Report on the Deliberation Results

September 2, 2025
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Brand Name	Fujichenon Granular Tablets 125
Non-proprietary Name	Chenodeoxycholic Acid (JAN*)
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	February 26, 2025

Results of Deliberation

In its meeting held on August 29, 2025, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 10 years. The drug product is not classified as a poisonous drug or a powerful drug.

Approval Condition

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

** Japanese Accepted Name (modified INN)*

Review Report

August 18, 2025
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	Fujichenon Granular Tablets 125
Non-proprietary Name	Chenodeoxycholic Acid
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	February 26, 2025
Dosage Form/Strength	Tablets: Each tablet contains 25 mg of chenodeoxycholic acid. One packet contains 5 tablets (a total of 125 mg of chenodeoxycholic acid).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage, and (8-2) Drug in an additional dosage form (not during the re-examination period)
Items Warranting Special Mention	Orphan drug (Orphan Drug Designation No. 552 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 1216-1 dated December 16, 2022)
Reviewing Office	Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of cerebrotendinous xanthomatosis, 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. The product 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.

Indication

Cerebrotendinous xanthomatosis

Dosage and Administration

The usual starting dose for adults is 250 mg/day of chenodeoxycholic acid, followed by a dose increase in increments of 250 mg up to the maintenance dose of 750 mg/day, which is orally administered in 3 divided

doses daily on consecutive days. The dose may be adjusted as appropriate according to the patient's condition; however, the daily dose should not exceed 1000 mg, and the single dose should not exceed 375 mg.

The usual starting dose for children is 5 mg/kg/day of chenodeoxycholic acid, followed by a dose increase in increments of 5 mg/kg up to the maintenance dose of 15 mg/kg/day, which is orally administered in 3 divided doses daily on consecutive days. The dose may be adjusted as appropriate according to the patient's condition; however, the daily dose should not exceed 15 mg/kg or a total of 750 mg, and the single dose should not exceed 250 mg.

Approval Condition

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

Attachment

Review Report (1)

July 4, 2025

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	Fujichenon Granular Tablets 125
Non-proprietary Name	Chenodeoxycholic Acid
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	February 26, 2025
Dosage Form/Strength	Tablets: Each tablet contains 25 mg of chenodeoxycholic acid. One packet contains 5 tablets (a total of 125 mg of chenodeoxycholic acid).

Proposed Indication

Cerebrotendinous xanthomatosis

Proposed Dosage and Administration

The usual starting dose for adults is 250 mg/day of chenodeoxycholic acid, followed by a dose increase in increments of 250 mg up to the maintenance dose of 750 mg/day, which is orally administered in 3 divided doses daily. The dose may be adjusted as appropriate according to the patient's condition; however, the daily dose should not exceed 1000 mg, and the maximum single dose should be 375 mg.

The usual starting dose for children is 5 mg/kg/day of chenodeoxycholic acid, followed by a dose increase in increments of 5 mg/kg up to the maintenance dose of 15 mg/kg/day, which is orally administered in 3 divided doses daily. The dose may be adjusted as appropriate according to the patient's condition; however, the daily dose should not exceed 15 mg/kg or a total of 750 mg.

Table of Contents

List of Abbreviations

See Appendix.

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

Cerebrotendinous xanthomatosis (CTX) is an autosomal recessive genetic disorder caused by mutations in the *sterol 27-hydroxylase* (*CYP27A1*) gene. CYP27A1, which is encoded by the *CYP27A1* gene, is an essential enzyme in the synthesis of primary bile acids in the liver. In CTX patients, decreased CYP27A1 activity leads to a decrease in the synthesis of chenodeoxycholic acid (hereinafter referred to as "CDCA"), one of the primary bile acids, and an increase in the serum cholestanol concentration. Furthermore, since CDCA induces a negative feedback on cholesterol 7α-monooxygenase (CYP7A1), which is the rate-limiting enzyme in the bile acid synthesis pathway, the negative feedback mechanism on CYP7A1 does not function in CTX patients due to the decreased CDCA, resulting in increased cholestanol production. CTX presents with various clinical symptoms due to the deposition of elevated cholestanol in systemic organs such as the brain, spinal cord, and tendons. CTX is broadly classified into 3 forms: (a) classical form presenting with a variety of clinical symptoms (jaundice, cholestasis, diarrhoea, cataract, neurodevelopmental delay, epilepsy, gait disturbance, etc.); (b) spinal form presenting with spastic paraplegia as the main symptom; and (c) non-neurological form characterized by the absence of neurological symptoms.

In Japan, no drugs have been approved for the indication of "cerebrotendinous xanthomatosis." Although cholic acid (brand name: Orphacol Capsules 50 mg) is approved for the indication of inborn errors of bile acid metabolism including CTX, the Cerebrotendinous Xanthomatosis Management Guideline 2018 (approved by the Japanese Society of Neurology on May 23, 2018)[1)] states that the main treatment for CTX is replacement therapy with CDCA, and the CDCA product Chino Capsules 125[2)] (hereinafter referred to as "Chino Capsules") is used off-label in clinical practice. Treatment with CDCA is expected to normalize the feedback mechanism on CYP7A1, improve biochemical findings such as an increased serum cholestanol concentration, and suppress cholestanol accumulation in tissues.

In view of the above, the Japanese Society of Neurological Therapeutics submitted a request to the Ministry of Health, Labour and Welfare for the development of CDCA for the indication of CTX. The 31st meeting of the Study Group on Unapproved and Off-label Drugs of High Medical Need concluded that there is a high medical need to use CDCA for this indication. Accordingly, the applicant was requested to undertake the development. Given that early initiation of treatment is important for the genetic disorder, CTX, the applicant investigated dosage forms that can easily be taken, even by children, and developed Fujichenon Granular Tablets 125 (hereinafter referred to as "Fujichenon"), a mini-tablet formulation of CDCA (one packet contains 5 tablets).

The applicant has recently filed an application for marketing approval of Fujichenon, considering that its efficacy and safety for CTX have been demonstrated by clinical study results and other related information.

Although Fujichenon has not been approved outside Japan, other CDCA products with the indication of CTX have been approved in Europe and the US.

---

1) https://www.ctx-guideline.jp/wp-content/uploads/2021/04/141_19.pdf (last accessed on June 27, 2025)

2) The product was approved with the brand name of Chino Capsules "Fujimoto" for the indication of "dissolution of cholesterol gallstones without shell calcification" in May 1983, and the brand name was changed to "Chino Capsules 125" in March 2006.

In Japan, Fujichenon has been designated as an orphan drug with the intended indication of CTX (Orphan Drug Designation No. 552 of 2022 [*R4 yaku*]; PSEHB/PED Notification No. 1216-1 dated December 16, 2022).

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

The drug substance (CDCA) is listed in the Japanese Pharmacopoeia (JP). [redacted] is used as an intermediate in manufacture. The proposed specifications for the drug substance include the specifications for "chenodeoxycholic acid" (JP) as well as related substances (high performance liquid chromatography [HPLC]).

2.2 Drug product

2.2.1 Description and composition of the drug product and formulation development

The drug product is tablets (mini-tablets) each containing 25 mg of the drug substance. One packet contains 5 tablets. Excipients contained in the drug product are microcrystalline cellulose, carmellose calcium, methylcellulose, magnesium stearate, sucrose esters of fatty acids, hypromellose, macrogol 400, and talc.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of the following steps: acceptance test, [redacted], tableting, film coating, packaging, and labeling/storage/testing. [redacted] have been defined as critical steps. In-process control parameters and control values have been established for the following steps: [redacted]. The quality control strategy has been designed based on the following investigations (Table 1):

- Identification of critical quality attributes (CQAs)
- Quality risk assessment and identification of critical process parameters (CPPs)

Table 1. Summary of control strategy for the drug product

CQA	Control methods
Strength	Manufacturing process, specifications
Description	Specifications
Identification	Manufacturing process, specifications
Uniformity of dosage units	Manufacturing process, specifications
Dissolution	Manufacturing process, specifications

2.2.3 Control of the drug product

The proposed specifications for the drug product consist of strength, description, identification (thin-layer chromatography [TLC]), uniformity of dosage units (mass variation test), dissolution (HPLC), and assay (HPLC).

2.2.4 Stability of the drug product

Table 2 shows the main stability studies performed on the drug product. The results demonstrated the stability of the drug product. Photostability testing showed that the drug product was photostable.

Table 2. Stability studies of the drug product

Study	Primary batch	Temperature	Humidity	Storage condition	Storage period
Long-term	3 pilot-scale batches[a)]	25 ± 2°C	60 ± 5% RH	Aluminum-laminated film (polyethylene terephthalate/ polyethylene/aluminum foil/polyethylene/low-density polyethylene[b)]), carton	36 months
	3 commercial-scale batches				12 months[c)]
Accelerated	3 commercial-scale batches	40 ± 2°C	75 ± 5% RH		6 months

a) Pilot-scale batches are different from commercial-scale batches in [redacted] of the drug substance.
b) The layer of low-density polyethylene contacts with the drug product.
c) The stability study will continue up to [redacted] months.

In view of the above, a shelf life of 36 months was proposed for the drug product stored in an aluminum-laminated film package (polyethylene terephthalate/polyethylene/aluminum foil/polyethylene/low-density polyethylene) at room temperature, protected from light.

2.R Outline of the review conducted by PMDA

On the basis of the data submitted, the following review, and other information, PMDA has concluded that the quality of the drug substance and the drug product was controlled in an appropriate manner.

2.R.1 Stability of the drug product

The shelf life of the drug product was set based on the stability study results of pilot-scale batches manufactured using a drug substance that was different in [redacted] from the drug substance used in the manufacture of the proposed commercial formulation.

The applicant's explanation about the appropriateness of the proposed shelf life:
Pilot-scale batches were manufactured using a drug substance (A-CDCA) synthesized with [redacted]-derived [redacted], which is also used in the manufacture of the existing CDCA product Chino Capsules, as the starting material. However, from the viewpoint of stable supply, the decision was made to manufacture the proposed commercial formulation using a drug substance (B-CDCA) synthesized with [redacted]-derived [redacted] as the starting material. Although A-CDCA and B-CDCA differ in terms of the starting material and origin as well as [redacted], both substances were confirmed to conform to the JP specifications, have the same crystalline form, and also the same [redacted]. As a result of comparing the impurity profiles of A-CDCA and B-CDCA by the purity test (HPLC) using several detectors ([redacted], [redacted], and [redacted]), 2 new related substances were detected in B-CDCA, which were not detected in A-CDCA. Therefore, the decision was made to control the contents of these related substances based on the [redacted] and [redacted] of the drug substance so that the content values would not exceed the threshold (0.10%) requiring structural determination and safety confirmation specified in the International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use (ICH) Q3A guideline (Revision of the Guideline on Impurities in New Drug Substances [PFSB/ELD Notification No. 1216001, dated December 16, 2002] and Partial Revision of "Revision of the Guideline on Impurities in New Drug Substances" [PFSB/ELD Notification No. 1204001, dated December 4, 2006]). As a result of evaluating the purity (HPLC) by stress testing (temperature, humidity, and light), neither A-CDCA nor B-CDCA showed any increases in

related substances. Based on the above, B-CDCA was determined to have equivalent quality to A-CDCA. The stability studies (long-term testing for 36 months, accelerated testing for 6 months, and stress testing [temperature, humidity, and light]) of pilot-scale batches manufactured using A-CDCA then showed stable quality without any changes. The results of the stability studies (long-term testing for 12 months, accelerated testing for 6 months, and stress testing [temperature, humidity, and light]) of the proposed commercial formulation manufactured using B-CDCA were similar to those of the pilot-scale batches. Therefore, the shelf life of the drug product was set as 36 months based on the results of the long-term testing of pilot-scale batches.

PMDA accepted the applicant's explanation.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

No new non-clinical pharmacology studies have been conducted for the present application. As primary pharmacodynamic studies, the effects of CDCA on the expression of CYP7A1 and 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase were investigated based on published articles. No published articles corresponding to secondary pharmacodynamics, pharmacodynamic drug interactions, or safety pharmacology were submitted. The main published articles are summarized in the following sections.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 FXR activation by various bile acids (CTD 4.2.1.1-2; reference data [*Mol Cell*. 1999;3:543-553])

Monkey kidney-derived CV-1 cells, induced to transiently express the *farnesoid X receptor* (*FXR*) and *retinoid X receptor* (*RXR*) genes, were treated with CDCA, deoxycholic acid (DCA), lithocholic acid (LCA), or cholic acid (CA) (each at 100 μmol/L). FXR activity was evaluated by a reporter assay approximately 45 hours after the treatment. Compared with the untreated cells, FXR activity was 346-fold in CDCA-treated cells, 246-fold in DCA-treated cells, and 106-fold in LCA-treated cells. However, no FXR activity was observed in CA-treated cells .

3.1.1.2 Effect on the mRNA expression of FGF-19, SHP, and CYP7A1 in hepatocytes (CTD 4.2.1.1-4; reference data [*Pharmacol Res Perspect*. 2017;5:e00329])

Primary human hepatocytes were treated with vehicle or CDCA (0.1-100 μmol/L), and the messenger RNA (mRNA) expression levels of small heterodimer partner (SHP), fibroblast growth factor-19 (FGF-19), and CYP7A1 were evaluated by the quantitative polymerase chain reaction (qPCR) method 72 hours after the treatment. Treatment with CDCA (≥10 μmol/L) resulted in concentration-dependent increases in the mRNA expression levels of SHP and FGF-19 and a concentration-dependent decrease in the mRNA expression level of CYP7A1. The mRNA expression levels of SHP, FGF-19, and CYP7A1 after treatment with CDCA 100 μmol/L were approximately 4.5-fold, 1430-fold, and 0.01-fold, respectively, compared with the vehicle-treated cells.

3.1.1.3 Effect on the mRNA expression of BSEP in hepatocytes (CTD 4.2.1.1-4; reference data [*Pharmacol Res Perspect*. 2017;5:e00329])

Primary human hepatocytes were treated with vehicle or CDCA (0.1-100 μmol/L), and the mRNA expression level of the bile salt export pump (BSEP) was evaluated by the qPCR method 72 hours after the treatment. Treatment with CDCA (≥10 μmol/L) resulted in a concentration-dependent increase in the mRNA expression level of BSEP. The mRNA expression level of BSEP after treatment with CDCA 100 μmol/L was approximately 8.9-fold, compared with the vehicle-treated cells.

3.1.2 *In vivo* studies

3.1.2.1 Effect on the mRNA expression of CYP7A1, CYP8B1, and SHP in mice (CTD 4.2.1.1-7; reference data [*Toxicol Appl Pharmacol*. 2015;283:57-64])

CDCA mixed in the diet (0.03-0.3 w/w%[3)]) was given to male C57BL/6 mice (approximately 9 weeks of age, 5 animals/group) for 7 days. In the control group, a standard diet was given to the animals. The mRNA expression levels of CYP7A1, sterol 12α-hydroxylase (CYP8B1), and SHP in the liver were evaluated using the hybridization method and streptavidin-biotin interaction. In all CDCA dose groups, the mRNA expression level of CYP7A1 was lower than that in the control group. The mRNA expression level of CYP8B1 was lower in the CDCA 0.3 w/w% group than in the control group. The mRNA expression level of SHP was higher in all CDCA dose groups than in the control group.

3.1.2.2 Inhibition of CYP7A1 and HMG-CoA reductase activities in hamsters (CTD 4.2.1.1-8; reference data [*J Lab Clin Med*. 1973;82:858-868])

Following daily oral administration of CDCA (43 mg/kg) or vehicle in male golden Syrian hamsters (12 animals/group) for 2 weeks, hepatic homogenates and microsomes were prepared. Hepatic homogenates were spiked with 4-^{14}C-labeled cholesterol and incubated for 30 minutes. CYP7A1 activity was then evaluated by measuring the radioactivity of the formed 4-^{14}C-labeled 7α-hydroxycholesterol. Hepatic microsomes were spiked with 3-^{14}C-labeled HMG-CoA and incubated for 30 minutes. HMG-CoA reductase activity was evaluated by measuring the radioactivity. The results showed that the CYP7A1 activity (mean ± standard error [SE]) was 0.090 ± 0.001 nmol/mg protein/hr in the vehicle group and 0.046 ± 0.005 nmol/mg protein/hr in the CDCA group, and the HMG-CoA reductase activity (mean ± SE) was 8.14 ± 0.41 nmol/mg protein/hr in the vehicle group and 3.16 ± 0.08 nmol/mg protein/hr in the CDCA group.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological action of CDCA

The applicant's explanation:

CDCA, a primary bile acid, is biosynthesized using cholesterol as the starting material in the liver. CYP7A1, which hydroxylates cholesterol at the 7α position, is the rate-limiting enzyme in the bile acid synthesis pathway, and CDCA suppresses CYP7A1 expression by negative feedback regulation. CYP27A1, which hydroxylates the C27-sterol side chain of cholesterol, is an essential enzyme in the synthesis of primary bile acids. In CTX

3) Concentration of CDCA in the diet.

patients, the biosynthesis of CDCA is markedly decreased due to decreased CYP27A1 activity, resulting in excessive production of cholestanol, which is derived from an intermediate metabolite of CDCA. Furthermore, the negative feedback mechanism on CYP7A1 does not function due to decreased CDCA, leading to further increases in cholestanol production. Cholestanol accumulates in various organs such as the brain, tendons, and blood vessels, resulting in disorders of these organs (*Neurological Medicine*. 2017;86:346-351). Therefore, administration of CDCA to CTX patients is expected to normalize the feedback mechanism on CYP7A1 and suppress cholestanol production.

The mechanism of action of CDCA to suppress CYP7A1 expression was investigated as follows: In the liver, FXR, a nuclear receptor for bile acids that serve as the ligand, forms a heterodimer with RXR, which is also a nuclear receptor, and thereby induces the expression of SHP, which suppresses the activities of other nuclear receptors (*J Bio Chem*. 2001;276:37735-37738). SHP has been reported to inhibit the function of liver receptor homolog-1 (LRH-1), which positively regulates CYP7A1 expression (*Mol Cell*. 2000;6:507-515). In studies using primary human hepatocytes or mice, CDCA activated FXR [see Section "3.1.1.1 FXR activation by various bile acids"], increased the mRNA expression level of SHP, and decreased the mRNA expression level of CYP7A1 [see Sections "3.1.1.2 Effect on the mRNA expression of FGF-19, SHP, and CYP7A1 in hepatocytes" and "3.1.2.1 Effect on the mRNA expression of CYP7A1, CYP8B1, and SHP in mice"]. Therefore, CDCA is considered to decrease CYP7A1 expression via FXR activation. In studies using primary human hepatocytes, CDCA increased the mRNA expression level of FGF-19 [see Section "3.1.1.2 Effect on the mRNA expression of FGF-19, SHP, and CYP7A1 in hepatocytes"]. FGF-19 has been reported to suppress the mRNA expression of CYP7A1 without affecting the mRNA expression level of SHP (*Genes Dev*. 2003;17:1581-1591), suggesting that the activation of FGF-19-mediated pathways may also be involved in the suppression of CYP7A1 mRNA expression by CDCA. Furthermore, in the study using hamsters, CDCA suppressed the activity of HMG-CoA reductase, which is the rate-limiting enzyme in cholesterol synthesis [see Section "3.1.2.2 Inhibition of CYP7A1 and HMG-CoA reductase activities in hamsters"]. A published report showed that combination therapy with CDCA and HMG-CoA reductase inhibitors reduced blood cholestanol levels than CDCA monotherapy in CTX patients (*Metabolism*. 1999;48:233-238). These findings suggest that the inhibition of cholesterol synthesis via decreased HMG-CoA reductase activity may also contribute to the reduction of blood cholestanol levels caused by CDCA in CTX patients. The expression of HMG-CoA reductase has been reported to be negatively regulated by SHP (*J Biol Chem*. 2006;281:807-812, *Dev Cell*. 2002;2:721-731), suggesting that the suppression of HMG-CoA reductase transcription via an increased mRNA expression level of SHP may be involved in the mechanism of action of CDCA to decrease the HMG-CoA reductase activity.

Based on the above, CDCA is considered to suppress cholestanol production mainly by decreasing CYP7A1 expression via FXR activation. CDCA is also considered to reduce cholestanol production by inhibiting cholesterol production via decreased HMG-CoA reductase activity.

PMDA's view:

The published articles submitted as data on primary pharmacodynamics demonstrate the effect of CDCA to decrease CYP7A1 expression. This effect can be expected to reduce cholestanol production in CTX patients. The efficacy in humans is further discussed in Section "7.R.2 Efficacy."

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

This application relates to a new indication and a new dosage. The non-clinical pharmacokinetic data have already been evaluated at the time of the initial approval of Chino Capsules, and no new study results have been submitted.

5. Toxicology and Outline of the Review Conducted by PMDA

No additional toxicity studies have been conducted for the present application.

Since no carcinogenicity study results were included in the submitted documents for the initial application of Chino Capsules, the carcinogenicity of CDCA was evaluated based on published articles and other relevant information. The main published articles are summarized in the following sections.

5.1 Carcinogenicity

Table 3 summarizes published articles on the carcinogenicity of CDCA. The applicant explained that promoter activity in the gastrointestinal tract was suggested, and that this activity was considered to be possibly attributable to LCA, a metabolite of CDCA.

Table 3. Information on the carcinogenic promoter activity of CDCA in published articles

Animal species	Route of administration	Administration period	Dose[a] (mg/kg/day)	Test method	Main findings	Attached data CTD
Female mice (C57BL/ 6J-Min/+)	Dietary	10 weeks	750	Carcinogenicity was investigated in colorectal cancer model mice fed a CDCA-mixed diet or a normal diet.	The number of tumors in the duodenum increased in the CDCA group compared with the normal diet group.	Reference 4.2.3.4.2-1 (*Carcinogenesis*. 1999;20:299-303)
Male rats (SD)	Dietary	6 weeks	77	The effect on initiator-induced lesions was investigated by the administration of NDEA and AOM,[b] followed by the administration of CDCA, in normal rats.	The number of aberrant crypt foci in the colon increased in the CDCA-treated group compared with the CDCA-untreated group.	Reference 4.2.3.4.2-2 (*Cancer Lett*. 1996;105:71-75)
Male rats (WKY/N)	Dietary	18 weeks	270	The effect on initiator-induced lesions was investigated by the administration of MNNG,[c] followed by the administration of CDCA in normal rats.	The number of pepsinogen-altered pyloric glands in the stomach did not increase in the CDCA group compared with the normal diet group.	Reference 4.2.3.4.2-3 (*Teratog Carcinog Mutagen*. 1992;12:179-186)
Male rats (F344)	Dietary	6 weeks	99	The effect on initiator-induced lesions was investigated by the administration of DEN[d] and partial hepatectomy followed by the administration of CDCA in normal rats.	The number and area of γ-glutamyl transpeptidase-positive foci in the liver did not increase in the CDCA-treated group compared with the CDCA-untreated group.	Reference 4.2.3.4.2-6 (*Gan*. 1984;75:871-875)
Male rats (F344)	Dietary	8 or 18 weeks	180	In an 8-week study, the effect on initiator-induced lesions was investigated by the administration of AOM,[e] followed by the administration of CDCA in normal rats. In an 18-week study, the carcinogenicity was investigated by the administration of CDCA in normal rats.	In the 8-week study, the number of aberrant crypt foci in the colon increased in the CDCA-treated group compared with the CDCA-untreated group. In the 18-week study, the number of aberrant crypt foci in the colon did not increase in the CDCA-treated group compared with the CDCA-untreated group.	Reference 4.2.3.4.2-7 (*Cancer Lett*. 1997;115:97-103)

a) The body weight and daily food intake of each animal were estimated in reference to background information on the body weight and food intake of the respective animal species. The dose was then calculated based on the dietary concentration of CDCA in the published article.
b) NDEA was intraperitoneally administered at 200 mg/kg once. AOM was intraperitoneally administered at 15 mg/kg twice at a 4-day interval.
c) Orally administered at 160 mg/kg.
d) Intraperitoneally administered at 200 mg/kg once.
e) Subcutaneously administered at 15 mg/kg twice at a 7-day interval.

5.2 Other studies

5.2.1 Studies on metabolites

The toxicity, including genotoxicity and carcinogenicity, of LCA and ursodeoxycholic acid (UDCA), major metabolites of CDCA, was evaluated based on published articles (Table 4 and Table 5).

For LCA, positive results were obtained in the comet assay and mouse lymphoma assay in the absence of S9; however, no neoplastic lesions were observed in carcinogenicity studies in rats or mice. On the other hand, the study investigating the effect on *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG)-induced lesions suggested that LCA may act as a carcinogenic promoter.

For UDCA, positive results were obtained in a bacterial reverse mutation assay and the *in vitro* micronucleus assay.

Table 4. Information on LCA in published articles

Study	Test system	Route of administration	Administration period	Dose	Main findings	Attached data CTD
Single dose	Mice (CF1)	Oral	Single dose	1000 mg/kg	Multiple foci of coagulative necrosis, bleeding from necrotic sites, and hyperproliferation of hepatic parenchymal cells were observed in the liver.	Reference 4.2.3.7.5-1 (*Gastroenterology*. 1978;74:188-192)
Repeated dose	Mice (B6C3F1)	Oral	7 weeks	464-2150 mg/kg/day (3 times/week)	Death was observed at ≥464 mg/kg/day.	Reference 4.2.3.7.5-2 (*Natl Cancer Inst Carcinog Tech Rep Ser*. 1979;175)
	Rats (F344)	Oral	7 weeks	464-2150 mg/kg/day (3 times/week)	Decreased body weight in males and increased body weight in females were observed at ≥464 mg/kg/day.	
	Rabbits (Strain unknown)	Oral	3 months	20 mg/kg/day	Hydropic degeneration of hepatocytes and cirrhosis were observed.	Reference 4.2.3.7.5-3 (*Nature*. 1960;186:250)
Bacterial reverse mutation assay	*Salmonella typhimurium*: TA1538	*In vitro*	-	100-500 μg/plate	The number of revertant colonies did not increase in the presence or absence of S9.	Reference 4.2.3.7.5-4 (*J Natl Cancer Inst*. 1977;59:1557-1559)
	Salmonella typhimurium: TA98, TA100	*In vitro*	-	TA98: 10-40 μg/mL TA100: 10-20 μg/mL	The number of revertant colonies did not increase in the presence or absence of S9.	Reference 4.2.3.7.5-5 (*Mutant Res*. 1985;158:45-51)
Comet assay	HT29 cells	*In vitro*	-	25-300 μmol/L	Positive in the absence of S9.	Reference 4.2.3.7.5-6 (*Free Radic Res*. 1997;26:135-144)
Mouse lymphoma assay	L5178Y cells	*In vitro*	-	5-100 μg/mL	Positive at ≥40 μg/mL in the absence of S9.	Reference 4.2.3.7.5-7 (*Environ Mol Mutagen*. 1991;17:196-219)
				42-115 μg/mL	Negative in the presence of S9 but positive at ≥61.1 μg/mL in the absence of S9.	Reference 4.2.3.7.5-8 (*Environ Mol Mutagen*. 1998;12:37-101)
				1.88-125 μg/mL	Negative in the presence and absence of S9.	Reference 4.2.3.7.5-9 (*Environ Mol Mutagen*. 1998;12:103-194)
Carcinogenicity	Mice (B6C3F1)	Oral	103 weeks	125 and 250 mg/kg/day (3 times/week)	Neoplastic lesions did not increase.	Reference 4.2.3.7.5-2 (*Natl Cancer Inst Carcinog Tech Rep Ser*. 1979;175)
	Rats (F344)	Oral	103 weeks	250 and 500 mg/kg/day (3 times/week)	Neoplastic lesions did not increase.	
Carcinogenicity: Effect on MNNG[a]-induced lesions	Rats (F344)	Intrarectal	46 weeks	125 mg/kg/day[b] (3 times/week)	The incidence of colonic tumors increased following administration of MNNG and LCA compared with the administration of MNNG alone.	Reference 4.2.3.7.5-10 (*Cancer Res*. 1979;39:1521-1524)
	Rats (F344)	Intrarectal	11 months	3.6-6.3 mg/kg/day[b] (5 times/week)	The incidence of colonic tumors increased following administration of MNNG and LCA, compared with the administration of MNNG alone.	Reference 4.2.3.7.5-11 (*J Natl Cancer Inst*. 1974;53:1093-1097)

Study	Test system	Route of administration	Administration period	Dose	Main findings	Attached data CTD
Pre- and postnatal development, including maternal function	Rats (SD)	Dietary	Gestation Days 0-20 or 21	Approximately 800 mg/kg/day	Liver injury in maternal animals, and decreased body weight, liver injury, and increased ALP in offspring were observed.	Reference 4.2.3.7.5-12 (*Teratology*. 1991;43:355-361)
	Rats (SD)	With drinking water	Gestation Days 0-19	Approximately 2000 mg/kg/day	Decreased body weight, decreased weight of both the placenta and liver, liver injury, and decreased ALP in fetuses and increased ALP in offspring were observed.	

a) Intrarectally administered at 21 mg/kg twice/week for 2 weeks (CTD 4.2.3.7.5-10); intrarectally administered at 27 to 35 mg/kg once (CTD 4.2.3.7.5-11).
b) The single dose of LCA in the published article was calculated in reference to background information on the body weight of rats.

Table 5. Information on UDCA in published articles

Study	Test system	Route of administration	Administration period	Dose	Main findings	Attached data CTD
Single dose	Mice (dd)	Oral	Single dose	5000 and 10000 mg/kg	LD_{50} was >10000 mg/kg.	Reference 4.2.3.7.5-13 (*The Clinical Report*. 1975;9:3159-3166)
	Rats (Wistar)	Oral		2000 and 5000 mg/kg	LD_{50} was >5000 mg/kg.	
Repeated dose	Rats (Wistar)	Oral	5 weeks	500, 1000, 2000, and 4000 mg/kg/day (6 times/week)	There were no toxic changes.	Reference 4.2.3.7.5-14 (*The Clinical Report*. 1975;9:3167-3181)
	Rats (Wistar)	Oral	3 months	500, 1000, 2000, and 4000 mg/kg/day (6 times/week)	Micronecrotic foci in the liver were observed at 2000 mg/kg/day, and suppressed weight gain was observed at 4000 mg/kg/day.	Reference 4.2.3.7.5-15 (*The Clinical Report*. 1975;9:3203-3208)
	Rats (Wistar)	Oral	6 months	500, 1000, 2000, and 4000 mg/kg/day (6 times/week)	Cholangitis, bile duct proliferation, and micronecrotic foci in the liver were observed at ≥1000 mg/kg/day. A tendency for an increase in deaths and suppressed weight gain was observed at 4000 mg/kg/day.	Reference 4.2.3.7.5-16 (*The Clinical Report*. 1975;9:3209-3222)
	Rhesus monkeys	Oral	6 months	40 and 100 mg/kg/day	There were no toxic changes.	Reference 4.2.3.7.5-17 (*Gastroenterology*. 1978;74:75-81)
Bacterial reverse mutation assay	*Salmonella typhimurium*: TA98, TA100	*In vitro*	-	20-50 μg/mL	Positive for TA98 at ≥40 μg/mL, and negative for TA100.	Reference 4.2.3.7.5-5 (*Mutant Res*. 1985;158:45-51)
	Salmonella typhimurium: TA100	*In vitro*	-	20-500 μg/2 mL top agar	Negative in the presence and absence of S9.	
In vitro micronucleus assay	Human peripheral blood lymphocytes	*In vitro*	-	10, 30, and 100 μg/mL	Positive at 100 μg/mL.	Reference 4.2.3.7.5-18 (*Mutant Res*. 2001;495:1-9)
Carcinogenicity: Effect on AOM[a]-induced lesions	Rats (F344)	Dietary	28 weeks	53 and 107 mg/kg/day[b]	The incidence of colonic tumors decreased following administration of AOM and UDCA compared with the administration of AOM alone.	Reference 4.2.3.7.5-19 (*Cancer Res*. 1994;54:5071-5074)
Carcinogenicity: Effect on MNU[c]-induced lesions	Rats (F344)	Dietary	27 weeks	42 and 212 mg/kg/day[b]	The incidence of colonic tumors decreased following administration of MNU and UDCA, compared with the administration of MNU alone.	Reference 4.2.3.7.5-20 (*Jpn J Cancer Res*. 1998;89:1009-1013)

Study	Test system	Route of administration	Administration period	Dose	Main findings	Attached data CTD
Study of administration prior to pregnancy and during the first trimester of pregnancy	Rats (Wistar)	Oral	Male: for 63 days prior to the start of mating, female: from 14 days prior to the start of mating to Gestation Day 7	250, 1000, and 2000 mg/kg/day	A tendency for a decrease in mating and pregnancy rates and a decrease in the number of live offspring were observed at 2000 mg/kg/day.	Reference 4.2.3.7.5-21 (*Pharmacometrics*. 1978;15:923-930)
Study of administration during the period of organogenesis	Mice (dd)	Oral	Gestation Days 7-12	300 and 1500 mg/kg/day	A decrease in the mean body weight of both maternal animals and fetuses was observed at 1500 mg/kg/day.	Reference 4.2.3.7.5-22 (*The Clinical Report*. 1975;9:3223-3242)
	Rats (Wistar)	Oral	Gestation Days 7-17	250, 1000, and 2000 mg/kg/day	An increase in dead fetuses consisting mainly of resorbed embryos and decreased body weight of fetuses and newborns were observed at 2000 mg/kg/day.	Reference 4.2.3.7.5-23 (*Pharmacometrics*. 1978;15:931-945)
	Rats (Wistar)	Oral	Gestation Days 9-14	300 and 4000 mg/kg/day	Suppressed weight gain of maternal animals and a decrease in the mean body weight of fetuses were observed at 4000 mg/kg/day.	Reference 4.2.3.7.5-22 (*The Clinical Report*. 1975;9:3223-3242)
	Rabbits (NZW)	Oral	Gestation Days 6-18	5, 10, and 20 mg/kg/day	There were no toxic changes.	Reference 4.2.3.7.5-24 (*Pharmacometrics*. 1978;5:1133-1140)
Study of administration during the perinatal and lactation period	Rats (Wistar)	Oral	From Gestation Day 17 to Postpartum Day 21	250, 1000, and 2000 mg/kg/day	Suppressed weight gain of maternal animals was observed at 2000 mg/kg/day.	Reference 4.2.3.7.5-25 (*Pharmacometrics*. 1978;15:1141-55)

a) Subcutaneously administered at 15 mg/kg once/week for 2 weeks.
b) Body wight and daily food intake were estimated in reference to background information on the body weight and food intake of rats. The dose was then calculated based on the dietary concentration of UDCA in the published article.
c) Intrarectally administered at 15 mg/kg 3 times/week for 3 weeks.

5.R Outline of the review conducted by PMDA

5.R.1 Use of CDCA in pregnant women or women who may be pregnant

Given that Chino Capsules, which contain the same active ingredient, CDCA, are contraindicated in pregnant women or women who may be pregnant, PMDA asked the applicant to explain the appropriateness of use of Fujichenon in the above population.

The applicant's explanation:

According to the reproductive and developmental toxicity study results submitted at the time of the application for marketing approval of Chino Capsules, the administration of CDCA resulted in increased organ weights and histological changes in the liver, kidney, and adrenal glands of normal rhesus monkey fetuses (*Toxicology*. 1974;2:239-246). In normal newborn and stillborn baboon infants, inflammatory cell infiltration, bile duct hyperplasia, and hepatic necrosis were observed in the liver (*Ann Surg*. 1976;184:490-499). The minimum toxic dose in these studies was 60 mg/kg/day in rhesus monkeys and 18 mg/kg/day in baboons. When each minimum toxic dose was compared with the maximum clinical dose of Fujichenon (1000 mg/day) based on

body surface area, the ratio was 1.2-fold for rhesus monkeys and 0.6-fold for baboons.[4)] However, based on the following considerations, the applicant considers that Fujichenon should not be specified as contraindicated in pregnant women or women who may be pregnant, and that administration may be acceptable if the expected therapeutic benefits outweigh the possible risks.

- Reports comparing the pool size of CDCA before and after its administration in patients with cholelithiasis (*J Clin Invest*. 1973;52:2809-2821, *Gastroenterology*. 1975;69:1301-1314) suggest that administration of approximately 1000 mg of CDCA increases the pool size by 1486 mg on average, compared with before administration. Taking into account the report that the pool size of CDCA in Japanese healthy adults ranges from 618 to 1235 mg (*J Japan Biliary Assoc*. 1989;3:456-462) and the report that the pool size of CDCA in CTX patients is 11% of that in the healthy population (*J Clin Invest*. 1985;76:744-751), the pool size of CDCA in CTX patients following administration of Fujichenon at the maximum clinical dose (1000 mg) is expected to be 1554 to 1622 mg, indicating that it is unlikely to greatly exceed that in the healthy population.
- In 7 CTX patients who continued CDCA treatment during pregnancy (a total of 11 pregnancies), although postpartum pre-eclampsia was observed in 1 patient, there were no CDCA-related adverse drug reactions affecting any of the patients during pregnancy or at delivery, or newborns. There were also no reports of events suggesting malformations, etc. in newborns. In 3 CTX patients who did not receive CDCA during pregnancy (including 1 patient who interrupted CDCA treatment during pregnancy) (a total of 8 pregnancies), deterioration of neurological symptoms was observed in 1 patient, elevated bilirubin was observed in 2 newborns, and mixed expressive-receptive language developmental disorder was observed in 1 newborn. In view of these points as well as the following reports, fetal development may be affected by substances such as cholestanol and bile alcohols if pregnant CTX patients are not treated (*Genet Med*. 2024;26:101086).
  - Among 4 pregnant CTX patients who did not receive CDCA, 1 stillbirth in 1 patient, and 2 miscarriages in 1 patient were observed (*Clin Neuropharmacol*. 2013:36;78-83).
  - Among 18 children born to 9 pregnant CTX patients who did not receive CDCA, intellectual disability was observed in 2 children (*Am J Med Genet*. 1988:31;11-16).

PMDA's view:

The applicant's explanation that the expected pool size of CDCA following administration of Fujichenon at the recommended clinical dose is unlikely to greatly exceed that in the healthy population is understandable. In view of the limited number of therapeutic options for CTX, etc., the decision not to specify use of Fujichenon in pregnant women as a contraindication is justified. In the submitted reproductive and developmental toxicity studies of CDCA, including studies other than those submitted at the time of the initial application for marketing approval, although a high embryo resorption rate was reported, teratogenicity in fetuses and newborns has not been observed (*Pharmacometrics*. 1978;15:1047-1055, *Pharmacometrics*. 1978;16:39-49, etc.). In addition, the underlying disease itself may affect fetuses and newborns. In view of these points, it is

[4)] When Fujichenon is administered at 1000 mg/day to a patient weighing 60 kg, the dose based on the body surface area is estimated to be 617 mg/m^2/day. When CDCA is administered at 60 mg/kg/day to monkeys (conversion factor of 12) or at 18 mg/kg/day to baboons (conversion factor of 20), the dose based on the body surface area is estimated to be 720 mg/m^2/day or 360 mg/m^2/day, respectively.

justified to provide information on the findings in fetuses observed in the nonclinical studies of CDCA and then include a precaution to ensure that Fujichenon should be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment.

5.R.2 Carcinogenicity of CDCA

The applicant's explanation:

Although there are no findings suggesting genotoxicity in the results of the reverse mutation assay, *in vivo* micronucleus assay, and dominant lethal test submitted at the time of the application for marketing approval of Chino Capsules, it has been reported that promoter activity of CDCA in the gastrointestinal tract was suggested as a result of dietary dosing in mice and rats (*Carcinogenesis*. 1999;20:299-303, *Cancer Lett*. 1996;105:71-75). There are also reports that the administration of MNNG and CDCA did not affect the incidence of colon tumors in germ-free rats, but that an increased incidence of colon tumors was observed in conventional rats (*Cancer Res*. 1977;37:3238-3242) and that the administration of MNNG and LCA caused an increase in the incidence of colon tumors in both germ-free and conventional rats (*Cancer Res*. 1979;39:1521-1524). Based on these reports and the fact that CDCA is metabolized to LCA by enteric bacteria, the promoter activity suggested for CDCA may be attributable to its metabolite LCA.

There are no reports on the pool size of LCA in CTX patients. However, given that the pool size of CDCA in CTX patients following administration of Fujichenon at the maximum dose (1000 mg) is unlikely to greatly exceed that in the healthy population [see Section "5.R.1 Use of CDCA in pregnant women or women who may be pregnant"], the pool size of LCA following administration of Fujichenon, even at the maximum dose, is unlikely to greatly exceed that in the healthy population. Thus, carcinogenic promoter activity is considered unlikely when CDCA is administered to CTX patients.

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

The Japanese phase III study in CTX patients (Study FPF1011-03-01) used a formulation of Fujichenon that is identical to the proposed commercial formulation, except for the manufacturing process of the drug substance [see Section "2.R.1 Stability of the drug product"].

6.2 Clinical pharmacology

No clinical pharmacology studies of Fujichenon have been conducted. As reference data, published articles on CDCA treatment in CTX patients were submitted. The main published articles are summarized below.

6.2.1 Investigations in patients

6.2.1.1 Study on the levels of cholesterol and cholesterol metabolites in CTX patients (CTD 5.4.1-110; reference data [*J Lipid Res*. 2001;42:291-300])

The levels of cholesterol and cholesterol metabolites in the liver[5)] of 2 non-Japanese CTX patients (Patient 1 [a 40-year-old, CDCA-untreated male] and Patient 2 [a 42-year-old, 3-year CDCA-treated female]) were compared with those in the liver[6)] of healthy adults. Table 6 shows the results.

Table 6. Levels of cholesterol and cholesterol metabolites in the liver of non-Japanese CTX patients and healthy adults

Analyte	Patient 1 (CDCA-untreated)	Patient 2 (CDCA-treated)	Healthy adults (N = 4)
Cholesterol	84	68	61 ± 4
Cholestanol	2.4	1.0	0.16 ± 0.01
7α-hydroxycholesterol[a)]	331	139	38 ± 8
7α-hydroxy-4-cholesten-3-one[b)]	191	2.9	0.6 ± 0.1
7α, 12α-dihydroxy-4-cholesten-3-one[c)]	898	11	2.0 ± 0.3
5β-cholestane-3α, 7α, 12α, 25-tetrol[d)]	263	48	2.3 ± 0.6
5β-cholestane-3α, 7α, 12α, 23*R*, 25-pentol[d)]	514	44	1.7 ± 0.6
5β-cholestane-3α, 7α, 12α, 24*R*, 25-pentol[d)]	144	8.2	3.2 ± 0.9
5β-cholestane-3α, 7α, 12α, 24*S*, 25-pentol[d)]	91	2.0	2.2 ± 0.4
5β-cholestane-3α, 7α, 12α, 25, 27-pentol[d)]	6.1	3.2	1.3 ± 0.3
27-hydroxycholesterol[e)]	<0.2	<0.2	7.5 ± 0.8
5β-cholestane-3α, 7α, 12α, 27-tetrol[e)]	<0.05	<0.05	0.15 ± 0.03

Unit: "nmol/mg protein" for cholesterol and cholestanol, and "pmol/mg protein" for others.
Expressed as individual data for patients, and as mean ± standard error for healthy adults.

a) CYP7A1-mediated metabolite of cholesterol
b) HSD3B7-mediated metabolite of 7α-hydroxycholesterol
c) CYP7A1- and CYP8B1-mediated metabolite of cholesterol
d) Intermediate metabolite in the metabolism to cholic acid (a kind of bile alcohol)
e) CYP27A1-mediated metabolite of cholesterol

6.R Outline of the review conducted by PMDA

6.R.1 Bile acid kinetics following administration of Fujichenon in adult and pediatric CTX patients

The applicant's explanation:

CDCA is a major bile acid that is formed via the metabolism of cholesterol by CYP7A1, which is the rate-limiting enzyme for bile acid synthesis, and other enzymes. Once synthesized in the liver, CDCA is mainly conjugated with amino acids, excreted into the bile via BSEP, etc., and secreted with bile into the duodenal lumen after meals, etc. The secreted CDCA or its amino acid conjugates are absorbed in the gastrointestinal tract, either passively (*Bifidus*. 1992;5:157-172) or actively via the apical-dependent bile acid transporter (ASBT) (*KAGAKU TO SEIBUTSU*. 2014;52:301-307), transferred to the portal blood, and then reabsorbed in the liver via Na^+/taurocholate cotransporting polypeptide (NTCP) or organic anion transporting polypeptide (OATP) 1B1/1B3. Therefore, CDCA is mostly present in hepatobiliary and gastrointestinal tissues that are involved in enterohepatic circulation, and its transfer to the peripheral blood is limited (*KAGAKU TO SEIBUTSU*. 2014;52:301-307, *J Japan Biliary Assoc*. 2011;25:189-195, etc.). To accurately evaluate the absorption of CDCA, it is necessary to measure the amount of CDCA excreted into bile by administering CDCA and collecting bile samples. On the other hand, since this evaluation method is highly invasive, the pharmacokinetics of CDCA in CTX patients were evaluated based on the existing knowledge.

5) Patient 1 underwent a liver biopsy in the histological examination at the time of the CTX diagnosis. Patient 2 died of pneumonia and a liver specimen was obtained 1 hour after death.
6) Liver specimens were obtained from 4 healthy non-Japanese adults who died unexpectedly and whose livers became available because no suitable recipients for liver transplantation could be found.

When Fujichenon is administered to adult CTX patients, it is considered to be absorbed from the gastrointestinal tract and to enter the enterohepatic circulation, like endogenous CDCA. The pharmacokinetics of CDCA in children were investigated as follows: Since the absorption process of CDCA via passive transport in the gastrointestinal tract is considered not to markedly change from fetal development through adulthood, the extent of absorption via passive transport is also considered not to differ substantially between adults and children. On the other hand, age- and growth-related differences in the expression of transporters (BSEP, ASBT, NTCP, OATP1B1/1B3, etc.) involved in the enterohepatic circulation have been investigated in the following reports, suggesting that some transporters related to the pharmacokinetics of CDCA in neonatal and pediatric CTX patients have matured to the same extent as in adults.

- The results of investigating the expression level of BSEP in each age group are as follows: The expression level of BSEP protein (median [range]; the same applies hereinafter) was 18.4 [11.4, 33.7] pmol/g tissue in fetuses,[7)] 35.9 [10.6, 49.8] pmol/g tissue in newborns,[8)] and 47.7 [40.3, 67.0] pmol/g tissue in adults (*Drug Metab Dispos*. 2016;44:1005-1013).
- The results of investigating the expression of ASBT protein in the gastrointestinal tract of newborns and children are as follows: The expression of ASBT protein was confirmed in only 1 of 12 samples from newborns or infants (0.5-48 weeks of age), whereas the protein was confirmed in all 7 samples from children (60-417 weeks of age) (*Int J Pharm*. 2024;654:1-10).
- The results of investigating the expression of NTCP and OATP1B1/1B3 in each age group are as follows: In liver samples of fetuses,[9)] newborns (premature newborns[10)] and full-term newborns[11)]), children,[12)] and adults, the protein expression level of NTCP tended to increase in the order of fetuses, newborns, children, and adults, whereas that of OATP1B1/1B3 was generally similar across the age groups (*Eur J Pharm Sci*. 2018;124:217-227).

Additionally, the following reports have described age- and growth-related differences in the expression of CYP7A1 involved in the biosynthesis of bile acids and FXR, a nuclear receptor involved in negative feedback on CYP7A1 expression. The mechanism of negative feedback on CYP7A1 is considered to be active to a certain extent in children too, although there may be age-related differences.

- When the expression level of CYP7A1 was evaluated using the plasma concentrations of 7α-hydroxy-4-cholesten-3-one (C4), a CYP7A1-mediated metabolite of cholesterol, C4 was not detected in plasma until 30 weeks of gestation in full term and premature newborns and tended to increase thereafter to approximately 3 ng/mL by 40 weeks of gestation (*J Matern Fetal Neonatal Med*. 2020;33:987-992). Compared with a reported C4 concentration of 22.3 ng/mL in healthy adults (*Neurogastroenterol Montil*. 2009;21:734-e43), the plasma C4 concentration in newborns was low, suggesting that the expression level of CYP7A1 may be low in newborns.
- When the mRNA expression level of FXR was investigated in liver samples of fetuses at 14 to 20 weeks

7) The median gestational age [range] was 23.2 [16.4, 37.9] weeks.
8) The median gestational age [range] was 35.1 [27.1, 41.0] weeks. The median postnatal age [range] was 1 [0, 11.4] weeks.
9) The median gestational age [range] was 23.4 [15.3, 41.3] weeks.
10) The median gestational age [range] was 30.2 [24.9, 36.7] weeks. The median postnatal age [range] was 1.0 [0.14, 11.4] weeks.
11) The median gestational age [range] was 40.0 [39.7, 41.3] weeks. The median postnatal age [range] was 3.86 [0.29, 18.1] weeks.
12) The median postnatal age [range] was 4.13 [1.08, 7.44] years.

of gestation and adults, the mRNA expression level of FXR in fetuses was 75% of that in adults, indicating that FXR expression is present to some extent in fetuses (*J Hepatol*. 2005;43:472-477).

In pediatric CTX patients, as in adults, decreased CYP27A1 activity is considered to cause a decrease in CDCA production and an increase in cholestanol production. Based on the above reports, administration of Fujichenon is expected to reduce serum cholestanol concentration.

PMDA's view:
Fujichenon administered to CTX patients is considered to basically show similar kinetics to endogenous CDCA. When Fujichenon is administered to pediatric CTX patients, CDCA is expected to be passively absorbed from the gastrointestinal tract. Transporters (ASBT, NTCP, BSEP, etc.) involved in the enterohepatic circulation of bile acids are expressed to a certain extent during childhood. Based on these considerations, bile acid kinetics following administration of Fujichenon in pediatric CTX patients are unlikely to differ substantially from those in adult CTX patients. In addition, considering that the expression of FXR, which is involved in the negative feedback mechanism of CDCA for CYP7A1, has also been observed in fetuses, treatment with Fujichenon is expected to reduce serum cholestanol concentrations, which are increased due to CYP27A1 deficiency in pediatric CTX patients as well. On the other hand, it has been reported that there may be differences in the expression levels of transporters involved in the enterohepatic circulation of bile acids and CYP7A1, which is involved in bile acid synthesis, depending on the stage of the growth process. Therefore, the magnitude of the effect of Fujichenon on CTX may differ between adult and pediatric patients when administered at the same dosage, and the recommended clinical dosage may also differ. Therefore, the appropriateness of the dosage and administration of Fujichenon in pediatric CTX patients is further discussed in Section "7.R.5.2 Dosage and administration for pediatric patients."

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

The applicant submitted efficacy and safety evaluation data, in the form of results data from the study shown in Table 7.

Table 7. List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Population	N	Outline of dosage regimen	Main endpoints
Evaluation	Japanese	FPF1011-03-01	III	CTX patients	15	The following dose was orally administered in 3 divided doses daily on consecutive days. • In CDCA-naïve patients, treatment with Fujichenon was started at 250 mg/day for adults and 5 mg/kg/day for children. In adults, the dose was escalated every 2 weeks to 500 mg/day and then to 750 mg/day. In children, the dose was escalated every 2 weeks to 10 mg/kg/day and then to 15 mg/kg/day. • In CDCA-experienced patients, treatment with Fujichenon was started at the dose of the CDCA product before enrollment in the study, and the dose was escalated stepwise to 750 mg/day for adults and 15 mg/kg/day for children. • The dose of Fujichenon after dose escalation was 750 mg/day for adults and 15 mg/kg/day for children, in principle, and could be adjusted as appropriate according to the symptoms and other conditions. The maximum dose was set at 1000 mg/day for adults, and 15 mg/kg/day and 750 mg/day for children.	Efficacy Safety

7.1 Japanese phase III study (CTD 5.3.5.2.1; Study FPF1011-03-01; August 2020 to October 2022)

An open-label, single-group study was conducted to investigate the efficacy and safety of Fujichenon in CTX patients (target sample size, ≥5 subjects in the adult cohort and ≥1 subject in the pediatric cohort[13]).

The main inclusion criteria were as follows: Adult (≥18 years of age) or pediatric (≥0 and <18 years of age) CTX patients whose diagnostic category was "definite" or "probable" based on the diagnostic criteria for CTX (Table 8), or who had serum cholestanol concentrations of ≥4.5 μg/mL and mutations in the *CYP27A1* gene.

Table 8. Diagnostic criteria for CTX

Criteria	Diagnostic category
A: Having any of the following symptoms: tendon xanthomas, progressive neurological symptoms or mental retardation, juvenile-onset cataract, juvenile-onset coronary disease, childhood- or juvenile-onset chronic diarrhoea, juvenile-onset osteoporosis, and neonatal- or infantile-onset prolonged jaundice and cholestasis.	Definite: All of A to D are met. Probable: A, B, and D are met. Possible: A and B are met.
B: Having serum cholestanol concentrations ≥4.5 μg/mL.	
C: Having mutations in the *CYP27A1* gene.	
D: Not having any of the following diseases: familial hypercholesterolemia, sitosterolemia, obstructive biliary tract disease, or hypothyroidism.	

This study consisted of a run-in period (12 weeks) and a treatment period (52 weeks). During the run-in period, CDCA-experienced patients continued the CDCA treatment at the dose used prior to enrollment in the study, and CDCA-naïve patients did not receive CDCA. During the treatment period, Fujichenon was orally administered 3 times daily on consecutive days, and the daily doses of Fujichenon in the adult and pediatric cohorts were specified based on the status of previous treatment with CDCA products, etc., as shown in Table 9. The dose of Fujichenon could be adjusted as appropriate according to the subject's symptoms and other conditions.

[13] A total of 40 CTX patients have been confirmed in Japan (*J Hum Genet*. 2018;63:271-280). Taking feasibility into account, the target sample size was set as ≥5 subjects in the adult cohort and ≥1 subject in the pediatric cohort. No success criteria were established in the study.

Table 9. Dose of Fujichenon in the treatment period

<table>
<tr><th rowspan="2">Cohort</th><th rowspan="2">Status of previous treatment with CDCA products</th><th rowspan="2">Dose of CDCA before enrollment</th><th colspan="3">Dose of Fujichenon</th></tr>
<tr><th>Starting dose</th><th>Until Week 6</th><th>After Week 6</th></tr>
<tr><td rowspan="4">Adult cohort</td><td>CDCA-naïve</td><td>-</td><td>250 mg/day</td><td>The dose was increased to 500 mg/day at Week 2 and to 750 mg/day at Week 4, and the treatment was continued thereafter.</td><td rowspan="4">750 mg/day in principle.[a)]
The dose could be increased up to 1000 mg/day.[b)]</td></tr>
<tr><td rowspan="3">CDCA-experienced</td><td><500 mg/day</td><td rowspan="3">Same as the dose of CDCA in the run-in period</td><td></td></tr>
<tr><td>≥500 mg/day and <750 mg/day</td><td>The dose was increased to 750 mg/day at Week 2, and the treatment was continued thereafter.</td></tr>
<tr><td>≥750 mg/day</td><td>Treatment at the starting dose was continued.</td></tr>
<tr><td rowspan="4">Pediatric cohort</td><td>CDCA-naïve</td><td>-</td><td>5 mg/kg/day (up to 250 mg/day)</td><td>The dose was increased to10 mg/kg/day (up to 500 mg/day) at Week 2 and to 15 mg/kg/day (up to 750 mg/day) at Week 4, and the treatment was continued thereafter.</td><td rowspan="4">15 mg/kg/day (up to 750 mg/day), in principle.[a)]</td></tr>
<tr><td rowspan="3">CDCA-experienced</td><td><10 mg/kg/day</td><td rowspan="3">Same as the dose of CDCA in the run-in period</td><td></td></tr>
<tr><td>≥10 mg/kg/day and <15 mg/kg/day</td><td>The dose was increased to 15 mg/kg/day (up to 750 mg/day), and the treatment was continued thereafter.</td></tr>
<tr><td>≥15 mg/kg/day</td><td>Treatment at the starting dose was continued.</td></tr>
</table>

-: Not applicable

a) In subjects with a Fujichenon dose <750 mg/day at Week 6, if there were no safety problems, the dose could be increased to 750 mg/day in increments of 250 mg/day every 2 weeks.

b) In subjects with a Fujichenon dose ≥750 mg/day at or after Week 6, if there were no safety problems and a further treatment effect could be expected, the dose could be increased to 1000 mg/day in increments of ≤250 mg/day.

c) In subjects with a Fujichenon dose <15 mg/kg/day at or after Week 6, if there were no safety problems, the dose could be increased to 15 mg/kg/day (up to 750 mg/day) in increments of 5 mg/kg/day every 2 weeks. The maximum dose was 15 mg/kg/day and 750 mg/day.

The adult cohort enrolled 15 subjects (3 CDCA-naïve patients and 12 CDCA-experienced patients). All of these subjects received Fujichenon and were included in the safety analysis set and the intent-to treat (ITT) population. The ITT population was used as the primary efficacy analysis population. The study was discontinued in 2 CDCA-experienced patients (1 subject due to "withdrawal of consent" and 1 subject based on the "investigator's judgment"[14)]).

No subjects were enrolled in the pediatric cohort.

Figure 1 shows the efficacy results in the adult cohort, as assessed by the time course of serum cholestanol concentrations during the study period, which was the primary endpoint. Table 10 shows serum cholestanol concentrations at the time of the CTX diagnosis, at baseline in the treatment period, and at Week 52, as well as the changes in serum cholestanol concentrations.

[14)] The subject experienced worsening of cholelithiasis (not related to Fujichenon) after receiving Fujichenon and underwent cholecystectomy. In consideration of potential effects of cholecystectomy on evaluation, the study for this subject was discontinued.

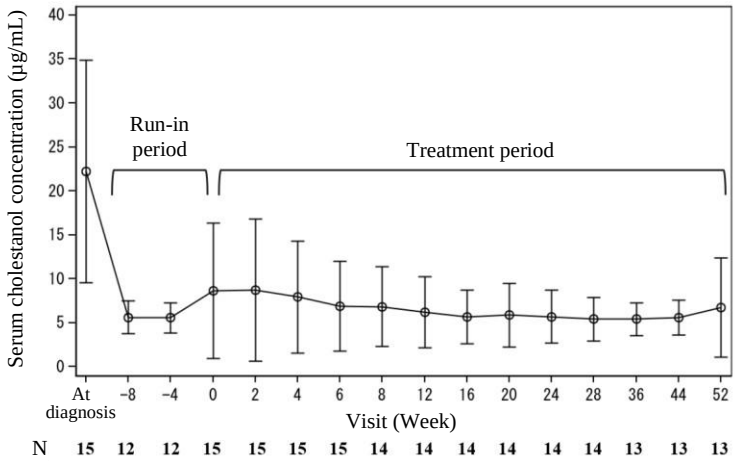

Figure 1. Time course of serum cholestanol concentrations during the study period (ITT population [only CDCA-experienced patients for the run-in period]; mean ± standard deviation)

Table 10. Serum cholestanol concentrations and their changes (ITT population)

Item	Before the run-in period	Treatment period	
	At CTX diagnosis (N = 15)	At baseline (N = 15)	At Week 52 (N = 13)
Serum cholestanol concentration	22.25 ± 12.66	8.66 ± 7.70	6.73 ± 5.67
Change from the time of CTX diagnosis	-	−13.59 ± 15.88	−16.64 ± 14.94
Change from baseline	-	-	−2.22 ± 8.56

Unit, μg/mL; mean ± standard deviation; -, not applicable

The safety results are as follows: Adverse events were observed in 73.3% (11 of 15) of subjects. Adverse events that occurred in ≥2 subjects during the treatment period were pyrexia (26.7% [4 of 15 subjects]), contusion (20.0% [3 of 15 subjects]), nasopharyngitis (13.3% [2 of 15 subjects]), and hepatic function abnormal (13.3% [2 of 15 subjects]). Adverse drug reactions were observed in 20.0% (3 of 15) of subjects (hepatic function abnormal [2 subjects] and flatulence [1 subject]).

There were no deaths. Serious adverse events were observed in 13.3% (2 of 15) of subjects (cholelithiasis and pyrexia [1 subject each]); however, neither of these events was assessed as an adverse drug reaction. No adverse events led to treatment discontinuation.

7.R Outline of the review conducted by PMDA

7.R.1 Development policy of Fujichenon

The applicant's explanation about the development policy of Fujichenon:

CTX is an autosomal recessive genetic disorder caused by mutations in the *CYP27A1* gene. In CTX patients, decreased activity of CYP27A1, an enzyme that is essential for the synthesis of primary bile acids, leads to a decrease in the production of bile acids including CDCA and an increase in the serum cholestanol concentration. Deposition of increased cholestanol in systemic organs causes organ disorders such as cerebellar ataxia, extrapyramidal symptoms, tendon xanthoma, and cataract. In Japan and overseas, there are many case reports evaluating the efficacy of CDCA in the treatment of CTX. In Japan, the Cerebrotendinous Xanthomatosis Management Guideline 2018 (approved by the Japanese Society of Neurology on May 23, 2018) positions replacement therapy with CDCA as the main treatment for CTX, stating that treatment with CDCA improves biochemical findings such as increased serum cholestanol concentration and prevents cholestanol accumulation

in the tissues. Overseas, CDCA is considered to be effective for CTX and is positioned as the standard treatment for CTX (*Orphanet J Rare Dis*. 2021;16:353, https://www.ncbi.nlm.nih.gov/books/NBK1409 [last accessed on June 27, 2025]). In Japan, however, no CDCA products have been approved for the indication of CTX, and a CDCA product that has been approved for another indication (Chino Capsules) has been used off-label for the treatment of CTX.

Against the above-mentioned background, the Japanese Society of Neurological Therapeutics submitted a development request for CDCA products with the indication of adult CTX to the Ministry of Health, Labour and Welfare. At the 31st meeting of the Study Group on Unapproved and Off-label Drugs of High Medical Need, the medical need was considered to be high, and the applicant was requested to undertake the development of this drug. It has been reported that once serious neuropsychiatric symptoms of CTX become manifest, only limited improvement of the symptoms can be achieved with treatment (*Eur J Neurol*. 2011;18:1203-1211, *Pediatrics*. 2009;123:143-147). In view of this, the applicant decided to include pediatric CTX patients in the target population for the development of Fujichenon, which led to the decision to develop Fujichenon as a mini-tablet formulation that can easily be taken by children, instead of adding CTX to the indication of the existing CDCA product Chino Capsules. In addition to this background, the following points were also considered in the development of Fujichenon: (a) It is difficult to conduct a clinical study on a scale that can statistically demonstrate its efficacy, because the number of CTX patients confirmed in Japan was 40 according to an epidemiological survey (*J Hum Genet*. 2018;63:271-280); (b) It is difficult to conduct a clinical study including a placebo group because CTX is a serious disease presenting with progressive neurological symptoms, etc. Based on these considerations, the applicant decided to conduct an open-label, single-arm study in Japan and to explain the efficacy and safety of Fujichenon using the study results, together with use experience and study reports of existing CDCA products.

PMDA's view:
CTX is a genetic disorder and requires continuous treatment from childhood. It is therefore appropriate to conduct the development by including pediatric CTX patients in addition to adult CTX patients who are the target population of the development request. The development of the mini-tablet formulation in consideration of the ease of administration for pediatric patients is also appropriate. In addition, considering the feasibility issues due to the rarity of the disease, and the existing off-label use of CDCA products for CTX in Japan, as well as the use experience of CDCA for CTX in Japan and overseas, the development strategy of Fujichenon, namely, to conduct an open-label, single-arm study in Japan and to evaluate the efficacy and safety of Fujichenon based on the study results and published reports, is considered appropriate. The efficacy and safety of Fujichenon are discussed in the following sections.

7.R.2 Efficacy

The applicant's explanation about the efficacy of Fujichenon based on the Japanese phase III study results and published articles:

7.R.2.1 Efficacy in adults

7.R.2.1.1 Japanese phase III study

The applicant's explanation:

The primary efficacy endpoint of the Japanese phase III study was the time course of serum cholestanol concentrations during the study period. Serum cholestanol concentration is positioned as the biochemical finding in the diagnostic criteria and an indicator for the assessment of the treatment effect in the Cerebrotendinous Xanthomatosis Management Guideline 2018 (approved by the Japanese Society of Neurology on May 23, 2018). Figure 1 and Table 10 show the results [see Section "7.1 Japanese phase III study"]. The mean serum cholestanol concentration decreased after administration of Fujichenon compared with the value at the time of the CTX diagnosis, and tended to remain low throughout the treatment period even when compared with the baseline of the treatment period. Table 11 shows the results of the main secondary endpoints. These results tended to be generally maintained.

Table 11. Results of main secondary endpoints (Japanese phase III study [treatment period]: ITT population)

Endpoint			At baseline (N = 15)	At Week 28 (N = 14)	At Week 52 (N = 13)
MMSE-J			26.5 ± 4.1	26.0 ± 3.8	25.8 ± 4.2
Rankin Scale	No symptoms		0 (0/14)	7.1 (1/14)	7.7 (1/13)
	No disabilities		21.4 (3/14)	21.4 (3/14)	23.1 (3/13)
	Mild		28.6 (4/14)	21.4 (3/14)	15.4 (2/13)
	Moderate		21.4 (3/14)	21.4 (3/14)	23.1 (3/13)
	Moderate to severe		28.6 (4/14)	21.4 (3/14)	30.8 (4/13)
	Severe		0 (0/14)	7.1 (1/14)	0 (0/13)
	Death		0 (0/14)	0 (0/14)	0 (0/13)
Brain MRI	With abnormalities		66.7 (10/15)	64.3 (9/14)	69.2 (9/13)
	Compared with baseline	Improved	-	0 (0/14)	0 (0/13)
		Unchanged	-	100 (14/14)	100 (13/13)
		Worsened	-	0 (0/14)	0 (0/13)
Spine MRI	With abnormalities		60.0 (9/15)	57.1 (8/14)	61.5 (8/13)
	Compared with baseline	Improved	-	0 (0/14)	0 (0/13)
		Unchanged	-	100 (14/14)	100 (13/13)
		Worsened	-	0 (0/14)	0 (0/13)
Bone density	Lumbar spine (g/cm^2)		0.84 ± 0.13	0.85 ± 0.14	0.85 ± 0.13
	Femoral neck (g/cm^2)		0.67 ± 0.16	0.66 ± 0.16	0.66 ± 0.15

MMSE-J and bone density: Mean ± standard deviation
Rankin Scale, brain MRI, and spine MRI: Proportion % (number of applicable subjects / number of subjects evaluated)
-: Not applicable

Figure 2 and Table 12 show the results of the primary endpoint by the status of previous treatment with CDCA products. Serum cholestanol concentrations in CDCA-naïve patients (3 subjects) gradually decreased from Week 4 compared with the baseline of the treatment period and remained low from Week 36 onward. In CDCA-experienced patients (12 subjects), serum cholestanol concentrations had decreased at baseline in the treatment period, compared with the value at the time of the CTX diagnosis, and were maintained at a similar level as at baseline after the start of treatment with Fujichenon throughout the study period.

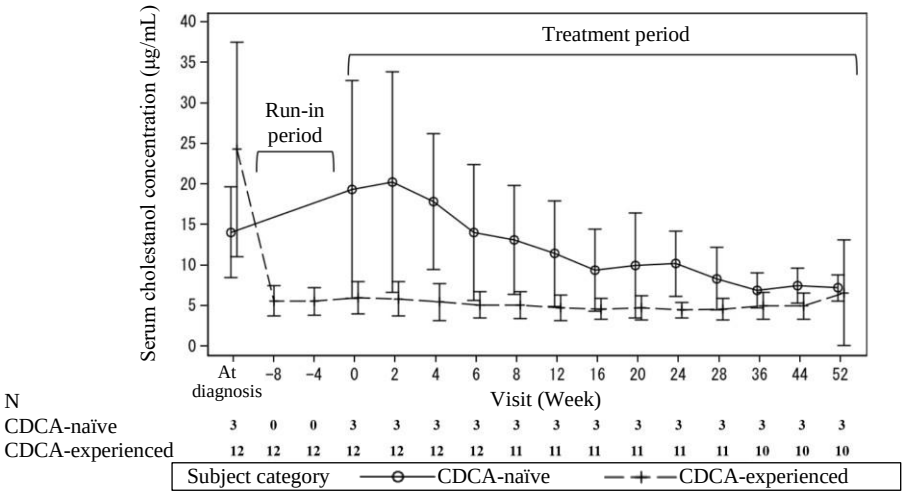

Figure 2. Time course of serum cholestanol concentrations during the study period by treatment status (Japanese phase III study: ITT population; mean ± standard deviation)

Table 12. Serum cholestanol concentrations and their changes by treatment status (Japanese phase III study: ITT population)

Item	CDCA-naïve			CDCA-experienced		
	At CTX diagnosis (N = 3)	At baseline (N = 3)	At Week 52 (N = 3)	At CTX diagnosis (N = 12)	At baseline (N = 12)	At Week 52 (N = 10)
Serum cholestanol concentration	14.07 ± 5.58	19.33 ± 13.42	7.20 ± 1.60	24.29 ± 13.25	5.99 ± 1.97	6.59 ± 6.49
Change from the time of CTX diagnosis	-	5.27 ± 9.19	−6.87 ± 3.99	-	−18.30 ± 13.58	−19.57 ± 15.90
Change from baseline	-	-	−12.13 ± 12.01	-	-	0.76 ± 4.79

Unit, μg/mL; mean ± standard deviation; -, not applicable

Figure 3 shows changes from baseline in the serum cholestanol concentration by the disease form of CTX (classical form [11 subjects], spinal form [3 subjects], and non-neurological form [1 subject]). In the patient group with classical form CTX, the change from baseline tended to be larger than that in other groups. This was considered because all 3 CDCA-naïve patients had the classical form of CTX. The efficacy of Fujichenon did not tend to differ among the different disease forms.

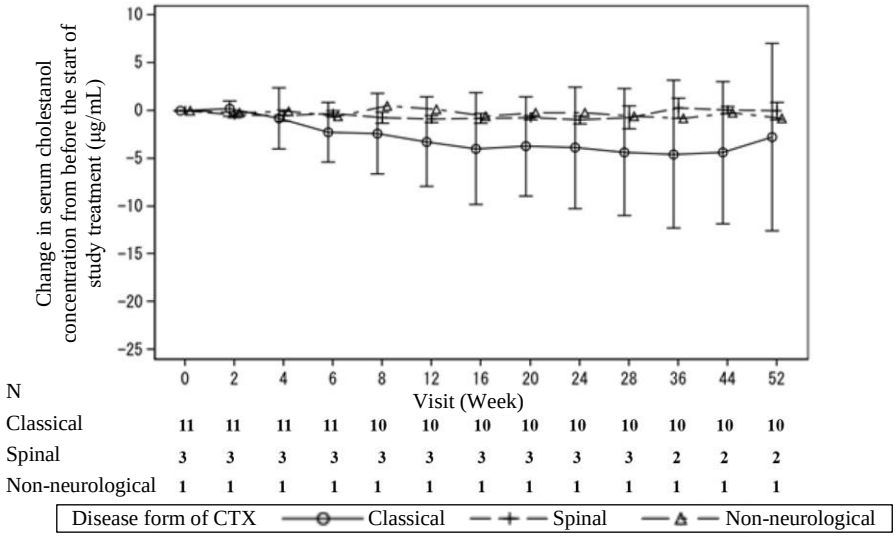

Figure 3. Change in serum cholestanol concentration from the baseline of the treatment period by disease form (Japanese phase III study: ITT population; mean ± standard deviation)

As described above, the results of the Japanese phase III study suggest the efficacy of Fujichenon for CTX.

7.R.2.1.2 Published articles

The applicant's explanation:

CDCA products have been used for the treatment of CTX for more than 30 years in Japan. A search was conducted for published articles reporting the efficacy of CDCA in Japanese adult CTX patients.[15)] The results showed 21 reports on a total of 28 patients treated with CDCA. In articles published since 2010 that include information on the dose of CDCA (Table 13), the observed symptoms varied among individual patients, and some patients did not show improvement in clinical symptoms, even after receiving CDCA. However, serum cholestanol concentrations decreased in all patients, and improvements in clinical symptoms, such as a reduction in the size of tendon xanthoma and improvement in cognitive function, were reported in some patients.

Table 13. Main published articles on CDCA treatment in Japanese adult CTX patients (since 2010)

No	Article	Age/sex	Dose of CDCA	Time course of serum cholestanol concentrations (μg/mL)	Description on the main CTX-related symptoms
1	*Prog Med*. 2013;33:1659-1661	45 years/female	375 mg/day	5.8 (before the start of treatment) → 2.9 (treatment duration unknown)	No descriptions.
2	*Neurological Therapeutics*. 2013;30:357-361	42 years/male	250-500 mg/day	31.2 (before the start of treatment) → 6.1 (after approx. 1 month of treatment)	Improvement of motor, swallowing, and cognitive functions, and reduction in the size of tendon xanthoma were observed.
3	*Intern Med*. 2014;53:2725-2729	47 years/male	750 mg/day	35.6 (before the start of treatment) → 4.1 (after approx. 1 year of treatment)	There was no worsening of clinical symptoms or findings.
4	*Intern Med*. 2018;57:1611-1616	50 years/female	500 mg/day	25.2 (before the start of treatment) → 7.8 (after 6 months of treatment) → 4.5 (after 12 months of treatment) → 5.4 (after 18 months of treatment)	Recurrence of surgically resected tendon xanthoma was prevented.
5	*Japanese Journal of Clinical Dermatology*. 2018;72:169-174	53 years/female	375 mg/day	23 (before the start of treatment) → 12 (after approx. 6 months of treatment)	Slight improvement of cognitive function was observed.
6	*Neurol Clin Neurosci*. 2019;7:209-211	43 years/female	625 mg/day	27.6 (before the start of treatment) → 5.0 (after approx. 1 year of treatment)	Slight improvement of gait disturbance was observed.
7	*Intern Med*. 2020;59:2587-2591	61 years/male	125-250 mg/day	14.1 (before the start of treatment) → 9.1 (after 21 days of treatment)	No descriptions.

[15)] Search formula, "cerebrotendinous xanthomatosis" and "chenodeoxycholic acid"; databases searched, JAMAS, Embase, and MEDLINE.

No	Article	Age/sex	Dose of CDCA	Time course of serum cholestanol concentrations (μg/mL)	Description on the main CTX-related symptoms
8	*BMC Neurol*. 2022;22:193	30 years/female	15 mg/kg/day	33.6 (before the start of treatment) → <5.0 (after approx. 60 months of treatment)	Early improvement of diarrhoea, normalization of electroencephalogram abnormalities, and improvement of IQ were observed. No neurological symptoms developed, except for transient obsessive-compulsive disorder. There was no worsening of MRI findings or bone density.
9		32 years/male	750 mg/day	27.5 (before the start of treatment) → <5.0 (after approx. 60 months of treatment)	Rapid disappearance of diarrhoea was observed. There were no changes in electroencephalogram abnormalities, but worsening of neuropsychiatric symptoms such as dysarthria, dysphagia, and spastic paraplegia were observed. On MRI, progressive signal abnormality and diffuse atrophy of the cerebellum were observed.

As described above, based on the results of the Japanese phase III study and information from published articles, Fujichenon is considered to be effective in adult CTX patients.

PMDA's view based on the applicant's explanations in Sections 7.R.2.1.1 and 7.R.2.1.2:
Considering the pathology of CTX and the mechanism of action of Fujichenon, the primary endpoint of the Japanese phase III study, which was defined as the time course of serum cholestanol concentrations, is appropriate. The results of the Japanese phase III study showed that serum cholestanol concentrations tended to be maintained in CDCA-experienced patients and tended to decrease in CDCA-naïve patients after administration of Fujichenon compared with before administration. The Japanese phase III study also confirmed that the efficacy of Fujichenon does not clearly differ by the disease form of CTX. Published articles on CDCA treatment in adult CTX patients include reports of decreased cholestanol concentrations and improvements in clinical symptoms, including cognitive function. Long-term maintenance of the efficacy was also confirmed in some reports. In view of the above review, as well as the fact that treatment with CDCA products is positioned as the standard treatment for CTX in Japan and overseas, Fujichenon can be expected to have efficacy in adult CTX patients.

7.R.2.2 Efficacy in children

The applicant's explanation:
Pediatric patients were not enrolled in the Japanese phase III study, although a pediatric cohort was planned and measures to promote subject enrollment, such as educational activities on CTX through relevant academic societies and extension of the enrollment period, were taken. Therefore, the efficacy in pediatric CTX patients was evaluated based on published articles. As a result of a search for published articles in Japan on CDCA use in pediatric CTX patients, 1 report was identified (*Neurological Therapeutics*. 2016;33:S198). In this article, CDCA (dose unknown) was administered to a 14-year-old CTX patient, and the cholestanol concentration decreased (23.9 μg/mL before administration and 3.4 μg/mL after administration), with disappearance of

tremor of the fingers in both hands and improvement in the intelligence quotient (IQ). This article did not include safety information.

While reports on pediatric CTX patients are limited in Japan, no differences in the mechanism of development, diagnostic criteria, or treatment method for CTX between Japan and foreign countries have been identified (Cerebrotendinous Xanthomatosis Management Guideline 2018. *Orphanet J Rare Dis*. 2021;16:353, https://www.ncbi.nlm.nih.gov/books/NBK1409 [last accessed on June 27, 2025]). Therefore, the efficacy of CDCA in pediatric CTX patients was investigated by searching for published articles on efficacy in non-Japanese pediatric CTX patients.[16)] The search identified 29 published articles on a total of 89 patients (including duplicates). These included articles published since 2019 in which CDCA was administered to pediatric CTX patients aged ≤15 years and the dose of CDCA and the time course of serum cholestanol concentrations before and after administration of CDCA could be confirmed. Table 14 shows these articles. In all of these reports, serum cholestanol concentration decreased. Of the 89 patients identified in the published articles, 55 patients had a documented decrease in serum cholestanol concentration after receiving CDCA, and improvement in diarrhoea (31 patients), improvement in intellectual disorder/mental retardation (14 patients), and improvement in epilepsy (2 patients) were also reported in some patients. According to the data tabulation based on 26 patients in 13 published articles on CDCA treatment in pediatric CTX patients that include information on serum cholestanol concentrations before administration of CDCA,[17)] the serum cholestanol concentration (mean ± standard deviation [range]; the same applies hereinafter) before administration of CDCA in pediatric CTX patients (1.4 weeks to 17 years of age) was 24.2 ± 8.2 [8.36, 40.9] μg/mL. This was similar to the serum cholestanol concentration (22.25 ± 12.66 [7.2, 49.6] μg/mL) at the time of the CTX diagnosis in 15 adult CTX patients in the Japanese phase III study.

Table 14. Main published articles on CDCA treatment in non-Japanese pediatric CTX patients (since 2019)

No	Article	Age/sex	Dose of CDCA	Time course of serum cholestanol concentrations (μg/mL)	Description on the main CTX-related symptoms
1	*Turk Pediatri Ars*. 2019;54:113-118	7 years/male	10 mg/kg/day	21.89 (before the start of treatment) → 5.46 (after 2 years and 7 months of treatment)	There were no significant differences in plasma 25-hydroxy vitamin D concentration or bone density before and after administration.
2		13 years/male	10 mg/kg/day	22.39 (before the start of treatment) → 6.12 (after 2 years and 1 month of treatment)	There were no significant differences in plasma 25-hydroxy vitamin D concentration or bone density before and after administration.

[16)] Search formula, "cerebrotendinous xanthomatosis" and "chenodeoxycholic acid"; databases searched, Embase and MEDLINE.
[17)] Of 29 published articles on CDCA treatment in pediatric CTX patients (search formula, "cerebrotendinous xanthomatosis" and "chenodeoxycholic acid"; databases searched, Embase and MEDLINE), 13 articles that include information on serum cholestanol concentrations before administration of CDCA were included in the tabulation.

No	Article	Age/sex	Dose of CDCA	Time course of serum cholestanol concentrations (μg/mL)	Description on the main CTX-related symptoms
3	*Acta Neurol Belg*. 2019;119:343-350	7 years/male	10 mg/kg/day	21.89 (before the start of treatment) → 2.55 (after 3 months of treatment)	Improvement of tremor and cognitive function was observed. There were no cerebellar findings, changes in atactic gait, worsened symptoms, neurological worsening, or new neurological findings.
4		11 years/female	10 mg/kg/day	18.41 (before the start of treatment) → 7.95 (after 3 months of treatment)	Improvement of atactic gait, tremor, and cognitive function was observed. There was no neurological worsening, and no new neurological findings were observed.
5		12 years/male	10 mg/kg/day	22.3 (before the start of treatment) → 6.12 (after 1 year of treatment)	Improvement of atactic gait, tremor, and behavioral disorder was observed. There were no worsened symptoms, neurological worsening, or new neurological findings.
6		15 years/female	10 mg/kg/day	27.48 (before the start of treatment) → 2.83 (after 3 months of treatment)	Improvement of atactic gait and tremor was observed. There were no changes in psychiatric disorder, worsened symptoms, neurological worsening, or new neurological findings.
7	*Front Pediatr*. 2020;8:382	8 months/female	10-15 mg/kg/day	31.4 (before the start of treatment) → <5 (after 12 years and 4 months of treatment)	Liver function test values and abdominal ultrasonographic findings were normal. There were no complications of CTX, and xanthomas of the Achilles tendon or other regions were not observed.

In a foreign clinical study using CDCA in pediatric CTX patients (*Genet Med Open*. 2025;3:102862, https://mirumpharma.com/wp-content/uploads/2025/04/Dutta-R-ACMG-2025-Safety-and-tolerability-of-CDCA-in-pediatric-patients-with-CTX.pdf [last accessed on June 27, 2025]), CDCA at doses of 5, 10, or 15 mg/kg/day was administered in 3 divided doses to 5 pediatric CTX patients (4-14 years of age) for 24 weeks, and changes in plasma cholestanol concentration were investigated. Plasma cholestanol concentration decreased at Week 24, compared with baseline, in 4 of the 5 patients. According to a report on 14-year treatment with CDCA in 4 non-Japanese pediatric or adult CTX patients (*Pediatrics*. 2009;123:143-147), 2 patients who were diagnosed with CTX at the age of 2 and 7 years did not develop any CTX-related symptoms after receiving CDCA and had a favorable course over a long period. In the other 2 patients, who were diagnosed with CTX at the ages of 16 and 27 years, although serum cholestanol concentration decreased after administration of CDCA, decreased cognitive function, muscle weakness, and tendon xanthomas were observed.

In view of the above information obtained from published articles, Fujichenon can be expected to have efficacy in pediatric CTX patients as well, and it is important to initiate treatment for the neuropsychiatric symptoms of CTX at an early stage of the disease.

PMDA's view:

Although pediatric patients were not enrolled in the Japanese phase III study, transporters involved in the pharmacokinetics of CDCA are expressed to a certain extent even in childhood, and the bile acid kinetics following administration of CDCA in pediatric CTX patients are therefore not expected to differ substantially from those in adult CTX patients. In addition, FXR, the target of CDCA, is also expressed in childhood [see Section "6.R.1 Bile acid kinetics following administration of Fujichenon in adult and pediatric CTX patients"]. Thus, from the perspective of pharmacokinetics and the mechanism of action, Fujichenon can be expected to be effective in CTX in childhood, as in adulthood. Furthermore, based on the information from published articles, serum cholestanol concentrations can be confirmed to be high in pediatric CTX patients, as in adult CTX patients. In fact, there are several foreign articles reporting findings following CDCA treatment in pediatric CTX patients, such as a decrease in serum cholestanol concentration and improvement in subjective symptoms. There are also reports suggesting that early initiation of treatment is more useful. Taken all together, the conclusion that Fujichenon can be expected to have efficacy in pediatric CTX patients as well, is acceptable. The appropriateness of the dosage and administration of Fujichenon in pediatric CTX patients is further discussed in Section "7.R.5.2 Dosage and administration for pediatric patients."

7.R.3 Safety

The applicant's explanation about the safety of Fujichenon based on the Japanese phase III study and published articles:

7.R.3.1 Safety in adults

7.R.3.1.1 Results of the Japanese phase III study

Table 15 shows the incidence of adverse events by the status of previous treatment with CDCA or by the disease form of CTX in the Japanese phase III study. Serious adverse events observed were pyrexia (1 CDCA-naïve patient with classical form CTX) and cholelithiasis (1 CDCA-experienced patient with spinal form CTX), and neither of the events was assessed as an adverse drug reaction. One event resolved and the other improved with continued treatment with Fujichenon. No clear differences were observed in the incidences of adverse events after administration of Fujichenon by the status of previous treatment with CDCA or by the disease form of CTX.

Table 15. Incidence of adverse events by the status of previous treatment with CDCA or by the disease form of CTX (Japanese phase III study: safety analysis set)

Event	By the status of previous treatment		By disease form			Overall population (N = 15)
	CDCA-naïve (N = 3)	CDCA-experienced (N = 12)	Classical (N = 11)	Spinal (N = 3)	Non-neurological (N = 1)	
All adverse events	66.7 (2)	75.0 (9)	72.7 (8)	66.7 (2)	100.0 (1)	73.3 (11)
All adverse drug reactions	66.7 (2)	8.3 (1)	18.2 (2)	33.3 (1)	0 (0)	20.0 (3)
Death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events	33.3 (1)	8.3 (1)	9.1 (1)	33.3 (1)	0 (0)	13.3 (2)
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Liver disorder-related adverse events[a)]	33.3 (1)	8.3 (1)	9.1 (1)	33.3 (1)	0 (0)	13.3 (2)

MedDRA/J ver.27.1; incidence % (n)

a) Events classified under SOC "hepatobiliary disorders"

Table 16 shows the incidence of adverse events observed in ≥2 subjects in the overall population by the status of previous treatment with CDCA or by the disease form of CTX during the study period of the Japanese phase III study. Adverse drug reactions were observed in 20.0% (3 of 15) of subjects in the overall population. These adverse drug reactions were hepatic function abnormal (2 subjects; 1 CDCA-naïve patient with classical form CTX and 1 CDCA-experienced patient with spinal form CTX) and flatulence (1 subject; CDCA-naïve patient with classical form CTX). All of these were known events of CDCA products.

Table 16. Incidence of adverse events observed in ≥2 subjects in the overall population by the status of previous treatment with CDCA or by the disease form of CTX (Japanese phase III study: safety analysis set)

Event	By the status of previous treatment		By disease form			Overall population (N = 15)
	CDCA-naïve (N = 3)	CDCA-experienced (N = 12)	Classical (N = 11)	Spinal (N = 3)	Non-neurological (N = 1)	
All adverse events	66.7 (2)	75.0 (9)	72.7 (8)	66.7 (2)	100.0 (1)	73.3 (11)
Pyrexia	33.3 (1)	25.0 (3)	27.3 (3)	33.3 (1)	0 (0)	26.7 (4)
Contusion	0 (0)	25.0 (3)	18.2 (2)	0 (0)	100.0 (1)	20.0 (3)
Nasopharyngitis	0 (0)	16.7 (2)	9.1 (1)	33.3 (1)	0 (0)	13.3 (2)
Hepatic function abnormal	33.3 (1)	8.3 (1)	9.1 (1)	33.3 (1)	0 (0)	13.3 (2)

MedDRA/J ver.27.1; incidence % (n)

Based on the above, the Japanese phase III study showed that Fujichenon was well-tolerated in CTX patients at doses up to 1000 mg/day.

7.R.3.1.2 Published articles

Table 17 shows published articles on CDCA treatment in Japanese adult CTX patients that include safety information. Both articles refer to liver disorder-related events, which were known events of CDCA products. No safety information that is considered to correspond to death or a serious event was identified.

Table 17. List of published articles on the safety of CDCA in Japanese adult CTX patients

No	Article	Age/sex	Dose of CDCA	Description on safety
1	*J Neurol Sci*. 1994;125:22-28	Both age and sex unknown	300 mg/day	Liver disorder was observed 6 months after the start of treatment, and the treatment was discontinued.
2	*Intern Med*. 2020;59:2587-2591	61 years/male	250 mg/day	Treatment with CDCA 250 mg/day was started in the patient with alcoholic liver disease. Drug-induced liver disorder was observed after the start of treatment, and the dose was reduced to 125 mg/day.

As described above, no new concerns were raised, compared with the safety results obtained in the Japanese phase III study.

7.R.3.2 Safety in children

There were 7 published articles on CDCA treatment in non-Japanese pediatric CTX patients that included safety information. Table 18 summarizes these articles. No adverse drug reactions were observed after administration of CDCA in 16 of the 17 patients reported in these articles. In the remaining 1 patient, liver disorder-related events were observed after administration of CDCA. These events resolved after interruption of CDCA.

Table 18. List of published articles on the safety of CDCA in non-Japanese pediatric CTX patients

No	Article	Age/sex	Dose of CDCA	Description on safety
1	*Pediatrics*. 2009;123:143-147	2 years/female	750 mg/day	During the treatment period of 14 years, no adverse drug reactions were observed.
2		7 years/female	750 mg/day	During the treatment period of 14 years, no adverse drug reactions were observed.
3		16 years/male	1000 mg/day	During the treatment period of 14 years, no adverse drug reactions were observed.
4	*Eur J Pediatr*. 2016;175:143-146	1.4 weeks/female	5-15 mg/kg/day	Treatment was started at 15 mg/kg/day. Jaundice, pruritus, hepatomegaly, and increased AST and ALT were observed approximately 6 weeks after the start of treatment, and the treatment was interrupted approximately 8 weeks after the start of treatment. The size of the liver normalized within 1 month after the interruption of treatment, and liver enzyme levels normalized within 3 months after the interruption of treatment. Approximately 10 weeks after the interruption of treatment, the treatment was resumed at 5 mg/kg/day.
5	*J Pediatr Gastroenterol Nutr*. 2017;64:622	8 months/female	15 mg/kg/day	No adverse drug reactions were observed.
6	*J Inherit Metab Dis*. 2018;41:799-807	8 years/male	No descriptions	CDCA was well-tolerated and liver function was normal.
7		14 years/female	No descriptions	CDCA was well-tolerated and liver function was normal.
8		17 years/female	No descriptions	CDCA was well-tolerated and liver function was normal.
9	*Turk Pediatri Ars*. 2019;54:113-118	7 years/male	10 mg/kg/day	During the treatment period of 2 years and 7 months, no adverse drug reactions were observed.
10		13 years/male	10 mg/kg/day	During the treatment period of 2 years and 1 month, no adverse drug reactions were observed.
11		16 years/female	10 mg/kg/day	During the treatment period of 2 years and 7 months, no adverse drug reactions were observed.
12	*Acta Neurol Belg*. 2019;119:343-350	7 years/male	10 mg/kg/day	During the treatment period of 1 year, no adverse drug reactions were observed.
13		11 years/female	10 mg/kg/day	During the treatment period of 7 months, no adverse drug reactions were observed.
14		12 years/male	10 mg/kg/day	During the treatment period of 1 year, no adverse drug reactions were observed.
15		15 years/female	10 mg/kg/day	During the treatment period of 1 year, no adverse drug reactions were observed.
16		17 years/male	10 mg/kg/day	During the treatment period of 1 year, no adverse drug reactions were observed.
17	*Front Pediatr*. 2020;8:382	8 months/female	15 mg/kg/day	During the treatment period of 13 years, no adverse drug reactions were observed.

In the foreign clinical study using CDCA in pediatric CTX patients (*Genet Med Open*. 2025;3:102862, https://mirumpharma.com/wp-content/uploads/2025/04/Dutta-R-ACMG-2025-Safety-and-tolerability-of-CDCA-in-pediatric-patients-with-CTX.pdf [last accessed on June 27, 2025]), CDCA at doses of 5, 10, or 15 mg/kg/day was administered in 3 divided doses to 5 pediatric CTX patients (4-14 years of age) for 24 weeks. The results showed no serious adverse events. An event leading to study discontinuation was observed in 1 subject (blood bilirubin increased). However, no adverse drug reactions were observed.

Based on the above review, no significant safety concerns were identified from the published articles on CDCA in pediatric CTX patients.

PMDA's view based on the applicant's explanations in Sections 7.R.3.1 and 7.R.3.2:
Safety in adult CTX patients: In the Japanese phase III study, the adverse drug reactions observed (hepatic function abnormal and flatulence) were known events of CDCA products, and no serious adverse drug reactions were observed. In addition, none of the subjects, including those with serious adverse events, discontinued the treatment due to safety reasons. All of the events identified in published articles involved liver

disorders. Thus, when CDCA was administered to adult CTX patients, no concerns exceeding the safety profile of existing CDCA products were identified. Safety in pediatric CTX patients: Although the obtained information is limited, the only event identified in published articles was liver disorder in 1 patient, suggesting no safety concerns specific to pediatric CTX patients. As reviewed in Section "7.R.3.3 Liver disorder," if an appropriate precaution is taken concerning liver disorder, an adverse drug reaction of concern with the use of Fujichenon, the safety of Fujichenon can be managed. Therefore, the safety of Fujichenon is clinically acceptable in view of its efficacy.

7.R.3.3 Liver disorder

The applicant's explanation:

In the repeated-dose toxicity study of CDCA in rhesus monkeys, liver disorder was observed. The disorder was suppressed when the LCA concentration in the bile was decreased. In view of this and other related information, liver disorder after administration of CDCA may be attributable to LCA production due to the enteric bacteria-mediated metabolism of CDCA (*Lancet*. 1975;1:1082). Based on the above finding, the package insert of Chino Capsules includes a precaution that liver function tests should be performed during treatment and lists patients with serious liver disorder as a contraindication.

In a clinical study of Chino Capsules in patients with cholesterol gallstones, hepatic dysfunction[18)] was reported as an adverse drug reaction in 6 of 110 subjects who received Chino Capsules. The maximum ALT or AST level was <100 U and the event resolved in all 6 subjects. After the market launch of Chino Capsules, hepatic dysfunction[19)] was observed in 9 patients (8 patients with CTX and 1 patient with gallstones). The patient with gallstones had a complication of cirrhosis. The event observed in this patient (induction of liver failure symptoms) was serious and assessed as an adverse drug reaction. It was resolving with appropriate treatment after discontinuation of treatment with Chino Capsules. The events observed in 8 patients with CTX were non-serious and assessed as adverse drug reactions. All of these events resolved or were resolving, except for 1 patient with an unknown outcome.

In the Japanese phase III study of Fujichenon, hepatic function abnormal was observed in 13.3% (2 of 15) of subjects. Both events were non-serious, mild or moderate in severity, and resolved after treatment interruption or dose reduction of Fujichenon. Treatment with Fujichenon was continued in these 2 subjects. Liver disorder-related events were also reported in published articles on the safety of CDCA in Japanese adult CTX patients and non-Japanese pediatric CTX patients (Table 17 and Table 18).

Based on the above information, although liver disorder may be observed after administration of Fujichenon, reports of serious events were limited, and such events generally resolved with treatment interruption or other measures. The risk of liver disorder associated with treatment with Fujichenon is therefore considered acceptable in view of its benefits. However, it is necessary to include a precaution in the package insert that

[18)] Events of which the reported term is classified as hepatic dysfunction.
[19)] Events classified under SMQ "hepatic disorders" (broad).

liver function tests should be performed as needed and that patients should be carefully monitored during treatment with Fujichenon.

Although published articles on treatment with CDCA products in CTX patients with serious liver disorder were searched,[20] no relevant reports were identified. Considering that CDCA production in the body is decreased in CTX patients, whereas it is normal in cholelithiasis patients, the risk of liver disorder associated with treatment with Fujichenon may be lower in CTX patients with serious liver disorder than in cholelithiasis patients with serious liver disorder. Since CTX is a disease that causes serious neuropsychiatric symptoms, it is considered appropriate that the package insert should not contraindicate the use of Fujichenon in patients with serious liver disorder, but should allow its use, with a precaution that Fujichenon should be carefully administered to these patients while their condition is monitored.

PMDA's view:
Since liver disorder after administration of CDCA has been reported in the clinical studies and post-marketing experience of Chino Capsules, in the Japanese phase III study of Fujichenon, and in published articles on CDCA treatment in CTX patients, liver disorder is considered a risk associated with Fujichenon. However, the confirmed cases of liver disorder were generally mild or moderate, and resolved or were resolving with treatment interruption or other measures. Therefore, the risk of liver disorder can be managed by including a precaution that liver functions should be monitored during treatment with Fujichenon, and is acceptable in view of the drug's benefits. In addition, considering the risk-benefit balance of Fujichenon in CTX patients with serious liver disorder, the applicant's response, namely, not to specify these patients as contraindicated, unlike Chino Capsules, but to include a precaution that Fujichenon should be carefully administered to these patients while closely observing their condition, is justified. A final decision on the appropriateness of the precautions will be made based on the comments from the Expert Discussion.

7.R.4 Indication and clinical positioning

The applicant's explanation about the clinical positioning of Fujichenon:
A product containing cholic acid (CA) as the active ingredient is the only drug approved in Japan with indications related to CTX and is approved for the indication of "inborn errors of bile acid metabolism."[21] In CTX, decreased ability to synthesize primary bile acids results in reduced negative feedback on CYP7A1. It has been reported that administration of CA may normalize the negative feedback on CYP7A1 and inhibit the production of abnormal metabolites (*Liver disease in children*. *Cambridge University Press*. 2014.p567-586). However, in view of the efficacy and safety results of the Japanese phase III study as well as the following points, Fujichenon, a CDCA product, is considered the first-line therapy for CTX in Japan.

[20] Search formula, "cerebrotendinous xanthomatosis" and "chenodeoxycholic acid" and ("liver diseases" or "cholestasis"); databases searched, Embase and MEDLINE.
[21] Indicated for the following congenital enzyme deficiencies in the bile acid biosynthesis pathway, including CTX (CYP27A1 deficiency): 3β-HSD deficiency, Δ4-3-oxoR deficiency, CYP7B1 (oxysterol 7α-hydroxylase) deficiency, CYP7A1 (cholestarol 7α-hydroxylase) deficiency, AMACR (α-methylacyl-CoA racemase) deficiency, ACOX2 (acyl-CoA oxidase II) deficiency, DBD (D-bifunctional protein) deficiency, SCPx (sterol carrier protein X) deficiency, and ABCD3 (70-kDa peroxisomal membrane protein) deficiency.

- While both CA and CDCA act as FXR agonists and exert negative feedback on CYP7A1, CDCA has a stronger FXR activity than CA [see Section "3.1.1.1 FXR activation by various bile acids"], suggesting that the negative feedback on CYP7A1 is more potent with CDCA than with CA.
- A report states that CA is only effective for non-neurological symptoms in CTX patients (*Orphanet J Rare Dis*. 2014;9:179), and another report on the treatment of inborn errors of bile acid synthesis[22)] states that CA is not the first-line therapy but can be used only when there is a problem with the tolerability or efficacy of CDCA.
- The Cerebrotendinous Xanthomatosis Management Guideline 2018 (approved by the Japanese Society of Neurology on May 23, 2018) states that the main treatment for CTX is CDCA, and Chino Capsules, a product approved for marketing with the indication of "dissolution of cholesterol gallstones without shell calcification," are used off-label in actual clinical practice in Japan (*J Lipid Res*. 1991;32:223-229, *J Neurol Sci*. 1994;125:22-28, etc.).

Considering its mechanism of action, CDCA may also be effective for inborn errors of bile acid metabolism other than CTX. However, no published articles were identified that report the efficacy of monotherapy with CDCA for inborn errors of bile acid metabolism.

Based on the above review, and because the results of the Japanese phase III study in CTX patients demonstrated the efficacy of Fujichenon in CTX [see Section "7.R.2 Efficacy"] and showed that its safety is acceptable if appropriate precautions are provided [see Section "7.R.3 Safety"], the indication of Fujichenon was set as "cerebrotendinous xanthomatosis."

PMDA's view:
Based on the results of the Japanese phase III study in patients with CTX and published articles, Fujichenon can be expected to have efficacy, and its safety is acceptable in view of its demonstrated efficacy [see Sections "7.R.2 Efficacy" and "7.R.3 Safety"]. Therefore, setting the indication of Fujichenon as "cerebrotendinous xanthomatosis" is appropriate. Although CA is indicated for CTX in Japan, the provision of Fujichenon as the first-line therapy for CTX in clinical practice is considered to be meaningful in view of the following points: (a) CDCA has been reported to have a stronger FXR activity than CA in an *in vitro* investigation; (b) CDCA products have a certain level of clinical evidence for the treatment of CTX; and (c) CDCA is positioned as the standard treatment in the Japanese clinical management guidelines.

7.R.5 Dosage and administration

7.R.5.1 Dosage and administration for adult patients

The applicant's explanation:
The dosage regimen in the adult cohort of the Japanese phase III study was set as follows:

- Dosage regimen:

22) https://www.orpha.net/en/disease/detail/909 (last accessed on June 27, 2025)

Fujichenon was orally administered 3 times daily on consecutive days because a lower dose per administration was considered to ensure the safety of subjects.

- Administration method:
  In consideration of safety, Fujichenon was administered with dose escalation. The dose was escalated every 2 weeks, assuming a time to the steady state of approximately 10 days because the elimination half-life of CDCA is calculated to be approximately 2 days based on the metabolic turnover rate of the CDCA pool in healthy adults (*J Lipid Res*. 1994;35:1462-1468, etc.), and also taking the feasibility of the study into account.

- Standard dose:
  The Cerebrotendinous Xanthomatosis Management Guideline 2018 (approved by the Japanese Society of Neurology on May 23, 2018) recommends 750 mg/day as the dose of CDCA for adult patients with CTX. In addition, the starting dose of a CDCA product (brand name: Leadiant) approved in Europe is 750 mg/day. Therefore, the standard dose of Fujichenon was set at 750 mg/day.

- Starting dose:
  The initial dose of Fujichenon in CDCA-naïve patients was set at 250 mg/day in view of the following points: (a) The approved standard dose of Chino Capsules is 300 to 400 mg/day; (b) No serious adverse events were reported at 300 mg/day in Japanese case reports of CDCA treatment for CTX (*J Lipid Res*. 1991;32:223-229, *J Neurol Sci*. 1994;125:22-28, etc.), suggesting that CDCA is tolerable at this dose; (c) The interval for dose escalation up to the standard dose of 750 mg/day and the dosage form of Fujichenon.

  The initial dose for CDCA-experienced patients was set to be the same as the dose of CDCA prior to enrollment.

- Dose adjustment and maximum dose:
  The dose of Fujichenon could be adjusted as appropriate according to the subject's symptoms and other conditions. The maximum daily dose was set at 1000 mg/day, which is the same as the approved maximum dose of the CDCA product in Europe. The maximum single dose was set at 375 mg, because CDCA at doses up to 400 mg per administration is reported to be absorbed in the gastrointestinal tract and enter the enterohepatic circulation (*Gastroenterology*. 1977;73:300-309), and also taking into account the active ingredient contents per Fujichenon tablet (25 mg) and per packet (125 mg).

In the Japanese phase III study conducted with the above settings, the daily dose (median [range] (number of subjects) during the treatment period was 750 [125, 1000] mg (14 subjects) from Week 24 to Week 28, and 750 [125, 1000] mg (13 subjects) from Week 44 to Week 52. All 3 CDCA-naïve patients started treatment with Fujichenon at 250 mg/day. In 1 of the 3 subjects, an adverse drug reaction (hepatic function abnormal) occurred

at 250 mg/day. However, the dose could be escalated stepwise to 750 mg/day after confirming that there were no safety concerns for the subject.

During the study period, the dose of Fujichenon administered for the longest duration was 750 mg/day in 6 of 15 subjects. Serum cholestanol concentrations in 5 of the 6 subjects (excluding 1 subject[23)]) were generally maintained at low levels, and no particular safety concerns were identified. The daily Fujichenon dose of 1000 mg was administered to 4 of the 15 subjects. Although 1 of the 4 subjects discontinued the study due to withdrawal of consent, 2 subjects continued the treatment at 1000 mg/day until Week 52, and 1 subject underwent dose reduction to 750 mg/day due to diarrhoea (non-serious, not related to Fujichenon) and then continued the treatment at this dose until Week 52. The 2 subjects who continued the treatment at 1000 mg/day developed non-serious adverse events (dysarthria/pyrexia and face injury/musculoskeletal pain in 1 subject each). All of these events resolved or improved, and were not considered adverse drug reactions. The maximum single dose of Fujichenon 375 mg was administered to 5 of the 15 subjects (the maximum daily dose was 1000 mg in 4 subjects and 875 mg in 1 subject; all were CDCA-experienced patients). Of the 5 subjects, 1 subject (maximum daily dose, 1000 mg) discontinued the study due to withdrawal of consent, and 1 subject (maximum daily dose, 1000 mg) underwent dose reduction to 750 mg/day due to diarrhoea as described above. The remaining 3 subjects (maximum daily dose, 1000 mg in 2 subjects and 875 mg in 1 subject) continued the treatment with Fujichenon until Week 52. Of them, 1 subject (maximum daily dose, 875 mg) developed non-serious adverse events (otitis externa/immunisation reaction/nasopharyngitis/vomiting/menstruation irregular/head injury/contusion). All of these events resolved and were not considered adverse drug reactions.

As described above, the results of the Japanese phase III study demonstrated the efficacy of Fujichenon [see Section "7.R.2 Efficacy"] and showed that there were no significant tolerability problems [see Section "7.R.3 Safety"]. It is therefore appropriate to set the proposed dosage and administration based on the settings in the Japanese phase III study as follows: The starting dose is 250 mg/day of CDCA, followed by a dose increase up to 750 mg/day in increments of 250 mg, and the maintenance dose of 750 mg/day is administered in 3 divided doses daily on consecutive days; the dose is adjusted as appropriate according to the patient's condition; the maximum daily dose should be 1000 mg and the maximum single dose should be 375 mg. Although dose escalation every 2 weeks was adopted in the Japanese phase III study, there may be cases where the interval between hospital visits may need to be <2 weeks to closely observe the course for dose adjustment. Therefore, the interval for dose escalation was not specified in the dosage and administration. In the Japanese phase III study, CDCA-experienced patients started treatment with Fujichenon at the dose before enrollment. As a result, no particular safety concerns were raised and the efficacy also tended to be maintained in these patients. It is therefore appropriate to start treatment with Fujichenon at the same dose as existing CDCA products in CDCA-experienced patients.

[23)] A 5[redacted]-year-old CDCA-experienced patient. Treatment with Fujichenon was continued at 750 mg until Week 24. The dose was then increased to 1000 mg, but reduced to 750 mg due to diarrhoea (non-serious, not related to Fujichenon) at Week 28. This dose was continued until Week 52. Serum cholestanol concentrations were 10.4 μg/mL before the start of treatment with Fujichenon and generally <10 μg/mL during the study period. The concentration at Week 52 was 24.6 μg/mL. This subject was [redacted], and may therefore have had poor medication compliance after Week 44.

Furthermore, since Fujichenon is a mini-tablet formulation and one packet (aluminum package) contains five 25 mg tablets, patients may have to take the drug on a tablet basis according to the dose after opening the packet. Therefore, information necessary for the administration of Fujichenon, including the number of tablets required per administration and the storage period after opening, will be provided to healthcare professionals using the information materials.

PMDA's view:
The results of the Japanese phase III study demonstrated the efficacy of Fujichenon in adult CTX patients and suggested that its safety is acceptable. The daily doses in adult CTX patients reported in published articles were within the range of the setting in the phase III study (Table 13). The following dosage and administration of Fujichenon for adult CTX patients, which was set in accordance with the Japanese phase III study, is therefore appropriate: The starting dose of 250 mg/day is administered in 3 divided doses daily on consecutive days, followed by a dose increase up to 750 mg/day in increments of 250 mg/day if there are no safety concerns, and the standard dose of 750 mg/day is adjusted as appropriate according to the patient's condition. In view of the safety results of the Japanese phase III study and other related information, the maximum daily dose can be set at 1000 mg, and the maximum single dose at 375 mg. The starting dose of Fujichenon for patients who have used existing CDCA products off-label, which was set at the same dose level as the existing CDCA products in accordance with the Japanese phase III study, is also justified. It is appropriate to provide information on the dose at the time of switching in CDCA-experienced patients using the information materials.

The applicant explained that the interval for dose escalation is not specified in the dosage and administration. Considering that the dose may be escalated according to the patient's condition or background in actual clinical practice, it is not necessary to specify that the dose should be uniformly escalated every 2 weeks. However, given that the interval for dose escalation in the Japanese phase III study was set in consideration of the time required for CDCA to reach the steady state, it is appropriate to include a precaution in the package insert that the dose is escalated at approximately 2-week intervals. Since Fujichenon is a mini-tablet formulation and one packet contains several mini-tablets, the applicant's decision to provide information on the administration method required for actual use using the information materials and other documents, is appropriate.

A final decision on the justification of the wording and other details of the statements for Dosage and Administration and Precautions Concerning Dosage and Administration will be made based on the comments from the Expert Discussion.

7.R.5.2 Dosage and administration for pediatric patients

The applicant's explanation:
The dosage regimen in the pediatric cohort of the Japanese phase III study was set as follows:

- Dosage regimen:
  Fujichenon was orally administered 3 times daily on consecutive days, as in the adult cohort.

- Administration method:
  The dose was escalated every 2 weeks, as in the adult cohort.

- Standard dose:
  The Cerebrotendinous Xanthomatosis Management Guideline 2018 (approved by the Japanese Society of Neurology on May 23, 2018) recommends 15 mg/kg/day as the dose of CDCA for CTX in children. The maximum dose of the CDCA product approved in Europe for CTX in children is also 15 mg/kg/day. In view of these, the standard dose of Fujichenon in the pediatric cohort of the Japanese phase III study was set at 15 mg/kg/day, and the dose of Fujichenon could be adjusted as appropriate according to the subject's symptoms and other conditions.

- Starting dose:
  The starting dose of Fujichenon was set at 5 mg/kg/day, which is the same as the starting dose of the CDCA product approved in Europe. In the pediatric cohort, the dose in subjects weighing >50 kg may exceed the standard dose in the adult cohort. To ensure the safety of subjects, the maximum dose was specified as 250 mg/day at 5 mg/kg/day, 500 mg/day at 10 mg/kg/day, and 750 mg/day at 15 mg/kg/day.

- Dose adjustment and maximum dose:
  The dose of Fujichenon could be adjusted as appropriate according to the subject's symptoms and other conditions, as in adults. The maximum daily dose was set at 15 mg/kg/day and 750 mg/day, and the maximum single dose was set at 375 mg in reference to the maximum dose in the adult cohort.

However, since pediatric patients were not enrolled in the Japanese phase III study, the dosage and administration of Fujichenon for pediatric CTX patients is discussed as follows:

Information on the efficacy and safety of CDCA in pediatric CTX patients is limited. Among a total of 89 patients (including duplicate cases) identified from 29 published articles, the dose of CDCA was reported in 73 patients. Table 19 shows information on the dose in these 73 patients. CDCA was administered generally at 5 to 15 mg/kg/day in pediatric CTX patients. Accordingly, consistent with the dosing regimen in the phase III study, it was considered appropriate to set the starting dose of Fujichenon at 5 mg/kg/day and the standard and maximum doses at 15 mg/kg/day, with dose adjustment as appropriate according to the patient's condition. The dosage and dose escalation method for pediatric patients should be the same as those for adult patients; however, no clinical experience with Fujichenon in pediatric patients was obtained in the Japanese phase III study. Therefore, it was considered appropriate not to set the maximum daily dose and the maximum single dose in the same manner as for adult patients.

Table 19. Dose of CDCA in published articles on CDCA treatment in pediatric CTX patients

Dose of CDCA	N	Article
5-15 mg/kg/day	22	*Eur J Pediatr*. 2016;175:143-146, *Neurology*. 2019;92:e83-e95
10-15 mg/kg/day	3	*Front Pediatr*. 2020;8:382, *J Hepatol*. 2022;77:S533
5 mg/kg/day	2	*Egypt J Med Hum Genet*. 2023;24:34
10 mg/kg/day	8	*Turk Pediatri Ars*. 2019;54:113-118, *Acta Neurol Belg*. 2019;119:343-350
15 mg/kg/day	20	*Acta Paediatr*. 1996;85:932-936, *Eur J Pediatr*. 1998;157:313-316, *J Inherit Metab Dis*. 2008;31 Suppl 2:S387-S393, *J Pediatr Gastroenterol Nutr*. 2017;64:622, *JIMD Rep*. 2020;56:105-111
250 mg/day	1	*J AAPOS*. 2017;21 505-507
500 mg/day	1	*J Clin Lipidol*. 2017;11:819-820
750 mg/day	15	*J Neurol Sci*. 1994;122:102-108, *Pediatrics*. 2009;123:143-147, *Am J Med Sci*. 2012;343:332-333, *Clin Neuropharmacol*. 2013;36:78-83, *J Neurol*. 2013;260:268-274, *Calcif Tissue Int*. 2013;92:282-286, *J Inherit Metab Dis*. 2016;39:75-83, *Horm Res Paediatr*. 2016;86:339-340, *J Neurol*. 2017;264:862-874
1000 mg/day	1	*Pediatrics*. 2009;123:143-147

PMDA's view:

In published articles in non-Japanese pediatric CTX patients, CDCA was administered generally at 5 to 15 mg/kg/day (Table 19) and certain levels of efficacy and safety were reported [see Sections "7.R.2.2 Efficacy in children" and "7.R.3.2 Safety in children"]. According to the Cerebrotendinous Xanthomatosis Management Guideline 2018 (approved by the Japanese Society of Neurology on May 23, 2018), 15 mg/kg/day is recommended as the dose of CDCA for CTX in children. The guideline also states that, if treatment at 15 mg/kg/day is difficult, the treatment should preferably be continued at doses not causing adverse drug reactions, because decreases in serum cholestanol concentrations may be observed even at low doses. In addition, according to the dosage and administration for children (1-18 years of age) of the CDCA product approved in Europe, the starting dose is 5 mg/kg/day and the maximum dose is 15 mg/kg/day, administered in 3 divided doses. In view of the above, the dosage and administration for pediatric CTX patients can be set based on the specifications for the pediatric cohort in the Japanese phase III study, as explained by the applicant. Although the maximum single dose was set at 375 mg in the Japanese phase III study, pediatric patients were not enrolled in the study, and published articles provide no sufficient evidence to determine the appropriateness of the dose. Therefore, treatment at 375 mg as the maximum single dose should not be allowed. A final decision on the justification for setting of the dosage and administration and specific statements for related precautions will be made also taking account of the comments from the Expert Discussion.

7.R.6 Post-marketing investigations

The applicant's explanation:

In addition to the results of the conducted Japanese phase III study and information on safety and efficacy from published articles, clinical experience with the CDCA product Chino Capsules has been accumulated in Japan. Clinical experience with CDCA products in CTX patients has also been accumulated both in Japan and overseas. The safety specification of Fujichenon was considered based on these available data, as follows: Although treatment in pregnant women is contraindicated for Chino Capsules, it was considered appropriate not to contraindicate treatment with Fujichenon in these patients, but to allow its use [see Section "5.R.1 Use of CDCA in pregnant women or women who may be pregnant"]. It is therefore considered appropriate to include the risk of reproductive and developmental toxicity in pregnant CTX patients as the safety specification to be further clarified in the post-marketing setting. CTX is a rare disease and the number of patients treated with Fujichenon in the post-marketing setting is expected to be limited. In addition, the package insert will

include a precaution stating that Fujichenon should be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. In view of these points, it was considered appropriate that the pharmacovigilance plan for this safety specification consists of routine pharmacovigilance activities to collect information. Therefore, additional pharmacovigilance activities were determined unnecessary at present.

PMDA's view:
In view of the applicant's explanation and taking into account that Fujichenon is intended to supplement CDCA in CTX patients who are deficient in endogenous CDCA, the applicant's decision to monitor the proposed safety specification through routine pharmacovigilance activities and not to conduct additional pharmacovigilance activities, is considered appropriate. A final decision on the need for post-marketing surveillance and other details will be made based on the comments from the Expert Discussion.

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 inspection is currently ongoing. The results and PMDA's conclusion are reported in the Review Report (2).

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

The inspection is currently ongoing. The results and PMDA's conclusion are reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that Fujichenon has efficacy in the treatment of CTX, and that Fujichenon has acceptable safety in view of its benefits. The drug product is not classified as a poisonous drug or a powerful drug. Fujichenon is clinically meaningful because it offers a new treatment option for CTX patients. PMDA has concluded that Fujichenon may be approved if Fujichenon is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 18, 2025

Product Submitted for Approval

Brand Name	Fujichenon Granular Tablets 125
Non-proprietary Name	Chenodeoxycholic Acid
Applicant	Fujimoto Pharmaceutical Corporation
Date of Application	February 26, 2025

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).

At the Expert Discussion, the expert advisors supported the PMDA's conclusions concerning the indication and clinical positioning of Fujichenon described in the Review Report (1).

1.1 Efficacy

The expert advisors supported the PMDA's conclusion concerning the efficacy of Fujichenon described in "7.R.2 Efficacy" of the Review Report (1). The following comment was also raised:

- The target sample size of the Japanese phase III study was not set based on adequate power or estimation precision. In view of the limited number of enrolled patients, the efficacy of Fujichenon should be discussed by taking into account the time course of serum cholestanol concentrations in individual patients.

PMDA's explanation about the efficacy of Fujichenon:

Figure 4 and Figure 5 show the time course of serum cholestanol concentrations in individual patients by the status of previous treatment. In the CDCA-naïve population (N = 3) (Figure 4), the serum cholestanol concentration increased or showed no major changes from the time of the CTX diagnosis to the baseline of the treatment period. In the treatment period, the concentration tended to gradually decrease after the start of treatment with Fujichenon until Week 52 in all subjects. In the CDCA-experienced population (N = 12) (Figure 5), the serum cholestanol concentration decreased in the run-in period compared with the time of the CTX diagnosis in all subjects. In the treatment period, although a rapid increase in serum cholestanol concentration

was observed in 1 subject at Week 52, this subject may have had poor medication compliance after Week 44.[23)] Excluding this subject, serum cholestanol concentrations tended to be maintained. Thus, a certain level of efficacy of Fujichenon was confirmed based on the results of the time course of serum cholestanol concentrations in individual patients in the Japanese phase III study.

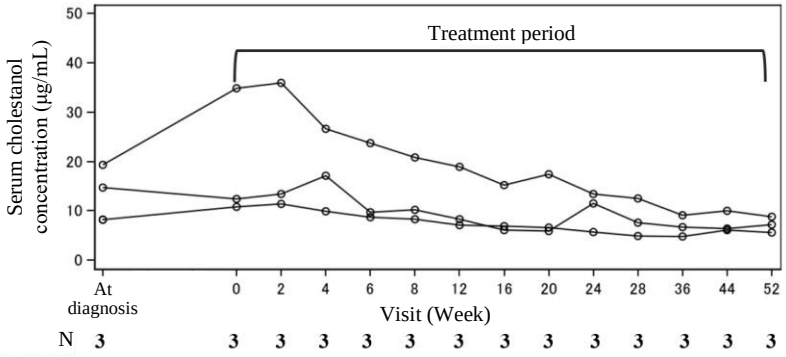

Figure 4. Time course of serum cholestanol concentrations in individual patients in CDCA-naïve population (Japanese phase III study: ITT population)

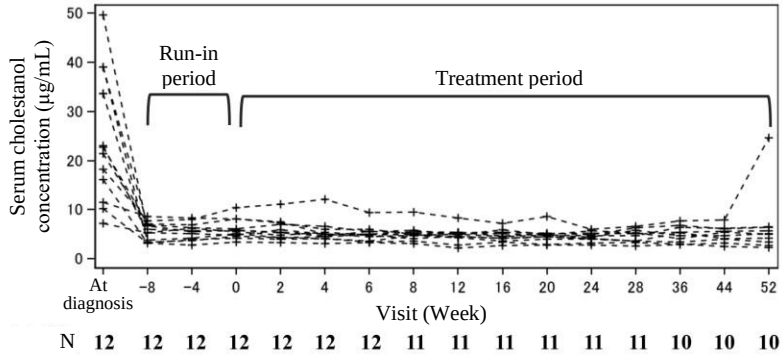

Figure 5. Time course of serum cholestanol concentrations in individual patients in CDCA-experienced population (Japanese phase III study: ITT population)

The expert advisors supported the above PMDA's conclusion.

1.2 Safety

The expert advisors supported the PMDA's conclusion concerning the safety of Fujichenon described in "7.R.3 Safety" of the Review Report (1), including the decision not to specify patients with serious liver disorder as a contraindication.

In the Expert Discussion, PMDA also asked for opinions on the following conclusions regarding precautions for patient populations, taking into account that Chino Capsules are contraindicated in "patients with serious pancreatobiliary disorder" and "patients with obstructive lesions in the hepatobiliary system" due to their choleretic effect. These conclusions were supported by expert advisors.

- Fujichenon should not be administered to patients with biliary obstruction because of concerns about further worsening of cholestasis due to its choleretic effects and bile acid excretion-promoting effects, and that such patients should be specified as contraindicated.

- Fujichenon should not be contraindicated in patients at risk of biliary obstruction, such as those with biliary stenosis or asymptomatic choledocholithiasis, but that a precaution for careful administration should be included, taking into account the seriousness of CTX, since cholestasis can be monitored by close observation of liver function and the patient's condition.
- "Patients with serious pancreatic disorders", which are contraindicated for Chino Capsules, may include pathological conditions associated with biliary tract obstruction. Given the concern for cholestasis due to the choleretic effect of CDCA, a precaution for patients with biliary tract obstruction or those at risk of biliary tract obstruction should be included in the package insert.

Based on the above, PMDA instructed the applicant to specify "patients with biliary obstruction" as a contraindication for Fujichenon and to include precautions for "patients with serious liver disorder" and "patients with lesions that may cause obstruction in the biliary system and patients with stones in the biliary tract" in the "Precautions Concerning Patients with Specific Backgrounds" section of the package insert. The applicant responded accordingly.

1.3 Dosage and administration

The expert advisors supported the PMDA's conclusion concerning the dosage and administration of Fujichenon described in "7.R.5 Dosage and administration" of the Review Report (1). Based on the review in "7.R.5 Dosage and administration" and the discussions at the Expert Discussion, PMDA concluded that it was appropriate to set the dosage and administration of Fujichenon, as well as the Precautions Concerning Dosage and Administration, as described below. The applicant responded accordingly.

Dosage and Administration

The usual starting dose for adults is 250 mg/day of chenodeoxycholic acid, followed by a dose increase in increments of 250 mg up to the maintenance dose of 750 mg/day, which is orally administered in 3 divided doses daily on consecutive days. The dose may be adjusted as appropriate according to the patient's condition; however, the daily dose should not exceed 1000 mg, and the single dose should not exceed 375 mg.

The usual starting dose for children is 5 mg/kg/day of chenodeoxycholic acid, followed by a dose increase in increments of 5 mg/kg up to the maintenance dose of 15 mg/kg/day, which is orally administered in 3 divided doses daily on consecutive days. The dose may be adjusted as appropriate according to the patient's condition. The daily dose should not exceed 15 mg/kg or a total of 750 mg, and the single dose should not exceed 250 mg.

Precautions Concerning Dosage and Administration

- The dose of Fujichenon should be increased to the maintenance dose at approximately 2-week intervals.
- For dose escalation in pediatric patients, the daily dose should not exceed 250 mg at 5 mg/kg, 500 mg at 10 mg/kg, and 750 mg at 15 mg/kg.

1.4 Risk management plan (draft)

The expert advisors largely supported the PMDA's conclusion described in "7.R.6 Post-marketing investigations" of the Review Report (1). The following comments were also raised:

- It is appropriate to continue to investigate the efficacy of Fujichenon on clinical symptoms, including neurological symptoms, which represent the true endpoints in CTX, even in the post-marketing setting. It is also useful to examine the appropriate duration for assessing the efficacy of Fujichenon on reduction of xanthomatosis and improvement of neurological symptoms in the post-marketing setting.
- Especially in pediatric CTX patients, long-term treatment with Fujichenon is required. Concerns such as liver disorder and potential tumorigenicity associated with long-term administration cannot be completely ruled out. Therefore, continued investigation of long-term safety is required in the post-marketing setting.

PMDA's explanation:

Although the efficacy of Fujichenon on the neurological symptoms, etc. of CTX was not clearly demonstrated in the Japanese phase III study, there are no issues that may affect the evaluation of the risk-benefit balance of Fujichenon that should be clarified through post-marketing surveillance in view of the following: (a) Early initiation of treatment with CDCA is also effective for clinical symptoms, as confirmed in several published articles [see Section "7.R.2.1.2 Published articles" of the Review Report (1)]; (b) Published articles and other information have confirmed that CDCA has certain levels of efficacy and safety in pediatric CTX patients [see Sections "7.R.2.2 Efficacy in children" and "7.R.3.2 Safety in children" of the Review Report (1)]. However, since the clinical experience of Fujichenon is limited, it is appropriate to collect information on the efficacy, safety, etc. of treatment with Fujichenon via routine pharmacovigilance activities.

The expert advisors supported the above PMDA's conclusion. In view of the review in "7.R.6 Post-marketing investigations" and the discussions at the Expert Discussion, as described above, PMDA has concluded that the risk management plan (draft) for Fujichenon should include the safety specification presented in Table 20, and that the applicant should conduct the additional pharmacovigilance activities and additional risk minimization activities presented in Table 21.

Table 20. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
Not applicable	• Reproductive and developmental toxicity in pregnant women	Not applicable
Efficacy specification		
Not applicable		

Table 21. Summary of the additional pharmacovigilance activities and additional risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance	• Provision of information collected through early post-marketing phase vigilance

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

2.1 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.

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

The new drug application data (CTD 5.3.5.2-1) 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.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition. The product has been designated as an orphan drug for the indication proposed under the present application. The re-examination period is 10 years.

Indication

Cerebrotendinous xanthomatosis

Dosage and Administration

The usual starting dose for adults is 250 mg/day of chenodeoxycholic acid, followed by a dose increase in increments of 250 mg up to the maintenance dose of 750 mg/day, which is orally administered in 3 divided doses daily on consecutive days. The dose may be adjusted as appropriate according to the patient's condition; however, the daily dose should not exceed 1000 mg, and the single dose should not exceed 375 mg.

The usual starting dose for children is 5 mg/kg/day of chenodeoxycholic acid, followed by a dose increase in increments of 5 mg/kg up to the maintenance dose of 15 mg/kg/day, which is orally administered in 3 divided doses daily on consecutive days. The dose may be adjusted as appropriate according to the patient's condition; however, the daily dose should not exceed 15 mg/kg or a total of 750 mg, and the single dose should not exceed 250 mg.

Approval Condition

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

Appendix

List of Abbreviations

A-CDCA	Chenodeoxycholic acid manufactured by [redacted]
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AOM	Azoxymethane
ASBT	Apical-dependent bile acid transporter
AST	Aspartate aminotransferase
B-CDCA	Chenodeoxycholic acid manufactured by [redacted]
BSEP	Bile salt export pump
CA	Cholic acid
CDCA	Chenodeoxycholic acid
Chino Capsules	Chino Capsules 125
CPP	Critical process parameter
CQA	Critical quality attribute
CTX	Cerebrotendinous xanthomatosis
CYP7A1	Cholesterol 7α-monooxygenase
CYP27A1	Sterol 27-hydroxylase
CYP8B1	Sterol 12α-hydroxylase
DCA	Deoxycholic acid
DEN	Diethylnitrosamine
FGF-19	Fibroblast growth factor-19
FXR	Farnesoid X receptor
Fujichenon	Fujichenon Granular Tablets 125
HMG-CoA	3-Hydroxy-3-methylglutaryl-coenzyme A
HPLC	High performance liquid chromatography
HSD3B7	3β-Hydroxy-Δ^5-C_{27}-steroid oxidoreductase
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICH Q3A guideline	Revision of the Guideline on Impurities in New Drug Substances (PFSB/ELD Notification No. 1216001, dated December 16, 2002) and Partial Revision of "Revision of the Guideline on Impurities in New Drug Substances" (PFSB/ELD Notification No. 1204001, dated December 4, 2006)
JP	Japanese Pharmacopoeia
ITT	Intent-to-treat
LCA	Lithocholic acid
LD_{50}	50% lethal dose
[redacted]	[redacted]
MMSE-J	Mini-Mental State Examination-Japan
MNNG	*N*-Methyl-*N'*-nitro-*N*-nitrosoguanidine
MNU	*N*-Nitroso-*N*-methylurea
mRNA	Messenger RNA
NDEA	*N*-Nitrosodiethylamine
NTCP	Na^+/taurocholate cotransporting polypeptide
NZW	New Zealand White
OATP	Organic anion transporting polypeptide
PMDA	Pharmaceuticals and Medical Devices Agency
qPCR	Quantitative polymerase chain reaction
RXR	Retinoid X receptor
SD	Sprague-Dawley

SHP	Small heterodimer partner
TLC	Thin-layer chromatography
UDCA	Ursodeoxycholic acid