia XR 0.2 mg/day or 0.4 mg/day is similar to that after administration of the existing Parmodia at the equivalent daily dose.

PMDA's view:
In PK of pemafibrate, Study CR-01 showed an increase in both t_{max} and $t_{1/2}$ after Parmodia XR administration than after the existing Parmodia administration (Table 4). Although the clinical study did not provide PK data after once daily administration of Parmodia XR 0.2 mg, the applicant presented results of the investigation on the difference in the exposure to pemafibrate between after the existing Parmodia administration and after Parmodia XR administration, which showed that (1) dose proportionality was observed in the exposure to pemafibrate ($AUC_{0\text{-}24h}$) after 4-week multiple administration of Parmodia XR 0.4 and 0.8 mg/day in patients with dyslipidemia showing a high TG level (Table 4), and (2) a linear relationship was observed in the exposure after the existing Parmodia administration within the dose range of ≥0.1 mg/day (0.1-1.6 mg/day) (attached document for the initial application of "Parmodia Tab. 0.1 mg"). These results suggest that administration of Parmodia XR 0.2 or 0.4 mg/day will achieve an exposure (AUC) comparable to that observed after administration of the existing Parmodia 0.2 or 0.4 mg/day, respectively.

Based on the above, the following rationale for the proposed dosage and administration of Parmodia XR is acceptable from the point of view of PK:
(a) Parmodia XR is administered once daily instead of twice daily for the existing Parmodia, taking into consideration the extended-release characteristics of pemafibrate.
(b) The usual daily dose and the maximum daily dose of Parmodia XR are matched to the usual daily dose and the maximum daily dose of the existing Parmodia, respectively.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted the results from 3 clinical studies as efficacy and safety evaluation data (Table 5) [for PK, see Section "6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA"].

2) Both $AUC_{0\text{-}24h}$ after Parmodia XR administration and $AUC_{0\text{-}12h}$ after the existing Parmodia administration reflect the pharmacokinetics after a single-dose administration until disappearance of pemafibrate from the blood. By taking into account that Parmodia XR was administered once daily in Study CR-01 whereas the existing Parmodia was administered twice daily, and that the daily dose of Parmodia XR is twice (0.4 mg/day) or 4 times (0.8 mg/day) that of the existing Parmodia (0.2 mg/day), $AUC_{0\text{-}12h}$ of pemafibrate after the administration of the existing Parmodia (0.2 mg/day) was multiplied by 4 or 8, respectively.

Table 5. Outline of main clinical studies

Data category	Region	Study code	Phase	Study population	No. of enrollments	Outline of dosage regimen	Main endpoints
Evaluation	Japan	CR-01	II	Patients with high TG[a]	63	Parmodia XR (0.4 or 0.8 mg once daily) or the existing Parmodia (0.1 mg twice daily) was administered orally under fasted or fed conditions for 4 weeks.	Efficacy Safety PK
		ER-02	III	Patients with high TG[b]	356	Parmodia XR (0.2 or 0.4 mg once daily after breakfast) or the existing Parmodia (0.1 mg twice daily after breakfast and after dinner) was administered orally for 12 weeks.	Efficacy Safety
		ER-03		Patients with high TG[c]	121	Parmodia XR 0.2 or 0.4 mg was administered orally once daily[d] in the morning or evening for 52 weeks.	

a Patients with fasting serum TG of ≥150 mg/dL and ≤500 mg/dL who are receiving lifestyle improvement guidance
b Patients with fasting serum TG of ≥200 mg/dL and ≤1000 mg/dL who are receiving lifestyle improvement guidance
c Patients with fasting serum TG of ≥150 mg/dL and ≤1000 mg/dL who are receiving lifestyle improvement guidance
d If fasting serum TG was ≥150 mg/dL during Week 8 to 40 of the treatment period, the dose of Parmodia XR was increased to 0.4 mg once daily following the completion of the tests at the next scheduled visit.

7.1 Japanese phase II study (Study CR-01, CTD 5.3.1.1-1, September to December 2019)

A randomized, single-blind,[3)] cross-over study was conducted to compare the efficacy, safety, and PK of Parmodia XR with the existing Parmodia in patients with dyslipidemia showing a high TG level (target sample size, 60 subjects [5 per group][4)]) at 3 study sites in Japan.

Subjects were randomized to treatment groups according to dynamic allocation using study site, sex, and use/non-use of hydroxymethylglutaryl coenzyme A reductase inhibitor (statin) as the factors. During the 2 treatment periods of 4 weeks after a screening period of ≤8 weeks, subjects received orally either Parmodia XR 0.4 or 0.8 mg once daily or the existing Parmodia (0.1 mg twice daily under fasted or fed conditions for 4 weeks (Table 3). Administration of fibrates was prohibited from 4 weeks before the screening up to the study completion, and administration of anion exchange resin was prohibited from one day before the study drug administration up to the study completion. Use of other therapeutic agents against dyslipidemia was permitted if the dosage regimen did not change from 4 weeks before the screening up to the study completion.

The main inclusion criteria were patients aged ≥20 years with dyslipidemia who met the criteria specified below:

- Fasting serum TG ≥150 mg/dL (or ≥200 mg/dL under fed conditions) by laboratory test within 6 months before informed consent
- Fasting serum TG ≥150 mg/dL and ≤500 mg/dL at screening

Of the total of 63 randomized subjects, 3 subjects discontinued the study because of adverse events, subjects' wish, or the investigator's discretion, and the remaining 60 subjects (n= 5/group) received the study drug and were included in the full analysis set (FAS) and the safety analysis population. The FAS was used as the primary efficacy analysis population. After the end of the study drug

3) Group assignment information was not disclosed to evaluators such as the investigator and the blinding was maintained. Subjects were required not to inform the investigator etc., of the treatment group or the type and other details of the study drug they were receiving.
4) By assuming the rate of change in serum TG from baseline to be similar between the combined Parmodia XR 0.4 mg/day group and the combined existing Parmodia 0.2 mg/day group, its variance to be 400 each, and the correlation coefficient between repeated time points to be 0.55, the number of subjects required to achieve noninferiority of the combined Parmodia XR 0.4 mg/day group to the combined existing Parmodia 0.2 mg/day group at the probability of ≥80% was calculated to be 60 (n = 5/group) at the non-inferiority margin of 10% and two-sided significance level of 0.05.

administration (after completion of Period 1), the study was discontinued in 1 subject by the request of the subject.

The primary efficacy endpoint was the rate of change from baseline[5)] in fasting serum TG at Week 4 in each treatment period. For the assessment of the primary endpoint, noninferiority of the combined Parmodia XR 0.4 mg/day group to the combined existing Parmodia 0.2 mg/day group was evaluated and, when the noninferiority was demonstrated, noninferiority of the combined Parmodia XR 0.8 mg/day group to the combined existing Parmodia 0.2 mg/day group was evaluated.

Table 6 shows the rate of change from baseline in fasting serum TG level at Week 4 in each treatment period. Both of the comparison between the combined Parmodia XR 0.4 mg/day group and the combined existing Parmodia 0.2 mg/day group and between the combined Parmodia XR 0.8 mg/day group and the combined existing Parmodia 0.2 mg/day group showed that the upper bound of 95% CI of the between-group difference of the least squares mean was below the pre-determined non-inferiority margin (10%[6)]), demonstrating the non-inferiority of the combined Parmodia XR 0.4 mg/day to the combined existing Parmodia 0.2 mg/day as well as the non-inferiority of the combined Parmodia XR 0.8 mg/day to the combined existing Parmodia 0.2 mg/day.

Table 6. Rate of change from baseline in fasting serum TG level at Week 4 in each treatment period (FAS)

	Combined Parmodia XR 0.4 mg/day (n = 40)	Combined Parmodia XR 0.8 mg/day (n = 40)	Combined existing Parmodia 0.2 mg/day (n = 40)
Baseline (mg/dL) [a]	229.0 ± 68.3	214.0 ± 58.6	220.9 ± 76.3
Week 4 (mg/dL)[a]	127.7 ± 40.2	124.8 ± 39.6	123.3 ± 39.3
Rate of change (%)[b]	−41.08 ± 2.046	−39.71 ± 2.046	−43.59 ± 2.046
Difference from combined existing Parmodia 0.2 mg (%) [95% CI]	2.51 [−1.46, 6.48]	3.88 [−0.09, 7.84]	-

a Mean ± standard deviation (SD)

b Least squares mean ± standard error (SE) (analysis conducted using a marginal model assuming a compound symmetry (CS) for the error variance-covariance matrix at the subject level, with assignment group combining dosing timings [under fasted condition, under fed condition], period [Period 1, Period 2], treatment [Parmodia XR 0.4 mg/day, Parmodia XR 0.8 mg/day, the existing Parmodia 0.2 mg/day], baseline level, study site, sex, and use/non-use of statins as fixed effects)

Table 7 shows the rate of change from baseline in fasting serum TG under fasted or fed condition at Week 4 in each treatment period.

5) If both the data 1 day before the study drug administration in the Period 1 (Day −1) and the data at Week 0 of the treatment period (Day 1) were available, their mean value was handled as the baseline value. If the value was available only at 1 time point before the study drug administration, the value obtained 1 day before the study drug administration in the Period 1 was used as the baseline value.

6) The non-inferiority margin was 10% by referring to the design of the confirmatory study on the existing Parmodia

Table 7. Rate of change from baseline in fasting serum TG under fasted or fed condition at Week 4 of each treatment period (FAS)

	Parmodia XR 0.4 mg/day		Parmodia XR 0.8 mg/day		Existing Parmodia 0.2 mg/day	
	Fasted condition (n = 20)	Fed condition (n = 20)	Fasted condition (n = 20)	Fed condition (n = 20)	Fasted condition (n = 20)	Fed condition (n = 20)
Baseline (mg/dL)[a]	234.5 ± 75.7	223.5 ± 61.5	232.8 ± 63.4	195.3 ± 47.7	237.6 ± 89.9	204.2 ± 57.2
Week 4 (mg/dL)[a]	135.9 ± 45.7	119.5 ± 32.9	135.4 ± 35.5	114.2 ± 41.6	132.7 ± 47.6	113.9 ± 26.8
Rate of change (%)[b]	−37.40 ± 2.858	−44.75 ± 2.858	−36.70 ± 2.875	−42.72 ± 2.875	−38.70 ± 2.876	−48.47 ± 2.876

a Mean ± SD

b Least squares mean ± SE (analysis conducted using a marginal model assuming a CS for the error variance-covariance matrix at the subject level, with assignment group combining dosing timings [under fasted condition, under fed condition], period [Period 1, Period 2], treatment [Parmodia XR 0.4 mg/day, Parmodia XR 0.8 mg/day, the existing Parmodia 0.2 mg/day], baseline level, study site, sex, and use/non-use of statins as fixed effects)

The incidence of adverse events observed after the start of the treatment period was 17.5% (7 of 40 subjects) in the combined Parmodia XR 0.4 mg/day group, 20.0% (8 of 40 subjects) in the combined Parmodia XR 0.8 mg/day group, and 12.5% (5 of 40 subjects) in the combined existing Parmodia 0.2 mg/day group. Adverse events that occurred in multiple subjects were nasopharyngitis (1 subject, 2 subjects, 2 subjects) and upper respiratory tract inflammation (0 subject, 1 subject, 1 subject).

There were no deaths, serious adverse events, or adverse events leading to discontinuation of the study drug.

7.2 Japanese phase III study

7.2.1 Confirmatory study (Study ER-02, CTD 5.3.5.1-1, March to September 2021)

A randomized, double-blind, parallel-group study was conducted to investigate the non-inferiority of Parmodia XR 0.2 mg/day and 0.4 mg/day to the existing Parmodia 0.2 mg/day in patients with dyslipidemia showing a high TG level (target sample size, 345 subjects [115 per group])[7)]) at 11 study sites in Japan.

Subjects were randomized to the Parmodia XR 0.2 mg/day group, the Parmodia XR 0.4 mg/day group, or the existing Parmodia 0.2 mg/day group according to dynamic allocation using study site, sex, timing of administration (fasted or fed), and use/non-use of statins as the factors. During the 12-week treatment period after a screening period of ≤8 weeks, subjects received orally Parmodia XR 0.2 or 0.4 mg once daily after breakfast or the existing Parmodia 0.1 mg twice daily after breakfast and dinner. The study drug was administered at the specified timing (under fasted or fed condition) throughout the study period according to the instruction of the investigator (or subinvestigator). Rules for concomitant drugs were the same as in Study CR-01 [see Section "7.1 Japanese phase II study].

7) The number of subjects required to achieve (a) and (b) below at the same time at the probability of ≥80% was calculated to be 115 per group. The estimates of the rate of change in serum TG from baseline in each group, inter-individual variance, and intra-individual variance were specified by referring to the results of the confirmatory study comparing the existing Parmodia and fenofibrate (Study K-877-17) and Study CR-01, and the discontinuation rate was assumed to be 6%.
(a) Under the assumption that the rate of change in serum TG from baseline is −45% in the Parmodia XR 0.4 mg/day group, −44% in the Parmodia XR 0.2 mg/day group, and −45% in the existing Parmodia 0.2 mg/day group and that both the interindividual variance and intra-individual variance are 250, non-inferiority of Parmodia XR 0.4 mg/day and 0.2 mg/day to the existing Parmodia 0.2 mg/day is demonstrated with the non-inferiority margin of 10% and the two-sided significance level of 0.05.
(b) Under the assumption that the rate of change in serum TG from baseline is −46% in the Parmodia XR 0.4 mg/day group and −44% in the Parmodia XR 0.2 mg/day group, and that both the interindividual variance and intra-individual variance are 234, the point estimate in the Parmodia XR 0.4 mg/day group is lower than the point estimate in the Parmodia XR 0.2 mg/day group.

The main inclusion criteria were patients aged ≥20 years with dyslipidemia who met the criteria specified below:

- Fasting serum TG ≥200 mg/dL in 2 consecutive measurements at screening
- Fasting serum TG ≤1000 mg/dL at screening

Of a total of 356 randomized subjects (119 in the Parmodia XR 0.2 mg/day group, 119 in the Parmodia XR 0.4 mg/day group, 118 in the existing Parmodia 0.2 mg/day group), 355 subjects (118, 119, 118) received the study drug and were included in the safety analysis population. The remaining 1 subject (in the Parmodia XR 0.2 mg/day group) who withdrew informed consent and requested discontinuation was excluded from the study. Of them, 353 subjects (117, 119, 117) with evaluable data for Week 4, 8, or 12 were included in FAS, and the FAS was used as the primary efficacy analysis population. Study discontinuation occurred in 6 subjects (3, 1, 2). The reasons for the discontinuation were consent withdrawal or requested discontinuation (3 subjects, 1 subject, 0 subjects) and adverse events (0 subjects, 0 subjects, 2 subjects).

The primary efficacy endpoint was the rate of change from baseline[8)] in TG at Week 4, 8, and 12. The primary endpoint was evaluated sequentially, as follows: (1) Non-inferiority of Parmodia XR 0.4 mg/day to the existing Parmodia 0.2 mg/day was evaluated and, if non-inferiority was confirmed; (2) non-inferiority of Parmodia XR 0.2 mg/day to the existing Parmodia 0.2 mg/day was evaluated; and if non-inferiority was confirmed again, then (3) whether the point estimate in the Parmodia XR 0.4 mg/day group is below the point estimate in the Parmodia XR 0.2 mg/day group was evaluated.

Table 8 shows the rate of change from baseline in the fasting serum TG at Week 4, 8, and 12. The difference (difference of least squares mean [95% CI]) of the primary endpoint between the Parmodia XR 0.4 mg/day group and the existing Parmodia 0.2 mg/day group was 0.00% [−4.79%, 4.79%], and the upper bound of 95% CI was below the pre-determined non-inferiority margin (10%[9)]), showing the non-inferiority of Parmodia XR 0.4 mg/day to the existing Parmodia 0.2 mg/day.

The difference [95% CI] in the primary endpoint between the Parmodia XR 0.2 mg/day group and the existing Parmodia 0.2 mg/day group was 4.20% [−0.62%, 9.02%], and the upper bound of 95% CI was below the pre-determined non-inferiority margin (10%[9)]), demonstrating the non-inferiority of Parmodia XR 0.2 mg/day to the existing Parmodia 0.2 mg/day.

Furthermore, the point estimate of the primary endpoint in the Parmodia XR 0.4 mg/day group and in the Parmodia XR 0.2 mg/day group was −48.00% and −43.80%, respectively, with the point estimate in the Parmodia XR 0.4 mg/day group falling below the point estimate in the Parmodia XR 0.2 mg/day group.

8) If the data at 2 screening tests and the data at Week 0 of the treatment period are available, their mean value was handled as the baseline value. If the value was available only at Week 0 of the treatment period, the value was used as the baseline data.
9) The non-inferiority margin was 10% by referring to the design of the confirmatory study on the existing Parmodia.

Table 8. Rate of change from baseline in fasting serum TG at Week 4, 8, and 12 (FAS)

	Parmodia XR 0.2 mg/day	Parmodia XR 0.4 mg/day	Existing Parmodia 0.2 mg/day
Baseline (mg/dL)[a]	338.6 ± 117.0 (117)	355.0 ± 157.5 (119)	354.2 ± 142.3 (117)
Week 4 (mg/dL)[a]	186.6 ± 97.4 (116)	177.1 ± 103.4 (119)	168.3 ± 70.4 (116)
Week 8 (mg/dL)[a]	180.2 ± 76.0 (116)	170.6 ± 75.9 (119)	179.2 ± 102.5 (117)
Week 12 (mg/dL)[a]	192.1 ± 90.6 (115)	166.5 ± 81.6 (118)	173.5 ± 80.7 (116)
Rate of change (%)[b]	−43.80 ± 1.731	−48.00 ± 1.713	−48.00 ± 1.728
Difference from Parmodia 0.2 mg (%) [95% CI]	4.20 [−0.62, 9.02]	0.00 [−4.79, 4.79]	-

a Mean ± SD (number of subjects)
b Least squares mean ± SE (repeated measures analysis of covariance (ANCOVA) using treatment group as a factor, baseline TG, sex, timing of administration of the study drug (fasted or fed), use/non-use of statins, and study site as covariates, and Week 4, 8, and 12 of treatment period as repeated time points)

Table 9 shows the results of rate of change from baseline in fasting serum total cholesterol (TC), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), and non-high density lipoprotein-cholesterol (non HDL-C) at Week 4, 8, and 12 of treatment period, the secondary endpoints.

Table 9. Rate of change (%)[a] from baseline in fasting serum TC, LDL-C, HDL-C, and non HDL-C at Week 4, 8, and 12 of treatment period (FAS)

	Parmodia XR 0.2 mg/day (n = 117)	Parmodia XR 0.4 mg/day (n = 119)	Parmodia 0.2 mg/day (n = 117)
TC	−4.14 ± 1.039	−2.63 ± 1.031	−4.98 ± 1.039
LDL-C (direct method)	6.71 ± 2.235	10.45 ± 2.217	7.11 ± 2.234
HDL-C (direct method)	14.75 ± 1.151	16.15 ± 1.140	16.59 ± 1.151
non HDL-C	−8.48 ± 1.333	−6.77 ± 1.324	−10.09 ± 1.334

a Least squares mean ± SE (repeated measures ANCOVA using treatment group as a factor, baseline level of each lipid parameter, sex, timing of administration of the study drug (fasted or fed), use/non-use of statins, and study site as covariates, and Week 4, 8, and 12 of treatment period as repeated time points)

Table 10 shows the incidence of adverse events.

Table 10. Incidence of adverse events (safety analysis population)

	Parmodia XR 0.2 mg/day (n = 118)	Parmodia XR 0.4 mg/day (n = 119)	Parmodia 0.2 mg/day (n = 118)
All events	17.8 (21)	26.9 (32)	25.4 (30)
Main events[a]			
Pyrexia	1.7 (2)	6.7 (8)	5.1 (6)
Malaise	0.8 (1)	4.2 (5)	2.5 (3)
Injection site pain	1.7 (2)	3.4 (4)	2.5 (3)
Headache	0 (0)	2.5 (3)	0.8 (1)
Vaccination site pain	0.8 (1)	1.7 (2)	0.8 (1)
ALT increased	1.7 (2)	0 (0)	0.8 (1)
Back pain	1.7 (2)	0 (0)	0.8 (1)
Blood ketone body increased	0 (0)	1.7 (2)	1.7 (2)
Rash	0 (0)	0.8 (1)	1.7 (2)
Urticaria	0 (0)	0.8 (1)	1.7 (2)
Eczema	0 (0)	0 (0)	1.7 (2)

% (number of subjects)
a Events observed in multiple subjects in any group

No death occurred. Serious adverse events other than deaths were observed in 2 subjects in the Parmodia XR 0.2 mg/day group (COVID-19, COVID-19 pneumonia) and in 1 subject in the existing Parmodia 0.2 mg/day group (COVID-19). Their causal relationship to the study drug was ruled out. Adverse events leading to discontinuation of the study drug were observed in 2 subjects in the existing

Parmodia 0.2 mg/day group (dizziness, myalgia). Their causal relationship to the study drug could not be ruled out, but their outcome was “resolved” (dizziness) and “recovering” (myalgia), respectively.

7.2.2 Long-term treatment study (Study K-877-ER-03 [Study ER-03], CTD 5.3.5.2-1 and 5.3.5.2-2, February 2021 to June 2022)

A randomized, open-label, parallel-group study was conducted to investigate the safety and efficacy of long-term administration of Parmodia XR in the morning or evening in patients with dyslipidemia showing a high TG level (target sample size, 110 subjects [55 per group]) at 16 study sites in Japan.

Subjects were randomized to treatment groups (morning administration or evening administration) according to dynamic allocation using study site, sex, timing of study drug administration (fasted or fed), and use/non-use of statins as the factors. After the screening period of ≤8 weeks, Parmodia XR was administered orally once daily in the morning or in the evening during the treatment period of 52 weeks. The starting dose was 0.2 mg/day. If fasting serum TG was ≥150 mg/dL at any time point during the treatment period of Week 8 to 40, the dose was increased to 0.4 mg/day after the test at the next scheduled visit (every 4 weeks from Week 12 to 44). The investigator (or subinvestigator) instructed each subject to adhere to the specified timing of study drug administration (either fasted or fed) throughout the study period. The rules for concomitant drugs were the same as those in Study CR-01 [see Section “7.1 Japanese phase II study].

The main inclusion criteria were patients aged ≥20 years with dyslipidemia who met the criteria specified below:

- Fasting serum TG ≥150 mg/dL in 2 consecutive measurements at screening
- Fasting serum TG ≤1000 mg/dL at screening

All of 121 randomized subjects (61 in the Parmodia XR morning administration group, 60 in the Parmodia XR evening administration group) received the study drug, and were included in FAS and the safety analysis population. FAS was used as the primary efficacy analysis population. Study discontinuation after the start of treatment occurred in 7 subjects (2, 5) because of adverse events. The final dose in 121 subjects who completed or discontinued the study was 0.2 mg/day in 39 subjects (17, 22) and 0.4 mg/day in 82 subjects (44, 38).

Table 11 shows the mean rate of change from baseline[10)] in fasting serum TG at the last assessment[11)] (the primary efficacy endpoint) and at the immediately preceding time point.

[10)] The mean of the levels at 2 screening tests and the level at Week 0 of treatment period was used as the baseline level.
[11)] At Week 52 or at discontinuation.

Table 11. Rate of change from baseline in fasting serum TG at the last and immediately preceding evaluation time point

	Entire Parmodia XR (n = 121)	Parmodia XR morning administration (n = 61)	Parmodia XR evening administration (n = 60)
Baseline (mg/dL)	264.0 ± 109.2	273.5 ± 107.0	254.5 ± 111.5
At the last and immediately preceding evaluation time points (mg/dL)	136.3 ± 58.9	145.7 ± 68.5	126.7 ± 45.8
Mean rate of change at the last and immediately preceding evaluation time points (%)	−45.71 ± 18.64	−44.82 ± 19.07	−46.61 ± 18.31

Mean ± SD

Table 12 shows the rate of change from baseline in other lipid parameter values at the last and immediately preceding evaluation time points.[12)]

Table 12. Rate of change from baseline in fasting serum TC, LDL-C, HDL-C, and non HDL-C levels at the last and immediately preceding evaluation time points (FAS)

		Entire Parmodia XR (n = 121)	Parmodia XR morning administration (n = 61)	Parmodia XR evening administration (n = 60)
TC	Baseline (mg/dL)	219.8 ± 37.9	214.3 ± 28.5	225.4 ± 45.1
	At the last and immediately preceding evaluation time points (mg/dL)	207.9 ± 33.9	208.5 ± 28.7	207.3 ± 38.7
	Mean rate of change at the last and immediately preceding evaluation time points (%)	−4.28 ± 13.49	−1.87 ± 12.91	−6.73 ± 13.73
LDL-C (direct method)	Baseline (mg/dL)	125.2 ± 36.3	120.4 ± 30.7	130.1 ± 40.9
	At the last and immediately preceding evaluation time points (mg/dL)	122.1 ± 30.8	122.3 ± 26.1	121.8 ± 35.2
	Mean rate of change at the last and immediately preceding evaluation time points (%)	2.43 ± 29.92	6.49 ± 30.19	−1.70 ± 29.32
HDL-C (direct method)	Baseline (mg/dL)	48.5 ± 10.0	47.3 ± 8.9	49.7 ± 10.9
	At the last and immediately preceding evaluation time points (mg/dL)	53.4 ± 11.9	52.7 ± 12.7	54.1 ± 11.0
	Mean rate of change at the last and immediately preceding evaluation time points (%)	10.82 ± 15.75	11.47 ± 16.90	10.15 ± 14.59
non HDL-C	Baseline (mg/dL)	171.4 ± 37.3	167.0 ± 27.6	175.8 ± 44.8
	At the last and immediately preceding evaluation time points (mg/dL)	154.6 ± 34.2	155.9 ± 29.9	153.2 ± 38.4
	Mean rate of change at the last and immediately preceding evaluation time points (%)	−8.17 ± 17.15	−5.47 ± 16.72	−10.91 ± 17.28

Mean ± SD

Table 13 shows the incidence of adverse events.

12) If data at the 2 screening tests and data at Week 0 of the treatment period were available, their mean value was handled as the baseline value. If the value was available only at Week 0 of the treatment period, the value was used as the baseline data.

Table 13. Incidence of adverse events (safety analysis population)

	Entire Parmodia XR (n = 121)	Parmodia XR morning administration (n = 61)	Parmodia XR evening administration (n = 60)
All events	83.5 (101)	86.9 (53)	80.0 (48)
Main events[a]			
Pyrexia	21.5 (26)	19.7 (12)	23.3 (14)
Arthralgia	9.9 (12)	9.8 (6)	10.0 (6)
Vaccination site pain	5.8 (7)	8.2 (5)	3.3 (2)
Malaise	5.8 (7)	4.9 (3)	6.7 (4)
Back pain	5.8 (7)	4.9 (3)	6.7 (4)
Nasopharyngitis	5.0 (6)	6.6 (4)	3.3 (2)
COVID-19	5.0 (6)	4.9 (3)	5.0 (3)
Hypertension	5.0 (6)	4.9 (3)	5.0 (3)
Headache	4.1 (5)	8.2 (5)	0 (0)
Menopausal symptoms	3.3 (4)	6.6 (4)	0 (0)
Tenosynovitis	3.3 (4)	4.9 (3)	1.7 (1)
Injection site pain	3.3 (4)	3.3 (2)	3.3 (2)
Pain in extremity	3.3 (4)	3.3 (2)	3.3 (2)
Stomatitis	3.3 (4)	1.6 (1)	5.0 (3)
Diabetes mellitus	3.3 (4)	1.6 (1)	5.0 (3)
Myalgia	3.3 (4)	1.6 (1)	5.0 (3)
Gastroenteritis	2.5 (3)	4.9 (3)	0 (0)
Gout	2.5 (3)	4.9 (3)	0 (0)
Diarrhoea	2.5 (3)	3.3 (2)	1.7 (1)
Cystitis	2.5 (3)	3.3 (2)	1.7 (1)
Glycosylated haemoglobin increased	2.5 (3)	3.3 (2)	1.7 (1)
Type 2 diabetes mellitus	2.5 (3)	3.3 (2)	1.7 (1)
Chronic gastritis	2.5 (3)	1.6 (1)	3.3 (2)
Arthropod sting	2.5 (3)	1.6 (1)	3.3 (2)
Blood CK increased	2.5 (3)	1.6 (1)	3.3 (2)
Rash	2.5 (3)	1.6 (1)	3.3 (2)
Gastrooesophageal reflux disease	2.5 (3)	0 (0)	5.0 (3)
Periodontal disease	2.5 (3)	0 (0)	5.0 (3)
Eczema	2.5 (3)	0 (0)	5.0 (3)

% (number of subjects events)

a Events reported in ≥2% of subjects in the entire Parmodia XR group

An adverse event leading to death occurred in 1 subject in the Parmodia XR evening administration group (myocardial infarction), but its causal relationship to the study drug was ruled out. Serious adverse events other than death occurred in 5 subjects in the Parmodia XR morning administration group (carotid artery stenosis, retinal haemorrhage, colon cancer, arrhythmia, bladder cancer) and in 2 subjects in the evening administration group (COVID-19, contusion). A causal relationship to the study drug was ruled out for all of the serious adverse events except arrhythmia. Adverse events leading to discontinuation of the study drug occurred in 4 subjects in the Parmodia XR evening administration group (myalgia, aortic valve stenosis/asthenia/myalgia/feeling abnormal, eczema, blood creatine kinase [CK] increased). A causal relationship to the study drug could not be ruled out for all events. The outcome was “unresolved” with aortic valve stenosis and “resolved” with all other adverse events.

7.R Outline of the review conducted by PMDA

7.R.1 Clinical positioning of Parmodia XR

The applicant’s explanation about the clinical positioning of Parmodia XR:

It is of clinical significance to develop Parmodia XR, a pemafibrate product that allows once daily administration, for the following reasons: (a) Parmodia, the existing product, needs to be administered twice daily, possibly compromising medication adherence; and (b) patients eligible for treatment with

Parmodia XR often have life-style diseases such as hypertension and type 2 diabetes mellitus, and most of the drugs for these diseases are administered once daily. Parmodia XR was developed as an extended-release tablet product that allows slower pemafibrate release than the existing Parmodia at the absorption site and provides similar efficacy and safety as those of the existing Parmodia by once daily administration. Results of clinical studies confirmed the efficacy and safety as intended. Thus, the clinical positioning is basically the same as that of the existing Parmodia, while Parmodia XR may possibly be selected by patients with poor medication adherence. In order to synchronize the timing of administration with concomitant drugs, an appropriate formulation, either the existing Parmodia (twice daily administration) or Parmodia XR (once daily administration), will be selected based on the dosing regimen of concomitant drugs (daily dosing frequency).

PMDA's view:
Based on the submitted clinical study data, once daily administration of Parmodia XR provides the same efficacy and safety as those achieved by the twice daily administration of the existing Parmodia [see Sections "7.R.2 Efficacy of Parmodia XR" and "7.R.3 Safety"], and making Parmodia XR available in clinical practice is meaningful because it offers a new treatment option for patients with dyslipidemia showing a high TG level, the patient group eligible for treatment with the existing Parmodia. Whereas the existing Parmodia may be administered at a dose less than 0.2 mg/day, the lowest clinically useful dose of Parmodia XR is 0.2 mg/day. For patient populations for whom the dose of Parmodia XR lower than 0.2 mg/day is deemed appropriate, the use of the existing Parmodia instead of Parmodia XR should be considered. Administration of Parmodia XR at a lower-than-usual dose will be discussed in Section "7.R.5 Dosage and administration."

7.R.2 Efficacy of Parmodia XR

(a) TG-lowering effect

The applicant's explanation about the TG-lowering effect of Parmodia XR:
The confirmatory study (Study ER-02) showed that, in patients with dyslipidemia showing a high TG level, rate of change from baseline in fasting serum TG at Week 4, 8, and 12 of the treatment period, the primary endpoint, achieved by the Parmodia XR 0.2 mg/day group and the Parmodia XR 0.4 mg/day group was non-inferior to the endpoint achieved by the existing Parmodia 0.2 mg/group, and that a greater extent of the decrease in the TG level was achieved by the Parmodia XR 0.4 mg/day group than by the Parmodia XR 0.2 mg/day group (Table 8). In Study ER-02, the rate [95% CI] of achieving the fasting serum TG level of <150 mg/dL at Week 12 in FAS was 37.4% [28.5%, 46.9%] in the Parmodia XR 0.2 mg/day group, 51.7% [42.3%, 61.0%] in the Parmodia XR 0.4 mg/day group, and 45.7% [36.4%, 55.2%] in the existing Parmodia 0.2 mg/day group. The long-term treatment study (Study ER-03) confirmed that the TG-lowering effect of Parmodia XR persists without attenuation. The percentage [95% CI] of subjects achieving the mean fasting serum TG level of <150 mg/dL at the last and immediately preceding evaluation time points was 70.2% [61.3%, 78.2%] in the entire Parmodia XR group (FAS). In the 82 subjects in Study ER-03 who increased the dose of Parmodia XR from 0.2 mg/day to 0.4 mg/day, the difference [95% CI] in the mean rate of change in the fasting serum TG level at the last and immediately preceding evaluation time points between before and after the dose increase was −11.4% [−15.7%, −7.1%] (FAS). These results suggest that Parmodia XR has

the same TG-lowering effect as that of the existing Parmodia and that increasing the dose of Parmodia XR is expected to provide a greater TG-lowering effect.

(b) Effect on lipid parameters other than TG

The applicant's explanation about the effect of Parmodia XR on lipid parameters other than TG:

In Study ER-02, both non HDL-C and HDL-C showed similar changes in the Parmodia XR 0.2 mg/day group, in the Parmodia XR 0.4 mg/day group, and in the existing Parmodia 0.2 mg/day group (Table 9). LDL-C showed a tendency to increase both in the Parmodia XR 0.2 mg/day group and in the Parmodia XR 0.4 mg/day group, but the extent was not significantly different from that of the existing Parmodia 0.2 mg/day group (Table 9). In Study ER-03, the long-term administration of Parmodia XR showed no tendency of aggravation of lipid parameter values other than TG (Table 12). The effect of Parmodia XR on lipid parameters other than TG is thus similar to that of the existing Parmodia.

PMDA's view:

Study ER-2 showed the non-inferiority of Parmodia XR 0.4 mg/day and Parmodia XR 0.2 mg/day to the existing Parmodia 0.2 mg/day in the rate of change from baseline in the fasting serum TG level, the primary endpoint, suggesting that both Parmodia XR 0.2 mg/day and Parmodia XR 0.4 mg/day have a TG-lowering effect similar to that with the usual dose of the existing Parmodia. As for the comparison of the efficacy between Parmodia XR 0.2 mg/day and Parmodia XR 0.4 mg/day, whereas the point estimate of the rate of change from baseline in fasting serum TG in Study ER-02 was similar between the 2 groups, increasing the dose of Parmodia XR from 0.2 mg/day to 0.4 mg/day is expected to achieve a further TG level reduction, given the rate of achieving the fasting serum TG level of <150 mg/dL observed in Studies ER-02 and ER-03 and the rate of change in the fasting serum TG level between before and after the dose increase in Study ER-03. Studies ER-02 and ER-03 showed a Parmodia XR-induced increase in LDL-C. Although the increase in LDL-C might possibly aggravate the treatment outcome, PMDA considers it acceptable to use Parmodia XR clinically in the same manner as the existing Parmodia, given the following findings: (1) The extent of LDL-C increase induced by Parmodia XR was not significantly different from that of the existing Parmodia, and (2) the tendency for an increase in LDL-C to become more pronounced with prolonged administration of Parmodia XR has not been observed. Precautions should be provided that patients on treatment with Parmodia XR should be monitored periodically for changes in serum lipid parameters including LDL-C as is the case with the existing Parmodia.

Currently, the suppressive effect of pemafibrate against a cardiovascular event has not been demonstrated in clinical studies (*N Engl J Med.* 2022;387:1923-34). It is therefore unclear whether, similar to the existing Parmodia, Parmodia XR suppresses the cardiovascular events by its TG-lowering effect in the entire Japanese patient population eligible for treatment with fibrates. The effect of pemafibrate on the risk of cardiovascular events through its TG-lowering, LDL-C-increasing, and other activities should be investigated in the future, taking into account the results of the post-marketing database survey to be conducted on Parmodia XR and the existing Parmodia [see Section "7.R.6 Post-marketing investigations].

7.R.3 Safety

PMDA concludes that Parmodia XR does not have problems to impair the clinical usefulness, as judged by incidences of adverse events in clinical studies, results of the discussions below, and the post-marketing safety information on the existing Parmodia. Based on the above, PMDA concludes that Parmodia XR has a clinically acceptable safety profile in patients with dyslipidemia showing a high TG level, given the efficacy of Parmodia XR demonstrated in Section "7.R.2 Efficacy of Parmodia XR."

7.R.3.1 Safety profile of Parmodia XR

The applicant's explanation about adverse events observed in clinical studies:

In either of the submitted studies, there was no significant difference in the safety profile among the Parmodia XR 0.2 mg/day group, the Parmodia XR 0.4 mg/day group, and the existing Parmodia 0.2 mg/day group. The existing Parmodia has not posed any new safety concern about pemafibrate after the market launch. The investigations outlined below were conducted on the anticipated risks associated with the administration of pemafibrate.

(a) Rhabdomyolysis

Rhabdomyolysis, an important identified risk of pemafibrate, was evaluated. Table 14 shows the incidence of rhabdomyolysis-related events[13)] in Studies ER-02 and ER-03, which showed no significant difference between Parmodia XR and the existing Parmodia.

Table 14. Incidence of rhabdomyolysis-related events (safety analysis population)

	Study ER-02 (administration period, 12 weeks)			Study ER-03 (administration period, 52 weeks)
	Parmodia XR		Existing Parmodia	Parmodia XR
	0.2 mg/day (n = 118)	0.4 mg/day (n = 119)	0.2 mg/day (n = 118)	0.2 to 0.4 mg/day (n = 121)
Rhabdomyolysis-related events	1.7 (2)	1.7 (2)	0.8 (1)	6.6 (8)
Blood CK increased	0.8 (1)	0.8 (1)	0 (0)	2.5 (3)
Blood Cr increased	0.8 (1)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	0.8 (1)	3.3 (4)
Renal impairment	0 (0)	0.8 (1)	0 (0)	1.7 (2)

% (number of subjects with events)

Rhabdomyolysis-related events leading to discontinuation of the study drug occurred in 1 subject in the existing Parmodia 0.2 mg/day group of Study ER-02 (myalgia) and in 3 subjects in the Parmodia XR group of Study ER-03 (myalgia in 2 subjects, blood CK increased in 1 subject). A causal relationship to the study drug could not be ruled out for any of the events, but they were recovering or resolved without intervention or by outpatient treatment.

No clinically relevant variations were observed in laboratory values related to rhabdomyolysis or renal impairment (blood CK, blood creatinine [Cr], and estimated glomerular filtration rate [eGFR]) in either of the studies.

13) MedDRA preferred term standardised MedDRA queries (MedDRA SMQ) "Rhabdomyolysis/Myopathy"

Table 15 shows renal impairment and use/non-use of statins in subjects who had rhabdomyolysis-related events in Study ER-02 or ER-03. Rhabdomyolysis-related events were observed in 4 patients with renal impairment who used a statin concomitantly, but they were mild (3 subjects) or moderate (1 subject) and the outcome was "recovered" in all of them. The risk of rhabdomyolysis did not show any tendency to increase in patients with renal impairment who used statins concomitantly.

Table 15. Renal impairment and use/non-use of statins in subjects with rhabdomyolysis-related events in Studies ER-02 and ER-03 (safety analysis population)

			Study ER-02 (administration period, 12 weeks)			Study ER-03 (administration period, 52 weeks)
			Parmodia XR		Existing Parmodia	Parmodia XR
			0.2 mg/day	0.4 mg/day	0.2 mg/day	0.2 to 0.4 mg/day
No. of subjects with rhabdomyolysis-related events			2	2	1	8
Breakdown	With renal impairment[a]	Statin co-administered	0	1	0	3
		Statin not co-administered	0	0	0	1
	Without renal impairment[b]		2	1	1	4

a eGFR <60 mL/min/1.73 m^2
b eGFR ≥60 mL/min/1.73 m^2

The above results suggest that the risk of rhabdomyolysis induced by Parmodia XR does not exceed the risk by the existing Parmodia, allowing control by the same precautions as those given in administering the existing Parmodia.

(b) Effect on liver

Due to the potential impact of pemafibrate on the hepatic function, the effect of Parmodia XR on the liver was assessed. Liver disorder[14)] occurred in 1.7% (2 of 118 subjects, alanine aminotransferase [ALT] increased in 2 subjects) in the Parmodia XR 0.2 mg/day group and in 0.8% (1 of 118 subjects, ALT increased) in the existing Parmodia 0.2 mg/day group in Study ER-02, but in no subjects in Study ER-03. There was no liver disorder leading to discontinuation of the study drug.

Aspartate aminotransferase (AST) increased to ≥3 times the upper limit of normal (ULN) in 0.8% (1 of 119) of subjects in the Parmodia XR 0.4 mg/day group of Study ER-02, in 0.8% (1 of 121) of subjects in the Parmodia XR group of Study ER-03, and ALT increased to ≥3 times the ULN in 0.8% (1 of 121) of subjects in the Parmodia XR group of Study ER-03.

Gallstone formation was reported in subjects treated with the existing Parmodia, while no adverse events corresponding to "Gallstone related disorders (SMQ)" were observed in subjects receiving Parmodia XR.

The above results suggest that the effect of Parmodia XR on liver function does not exceed the risk with the existing Parmodia and that the risk can be controlled by the same precautions as those with the existing Parmodia, including contraindication against "patients with serious liver disorder," "patients with hepatic cirrhosis with Child-Pugh class B or C or patients with biliary obstruction," and "patients with gallstone."

14) MedDRA SMQ "Drug related hepatic disorders - comprehensive search (SMQ)

(c) Administration in patients with renal impairment

Since the exposure to pemafibrate is higher in patients with renal impairment than in patients with a normal renal function, the effect of Parmodia XR in patients with renal impairment was investigated. Table 16 shows the incidence of adverse events by renal function in Studies ER-02 and ER-03. In the subpopulation with renal impairment (eGFR <60 mL/min/1.73 m^2) as well, the incidence of adverse events was similar between the Parmodia XR group and the existing Parmodia group. In Studies ER-02 and ER-03, inclusion/exclusion criteria were not specified for renal function-related laboratory values (eGFR, serum Cr). In subjects included these studies, eGFR was <30 mL/min/1.73 m^2 in only 2 subjects of Study ER-03. Neither of these 2 subjects showed death or serious adverse event other than death, but there are only limited safety data in patients with eGFR of <30 mL/min/1.73 m^2.

Table 16. Incidence of adverse events by renal function (safety analysis population)

Baseline eGFR	Study ER-02 (administration period, 12 weeks)			Study ER-03 (administration period, 52 weeks)
	Parmodia XR		Existing Parmodia	Parmodia XR
	0.2 mg/day	0.4 mg/day	0.2 mg/day	0.2-0.4 mg/day
<60 mL/min/1.73 m^2	n = 15	n = 19	n = 20	n = 22
Adverse events	20.0 (3)	31.6 (6)	15.0 (3)	81.8 (18)
Serious adverse events	6.7 (1)	0 (0)	0 (0)	0 (0)
Adverse events leading to discontinuation of the study drug	0 (0)	0 (0)	0 (0)	13.6 (3)
≥60 mL/min/1.73 m^2	n = 103	n = 100	n = 98	n = 99
Adverse events	17.5 (18)	26.0 (26)	27.6 (27)	83.8 (83)
Serious adverse events	1.0 (1)	0 (0)	1.0 (1)	7.1 (7)
Adverse events leading to discontinuation of the study drug	0 (0)	0 (0)	2.0 (2)	4.0 (4)

% (number of subjects with events)

Based on the results of the post-marketing clinical study (PALT02 study) conducted to investigate the PK and safety in patients with renal impairment receiving the existing Parmodia 0.1 mg twice daily for 12 weeks, the package insert of the existing Parmodia was revised in October 2022. In the revised package insert, contraindications for patients with renal impairment with serum Cr ≥2.5 mg/dL or creatinine clearance (CCr) <40 mL/min were removed, and related precautions were modified.

Given that the exposure to pemafibrate (AUC) in multiple administration at the same daily dose is similar between Parmodia XR and the existing Parmodia [see Section “6.R.1 Appropriateness of dosage and administration”] and that the effect of renal impairment on PK of pemafibrate is minor in patients receiving the existing Parmodia, Parmodia XR is unlikely to cause an increase in the exposure to pemafibrate markedly exceeding the extent expected from the results with the existing Parmodia by worsening of renal impairment. Given that the incidence of adverse events was similar between subjects with normal renal function and subjects with diminished renal function in clinical studies (Tables 15 and 16), the applicant considered it acceptable to administer Parmodia XR to patients with renal impairment with the same precautions as those for the existing Parmodia.

PMDA's view based on the applicant's explanation (a) through (c):
The submitted clinical study data do not pose any safety concerns unique to Parmodia XR compared with the existing Parmodia, including those for which precautions are raised with the existing Parmodia, such as the risk of rhabdomyolysis, the risk of liver disorder, and the risk of the use in patients with renal impairment. The applicant's policy to raise the same precautions as those against the existing Parmodia is appropriate. Precautions for the population, including patients with renal impairment, for whom a consideration of lower dose or dose reduction is required in the package insert of the existing Parmodia will be discussed in Section "7.R.5 Dosage and administration."

7.R.3.2 Measures against mix-up of Parmodia XR and existing Parmodia and against administration error

The applicant's explanation about the preventive measures against the risk of mix-up between Parmodia XR and the existing Parmodia:
There is a potential risk of mix-up between Parmodia XR and the existing Parmodia under the circumstances described below:
(a) Physician's error (mix-up of the prescription of Parmodia XR with the existing Parmodia)
(b) Pharmacist's error (mixing up while dispensing or providing incorrect dosing and usage instructions to the patient)
(c) Patient's error (the patient with past experience of taking the existing Parmodia or Parmodia XR uses the newly prescribed drug [Parmodia XR or the existing Parmodia] according to the wrong dosage regimen)

When the existing Parmodia is taken according to the dosage regimen for Parmodia XR (once daily), the ingested dose is smaller than the intended dose, posing no safety problem while possibly reducing the TG-lowering effect of pemafibrate. When Parmodia XR is taken according to the dosage regimen for the existing Parmodia (twice daily) by mistake, over-dose administration at twice the intended dose occurs. However, twice daily administration of Parmodia XR 0.4 mg is unlikely to pose serious safety concern because tolerability of multiple administration of Parmodia XR 0.8 mg has been confirmed in the clinical study [see Section "7.1 Japanese phase II study].

In order to prevent the mix-up between Parmodia XR and the existing Parmodia as described (a) to (c) above, the following measures will be taken: (1) The color scheme and design of both the drug product and packaging (including blister packs, bottle caps, and labels) for Parmodia XR will be intentionally differentiated from those of the existing Parmodia; and (2) the packaging of Parmodia XR will display either the words "once daily," "extended-release tablets," or "extended-release formulation" to prevent dosage errors. Additionally, the applicant plans to provide information to healthcare professionals to prevent the confusion between Parmodia XR and the existing Parmodia.

PMDA's view:
The following policy of the applicant is appropriate:
After the market launch of Parmodia XR, there will be both Parmodia XR and the existing Parmodia with different dosage regimens available for use in clinical practice. In order to prevent the mix-up, the applicant plans to enhance distinguishability through the color scheme, design, and labeling of the

formulation and packaging of both the existing Parmodia and Parmodia XR and provide information to healthcare professionals.

7.R.4 Indication

PMDA's view:

Parmodia XR was developed as a drug product that provides the same efficacy and safety by once daily administration as those of the existing Parmodia [see Section "7.R.1 Clinical positioning of Parmodia XR], and results of Studies ER-02 and ER-03 confirmed the efficacy and safety as intended by the applicant [see Sections "7.R.2 Efficacy of Parmodia XR" and "7.R.3 Safety"]. Accordingly, indicating Parmodia XR for "Hyperlipidemia (including familial hyperlipidemia)" as is the case with the existing Parmodia is considered appropriate.

7.R.5 Dosage and administration

7.R.5.1 Appropriateness of dosage and administration

The applicant's explanation about the dosage and administration of Parmodia XR:

Parmodia XR was developed as a drug product which, by once daily administration, provides the same efficacy and safety as those of the existing Parmodia [see Section "7.R.1 Clinical positioning of Parmodia XR"]. Study CR-01 showed that there is no significant difference in the exposure to pemafibrate (AUC) between once daily administration of Parmodia XR 0.2 or 0.4 mg/day and twice daily administration of the existing Parmodia [see Section "6.R.1 Appropriateness of dosage and administration"]. Study ER-02 compared the rate of the decrease in fasting serum TG by the Parmodia XR and by the existing Parmodia, and demonstrated that once daily administration of Parmodia XR 0.2 or 0.4 mg was non-inferior to twice daily administration of the existing Parmodia 0.1 mg, and that a greater TG-lowering effect is expected by Parmodia XR 0.4 mg/day than by 0.2 mg/day [see Section "7.R.2 Efficacy of Parmodia XR"]. Furthermore, Study ER-03 showed that there is no significant difference in the TG-lowering effect between Parmodia XR morning administration and Parmodia XR evening administration (Table 11). As for safety, neither Parmodia XR 0.2 mg/day nor 0.4 mg/day caused risk exceeding that induced by the existing Parmodia [see Section "7.R.3 Safety"].

Based on the above, the recommended usual dose of Parmodia XR is 0.2 mg/day as is the case with the existing Parmodia, and the dose 0.4 mg/day should be available for use to cope with the risk factors of onset/progression of arteriosclerosis necessitating a higher level of treatment target. Parmodia XR may be administered at any time of the day. In order to clarify the dosing guide for 0.4 mg/day, the proposed dosage and administration is modified as shown below.

Dosage and Administration (draft)

The usual adult dosage is 0.2 mg of pemafibrate orally administered once daily. The dose may be <u>increased</u> ~~adjusted according to the patient's age and symptoms. The maximum dose should be~~ <u>up to</u> 0.4 mg once daily <u>depending on the extent of the elevated triglyceride level</u>.

(The underline words are added to the proposed text.
The strikethrough words are deleted from the proposed text.)

Based on the results of each clinical study submitted, PMDA concludes it acceptable to handle each of the following dosage regimens equally: (a) Administration of Parmodia XR (0.2 mg) once daily and administration of the existing Parmodia (0.1 mg, the usual dose) twice daily and (b) administration of Parmodia XR (0.4 mg) once daily and administration of the existing Parmodia (0.2 mg, the maximal dose) twice daily. Accordingly, the modified dosage regimen proposed by the applicant is appropriate.

7.R.5.2 Administration in patients with renal impairment and patients on statin therapy

The applicant's explanation about Parmodia XR administration in patients with renal impairment with eGFR of <30 mL/min/1.73 m^2 and patients with abnormal renal laboratory values necessitating statin co-administration:

The same precautions for Parmodia XR as for the existing pemafibrate should be provided to these patients because (1) PK of pemafibrate is unlikely to differ between Parmodia XR and the existing Parmodia in patients with renal impairment, and (2) the incidence of adverse events with Parmodia XR in patients with renal impairment enrolled in the clinical studies on Parmodia XR did not tend to increase compared to the incidence observed with the existing Parmodia administration [see Section "7.R.3.1 Safety profile of Parmodia XR"].

The applicant's explanation about precautions for the existing Parmodia:

The package insert of the existing Parmodia include the following precautions: (a) If eGFR is <30 mL/min/1.73 m^2, pemafibrate should be started from the low dose or administered at a longer interval. The maximum dose should be 0.2 mg per day"; and (b) if coadministration of pemafibrate and a statin is necessitated in patients with abnormal renal laboratory data, pemafibrate should be started from a low dose. In the post-marketing clinical study (PALT02 study) of the existing Parmodia [see Section "7.R.3 Safety]), administration of the existing Parmodia to patients with severe renal impairment at 0.2 mg/day did not increase the exposure to pemafibrate compared to patients with mild renal impairment, and no particular safety problems were noted. Other clinical results obtained after the market launch of the existing Parmodia did not exhibit any indications of an increased risk of rhabdomyolysis in patients with renal impairment. The above precautions[15)] in the package insert of the existing Parmodia requiring administration at a low dose or at longer intervals in patients with renal impairment were established by referring to the package insert of fenofibrate. However, no additional data have been obtained to support the appropriateness of such administration methods after the market launch of the existing Parmodia. In particular, there have been no cases of administering the existing Parmodia according to any of the following procedures: (1) Administration at a low starting dose or at longer intervals to patients with renal impairment, or (2) starting administration at a lower-than-usual dose to patients with abnormal renal laboratory values who were on statin therapy. These findings suggest that, in patients with renal impairment with eGFR of <30 mL/min/1.73 m^2, administering pemafibrate 0.2 mg/day (the usual dose for the existing Parmodia) is acceptable but the dose should not be increased from the usual dose, given the limited use experience in this patient group. When co-administration of pemafibrate with a statin is necessitated in patients with abnormal

15) The package insert of the existing Parmodia at the initial approval (2017) included the following description: "Rhabdomyolysis with acute deterioration in renal function may occur. Prior to the use of pemafibrate, patients should undergo a renal function test. If serum creatinine is ≥2.5 mg/dL, administration should be continued. If serum creatinine is ≥1.5 mg/dL and <2.5 mg/dL, pemafibrate should be administered at a low starting dose or at longer intervals."

renal laboratory values, starting the administration at the usual dose is feasible if performed under periodic renal function tests.

Based on the above, the following cautions will be raised in the package insert of Parmodia XR: Rhabdomyolysis may occur in patients with renal impairment with eGFR of <30 mL/min/1.73 m.^{2} Pemafibrate should not be administered at a higher-than-usual dose in this patient group. Also, the following precautions will be provided: Should coadministration of pemafibrate with a statin be necessitated in patients with abnormal renal laboratory values, periodic renal function tests should be conducted. If aggravation of renal function is noted, pemafibrate should be discontinued immediately.

PMDA's view:
The submitted clinical study data show no clear tendency of increase in the incidence of adverse events in patients with renal impairment receiving Parmodia XR compared to those receiving the existing Parmodia. Additional precautions other than those for the existing Parmodia are unnecessary regarding administration to this patient group. Given the information available after the market launch of the existing Parmodia, Parmodia XR administration at the usual dose to patients with renal impairment with eGFR of <30 mL/min/1.73 m^2 is acceptable, but the dose should not be increased. The applicant's policy is appropriate currently. PMDA considers it acceptable to start Parmodia XR administration at the usual dose in patients with abnormal renal laboratory values on statin therapy on the assumption that periodic renal function tests are conducted as is the case with the existing Parmodia.

7.R.5.3 Administration in patients with hepatic impairment and in patients on treatment with drugs requiring cautions in coadministration

The applicant's explanation about Parmodia XR administration in the following patients for whom the package insert of the existing Parmodia warrants caution of dose reduction: (a) Patients with hepatic disorder (hepatic cirrhosis of Child-Pugh grade A etc.) or with a history of hepatic disorder and (b) patients on treatment with drugs requiring caution in co-administration (clopidogrel sulfate [clopidogrel], clarithromycin, human immunodeficiency virus [HIV] protease inhibitors):

(a) Patients with hepatic disorder (patients with hepatic cirrhosis of Child-Pugh grade A etc.) or with history of hepatic disorder

Results of the pooled analysis of multiple clinical studies administering the existing Parmodia for 12 or 52 weeks suggest that the risk of pemafibrate-induced hepatic impairment does not exceed the risk caused by fenofibrate. However, at the initial approval of the existing Parmodia, consideration of dose reduction was warranted as necessary, as is the case with fenofibrate, taking account of the following observations: (a) In the clinical study (Study K-877-10) conducted to assess PK after a single-dose administration of the existing Parmodia 0.2 mg in subjects with hepatic impairment and patients with normal hepatic function, the exposure to pemafibrate was higher in patients with hepatic cirrhosis of Child-Pugh grade A and in patients with hepatic steatosis than in subjects with normal hepatic function; and (b) there were only limited safety data in patients with hepatic impairment.

After the market launch of the existing Parmodia, a placebo-controlled clinical study (Study K-877-FL-01) was conducted to investigate the efficacy and safety of the existing Parmodia

0.4 mg/day administered for 72 weeks in patients with hepatic impairment (patients with nonalcoholic fatty liver disease [NAFLD] with high hepatic lipid content, high ALT, and high liver stiffness). Results showed that, compared to the placebo group, the existing Parmodia 0.4 mg/day group did not show any increase in the incidence of adverse events. Neither was worsening of liver function test nor increase in liver stiffness observed, eliminating safety concerns on the existing Parmodia 0.4 mg/day even in patients with hepatic disorder with possible increased exposure to pemafibrate. Administration of the existing Parmodia was not considered to increase the risk of hepatic disorder.

Given the information on the existing Parmodia after the market launch and on Parmodia XR regarding the PK profile and effect on the liver [see Section "7.R.3.1 Safety profile of Parmodia XR"], Parmodia XR need not be administered at a lower-than-usual dose (0.2 mg/day) to patients with hepatic disorder (patients with hepatic cirrhosis of Child-Pugh grade A etc.) or with a history of hepatic disorder, provided that they are closely monitored during the treatment.

(b) Patients on treatment with drugs requiring caution in co-administration (clopidogrel, clarithromycin, HIV protease inhibitors)

The clinical drug-drug interaction study of pemafibrate suggested an approximately 2-fold increase in the exposure to pemafibrate in the combination therapy than in pemafibrate monotherapy. In the initial approval of the existing Parmodia, the advice was included in the package insert warranting the dose reduction of pemafibrate as necessary in co-administering pemafibrate with the above drugs.

In the post-marketing placebo-controlled clinical study (PROMINENT study) conducted to assess the efficacy and safety of the existing Parmodia 0.4 mg/day in patients with type 2 diabetes mellitus at a high cardiovascular risk with the high TG level and low HDL-C level, no significant difference was observed in the incidence of adverse events between patients with clopidogrel co-administration and patients without co-administration. These results suggest that, although co-administration of the existing Parmodia with clopidogrel etc., increases the exposure to pemafibrate approximately 2-fold, there is no safety concern with the existing Parmodia 0.4 mg/day co-administered with clopidogrel.

Given the post-marketing information on the existing Parmodia and the PK profile of pemafibrate, the dose of Parmodia XR need not be reduced below the usual dose (0.2 mg/day) in co-administering with drugs such as clopidogrel for which caution is advised, provided that the patient's condition is carefully monitored.

PMDA's view:

Given the post-marketing information on the existing Parmodia, the use of Parmodia XR is acceptable for the following patient groups eligible for receiving the existing Parmodia 0.2 mg/day, at a dose of 0.2 mg/day while monitoring the patient's condition, as is the case with the existing Parmodia: (a) Patients with hepatic disorder (patients with hepatic cirrhosis of Child-Pugh grade A etc.) or with a history of hepatic disorder and (b) patients on treatment with drugs requiring caution in co-administration (clopidogrel, clarithromycin, HIV protease inhibitors). However, Parmodia XR should not be administered to patients for whom a reduced dosage below 0.2 mg/day of the existing Parmodia is deemed appropriate. Options other than Parmodia XR should be considered.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing investigations for Parmodia XR:

For reasons provided below, there are currently no safety concerns that require clarification after the market launch of Parmodia XR. Thus, a risk evaluation of each safety specification after the market launch of Parmodia XR is feasible by the conduct of the usual pharmacovigilance activities and inclusion of Parmodia XR-treated patients in the post-marketing database survey (cardiovascular survey) to be conducted as an efficacy survey/study on the existing Parmodia.

- The safety profile of Parmodia XR is demonstrated to be the same as that of the existing Parmodia.
- A total of 3674 patients (as of July 2, 2022) are enrolled in the ongoing specified use-results surveys (long-term use) on the existing Parmodia, and no safety concerns have been noted.
- The safety information accumulated in the most updated periodic safety report (No. 7) on the existing Parmodia does not reveal any risk requiring revision of "Precautions," etc.
- "Myalgia," "Rash," and "Pruritus" were added to the "Adverse reactions" section in the package insert of the existing Parmodia from the post-marketing safety information including spontaneous reports on the existing Parmodia. These events will also be included in the package insert of Parmodia XR to raise awareness.
- Including patients treated with Parmodia XR (expected sample size, approximately 700 subjects) in the post-marketing database survey under development on the efficacy of the existing Parmodia (cardiovascular event surveillance using Medical Information Database Network [MID-NET]) is expected to allow collection of laboratory data of renal and hepatic functions (serum Cr, AST, ALT, CK, etc.), serum lipid levels (TG, LDL-C, etc.), and cardiovascular events.

PMDA's view:

The applicant's policy on the post-marketing investigations is acceptable judging from the applicant's explanation and the following findings: (1) There is no significant difference in the exposure (AUC) to pemafibrate after 4-week multiple administration between Parmodia XR (once daily) and the existing Parmodia (twice daily) [see Section "6.R.1 Appropriateness of dosage and administration"], suggesting that Parmodia XR is unlikely to have a greater potential risk than the existing Parmodia from the aspect of PK; and (2) patient populations at a higher risk of adverse effects with Parmodia XR than with the existing Parmodia are unlikely.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that Parmodia XR has efficacy comparable to that of the existing Parmodia in patients with hyperlipidemia (including familial hyperlipidemia) who are eligible for treatment with fibrates, and that Parmodia XR has acceptable safety in view of its benefits. Parmodia XR is clinically meaningful because it offers a new therapeutic option for patients with hyperlipidemia who are eligible for treatment with fibrates. The contents of precautionary statements in the package insert, post-marketing investigations, etc., should be further discussed.

PMDA has concluded that Parmodia XR may be approved if Parmodia XR is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

May 11, 2023

Product Submitted for Approval

Brand Name	Parmodia XR Tablets 0.2 mg Parmodia XR Tablets 0.4 mg
Non-proprietary Name	Pemafibrate
Applicant	Kowa Company, Ltd.
Date of Application	September 12, 2022

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

In the sections below, "Parmodia Tab. 0.1 mg" is expressed as "the existing Parmodia" as indicated in the Appendix, unless specified otherwise.

1.1 Clinical positioning of Parmodia XR

PMDA concluded that making Parmodia XR available in clinical practice is meaningful because it offers a new treatment option for patients with dyslipidemia showing a high TG level, the patient group eligible for treatment with the existing Parmodia. In addition to this conclusion, the PMDA's conclusions described in Section "7.R.1 Clinical positioning of Parmodia XR" in the Review Report (1) were supported by the expert advisors.

1.2 Efficacy

The expert advisors supported the PMDA's conclusions described in Section "7.R.2 Efficacy of Parmodia XR" in the Review Report (1), including the PMDA's conclusion that both Parmodia XR 0.2 mg/day and Parmodia XR 0.4 mg/day have a TG-lowering effect similar to that with the usual dose of the existing Parmodia and that increasing the dose of Parmodia XR from 0.2 mg/day to 0.4 mg/day is expected to achieve a further TG level reduction. The following comments were raised from the expert advisors:

- The post-marketing clinical study of the existing Parmodia (PROMINENT study) failed to demonstrate the effect to suppress cardiovascular events (*N Engl J Med.* 2022;387:1923-34). In

terms of improving hypertriglyceridemia to suppress cardiovascular events, the clinical usefulness of pemafibrate is not clearly evident, as with other existing fibrate agents. Pemafibrate is nevertheless useful in improving hypertriglyceridemia for the prevention of acute pancreatitis.

1.3 Safety

The expert advisors supported the PMDA's conclusions described in Section "7.R.3.1 Safety profile of Parmodia XR" in the Review Report (1), including the PMDA's conclusion that there are no known safety concerns unique to Parmodia XR compared with the existing Parmodia. The expert advisors commented that (1) increased serum Cr levels and venous thrombosis should be regarded as adverse reactions to pemafibrate and information on these events should be disseminated; and (2) information on the incidence of venous thrombosis should be collected continuously, for the following reasons:

(i) In the post-marketing clinical study of the existing Parmodia (PROMINENT study), the incidence of venous thrombosis (including pulmonary thromboembolism) and chronic kidney disease was higher in the pemafibrate group than in the placebo group (*N Engl J Med.* 2022;387:1923-34).

(ii) A randomized comparative study of fenofibrate, a drug in the same class, suggested the risk of increased serum Cr levels, pulmonary thromboembolism, and deep vein thrombosis (*Lancet.* 2006;366:1849-61).

Based on the above, PMDA considers that, as soon as the clinical study report on the post-marketing clinical study of the existing Parmodia (PROMINENT study) becomes available, data contained in the report should be reviewed in detail and the necessity of issuing an alert about increased serum Cr and venous thrombosis (as risks associated with pemafibrate) should be discussed. PMDA also requested that the applicant take actions to ensure appropriate data collection regarding venous thrombosis occurring in patients receiving pemafibrate after the market launch. The applicant responded that the planned post-marketing database survey on both the existing Parmodia and Parmodia XR (cardiovascular events surveillance) [see Table 18] allows exploratory data collection regarding the incidences of venous thrombosis as well as cardiovascular events, the primary endpoint.

The expert advisors supported the PMDA's conclusions described in Section "7.R.3.2 Measures against mix-up of Parmodia XR and existing Parmodia and against administration error" in the Review Report (1), including the PMDA's conclusion supporting the applicant's plans to refine color schemes and design of the drug product and package of both the existing Parmodia and Parmodia XR and to provide relevant information to healthcare professionals.

1.4 Dosage and Administration

The expert advisors supported the PMDA's conclusions described in Section "7.R.5 Dosage and administration" in the Review Report (1), including the following PMDA's conclusion:

The modified dosage and administration (draft) shown in Section "7.R.5.1 Appropriateness of dosage and administration" in the Review Report (1) is appropriate. Administering Parmodia XR at the usual dose to patients with renal impairment with eGFR <30 mL/min/1.73 m^2 is acceptable, but the dose should not be increased in this population.

1.5 Risk management plan (draft)

The expert advisors supported the PMDA's conclusions described in Section "7.R.6 Post-marketing investigations" in the Review Report (1), including the following PMDA's conclusion:

Given the data obtained after the market launch of the existing Parmodia, the applicant should conduct a risk evaluation of each safety specification after the market launch of Parmodia XR by conducting the usual pharmacovigilance activities and by enrolling Parmodia XR-treated patients in the post-marketing database survey (cardiovascular survey) to be conducted as an efficacy survey/study on the existing Parmodia.

PMDA has concluded that the current risk management plan (draft) for Parmodia XR should include the safety and efficacy specifications presented in Table 17, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Table 18.

Table 17. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Rhabdomyolysis	• Increased LDL-cholesterol level	• Patients with hepatic impairment • Patients with renal impairment • Elderly patients aged ≥75 years • Long-term safety
Efficacy specification		
• Long-term efficacy of pemafibrate in clinical use • Reduction of cardiovascular events		

No change arises from the present application.

Table 18. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Specified use-results survey (long-term use) [existing Parmodia] • Post-marketing clinical study (cardiovascular outcome study) [existing Parmodia]	• Specified use-results survey (long-term use) [existing Parmodia] • Post-marketing database survey (cardiovascular events survey) [existing Parmodia, Parmodia XR] • Post-marketing clinical study (cardiovascular outcome study) [existing Parmodia]	Not applicable

Underlined part: Addition in this application

1.6 Specifications for [redacted] of [redacted]

PMDA concluded that the additional specification for [redacted] of [redacted] ([redacted]) was appropriate, given the results of batch analysis submitted. Based on this and the reviews presented in the Review Report (1), PMDA concluded that the quality of the drug substance and the drug product was controlled adequately.

1.7 Bioequivalence between the to-be-marketed formulations (Parmodia XR 0.2 mg and 0.4 mg tablets) and the formulation used in Study ER-02 (Parmodia XR 0.2 mg and 0.4 mg tablets)

The applicant submitted results of the dissolution study, which was still ongoing when the Review Report (1) was prepared. Based on the submitted data, PMDA confirmed the bioequivalence between

the to-be-marketed formulation and the formulation used in Study ER-02 for both Parmodia XR 0.2 mg and 0.4 mg tablets.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that Parmodia XR may be approved for the following indication and dosage and administration, with the following approval condition. Parmodia XR is not classified as a biological product or a specified biological product. The drug product is not classified as a poisonous drug or a powerful drug. The re-examination period of Parmodia XR is the remainder of the re-examination period for the approval of the existing Parmodia (Parmodia Tab. 0.1 mg) (until July 2, 2025).

Indication

Hyperlipidemia (including familial hyperlipidemia)

Dosage and Administration

The usual adult dosage is 0.2 mg of pemafibrate orally administered once daily. The dose may be increased up to 0.4 mg once daily depending on the extent of the elevated triglyceride level.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}12h}$	AUC from 0 to 12 hours after administration
$AUC_{0\text{-}24h}$	AUC from 0 to 24 hours after administration
BE	Bioequivalence
BE Guideline for Different Strengths	Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms (PMSB/ELD Notification No. 64 dated February 14, 2000, amended by PSEHB/PED Notification No. 0319-1 dated March 19, 2020)
BE Guidelines for Formulation Changes	Guideline for Bioequivalence Studies for Formulation Changes of Oral Solid Dosage Forms (PMSB/ELD Notification No. 67 dated February 14, 2000, partially revised by PSEHB/PED Notification No. 0319-1 dated March 19, 2020)
CCr	Creatinine clearance
CI	Confidence interval
CK	Creatine Kinase
Clopidogrel	Clopidogrel sulfate
C_{max}	Maximum plasma concentration
CQA	Critical quality attribute
Cr	Creatinine
CS	Compound Symmetry
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
HDL-C	High density lipoprotein-cholesterol
HDPE	High-density polyethylene
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
ICH Q1E Guideline	"Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003)
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LDL-C	Low density lipoprotein-cholesterol
MedDRA SMQ	MedDRA preferred term standardised MedDRA queries
MID-NET	Medical Information Database Network
NAFLD	Nonalcoholic fatty liver disease
non HDL-C	Non high density lipoprotein-cholesterol
The existing Parmodia	Parmodia Tab. 0.1 mg
Parmodia XR	Parmodia ER Tablets, Parmodia XR Tablets
PE	Polyethylene
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PP	Polypropylene
PPAR	Peroxisome proliferator-activated receptor
PVC	Polyvinyl chloride
PVDC	Polyvinylidene chloride
RH	Relative humidity
Statin	Hydroxymethylglutaryl coenzyme A reductase inhibitor
Study CR-01	Study K-877-CR-01
Study ER-02	Study K-877-ER-02
Study ER-03	Study K-877-ER-03
$t_{1/2}$	Elimination half-life
TC	Total cholesterol
TG	Triglyceride

t_{max}	Time to maximum plasma concentration
ULN	Upper limit of normal
UV/VIS	Ultraviolet-visible spectroscopy