1. NAME OF THE MEDICINAL PRODUCT

URECE® Tablets 0.5mg

URECE® Tablets 1mg

URECE® Tablets 2mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

URECE Tablets 0.5mg
Each tablet contains 0.5mg dotinurad.

URECE Tablets 1mg
Each tablet contains 1mg dotinurad.

URECE Tablets 2mg
Each tablet contains 2mg dotinurad.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Brand name		URECE Tablets 0.5mg	URECE Tablets 1mg	URECE Tablets 2mg
Dosage form		Tablet		
Color/ description		White to light yellowish white tablet, debossed with “FY321” on one side, and “0.5” on the other side	White to light yellowish white tablet, debossed with “1” on one side, “FY” and “322” divided by a score line on the other side	Very pale red tablet, debossed with “2” on one side, “FY” and “323” divided by a score line on the other side
Appearance	Face			
	Back			
	Side			
Identification code		FY321	FY322	FY323

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gout, hyperuricemia

4.2 Posology and method of administration

The usual initial adult dosage for oral use is 0.5mg of dotinurad once daily. Thereafter, the dose should be gradually increased as needed while monitoring the blood uric acid levels. The usual

maintenance dosage is 2mg once daily and may be adjusted according to the patient's condition up to a maximum dosage of 4mg once daily. Dotinurad can be taken regardless of meal.

4.3 Contraindications

Patients with a history of hypersensitivity to any of the ingredients of URECE.

4.4 Special warnings and precautions for use

PRECAUTIONS CONCERNING INDICATIONS

For administration of URECE, patients should be those who require pharmacological treatment, with reference to the latest treatment guidelines [See CLINICAL STUDIES]

PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

Since gouty arthritis (gout attack) may be induced by a rapid decrease in blood uric acid level in the early stage of treatment with urate-lowering drugs, the dosage of URECE should be started at 0.5mg once daily, followed by a gradual dose increase, for instance, to 1mg once daily after the first 2 weeks of treatment and then to 2mg once daily after 6 weeks of treatment. Patients should be carefully monitored after a dose increase. [See IMPORTANT PRECAUTIONS and CLINICAL STUDIES]

IMPORTANT PRECAUTIONS

i) URECE, a urate-lowering drug, may exacerbate gouty arthritis (gout attack) due to a decrease in blood uric acid level when used during gouty arthritis (gout attack). Treatment with URECE should not be started in patients with gouty arthritis (gout attack) until the symptoms have disappeared.
If gouty arthritis (gout attack) occurs during treatment with URECE, treatment should be continued without changing the dose level, and colchicine, non-steroidal anti-inflammatory drugs, and/or corticosteroids should be added according to the patient's condition. [See PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION]

ii) The pharmacological action of URECE causes an increase in uric acid excretion, especially in the early stages of administration, and if the urine is acidic, the patient may develop urinary calculus and resultant symptoms such as hematuria and renal colic. Urinary calculus should be prevented by increasing the water intake and thus increasing urine output, and by trying to alkalinize the urine. In this case, attention should be paid to the patient's acid-base balance.

iii) Since serious liver disorder has been reported with other uricosurics, patients should be carefully monitored through periodic liver function testing, etc., during administration of URECE. [See PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS]

PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

i) Patients with Complication or History of Diseases, etc.

a) Patients with urinary calculus

Do not administer unless deemed unavoidable for the sake of treatment. URECE may exacerbate

symptoms of urinary calculus by increasing the urinary excretion of uric acid due to its pharmacological effects. URECE has not been administered to patients with urinary calculus in clinical studies.

ii) Patients with Renal Impairment

a) Patients with severe renal impairment (eGFR < 30 mL/min/1.73 m^2)

Alternative treatment should be considered. Since URECE acts in the renal proximal tubules, its efficacy may be reduced depending on the severity of the renal impairment. In particular, URECE should not be administered in patients with oliguria or anuria, since it is not expected to be effective.

Patients with an eGFR < 30 mL/min/1.73 m^2 were excluded from clinical studies.

iii) Patients with Hepatic Impairment

Patients should be closely monitored. Serious liver disorder has been observed with other uricosurics.

Patients with serious liver disease or an AST or ALT ≧100 IU/L were excluded from clinical studies. [See IMPORTANT PRECAUTIONS]

PRECAUTIONS FOR CO-ADMINISTRATION

URECE should be administered with care when co-administered with the following drugs.

Drugs	Signs, symptoms, and measures	Mechanism and risk
Pyrazinamide	The effect of dotinurad may be reduced.	Metabolites of pyrazinamide are known to enhance uric acid reabsorption by URAT1 and may antagonize the uricosuric effect of dotinurad.
Salicylates Aspirin, etc.		Salicylates are known to inhibit uric acid excretion and may antagonize the uricosuric effect of dotinurad.

PRECAUTIONS CONCERNING USE

Precautions when Dispensing the Drug

For drugs that are dispensed in a press-through package (PTP), patients should be instructed to remove the drug from the package prior to use. If part of the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa, resulting in severe complications such as mediastinitis.

4.5 Interaction with other medicinal products and other forms of interaction

Oxaprozin

The pharmacokinetic parameters of dotinurad following single oral administration of dotinurad to healthy male adults (12 subjects) in the fed state at a dose of 4 mg or following oral co-administration of oxaprozin (600 mg) and dotinurad (4 mg) in the fed state on Day 6 preceded by repeated oral administration of oxaprozin in the fed state at a dose of 600 mg once daily for 5 days are shown below.

Table 1: Pharmacokinetic parameters following the administration of dotinurad alone and co-administration of oxaprozin in the fed state

Treatment group	C_{max}(ng/mL)	T_{max}(hr)	$T_{1/2}$(hr)	$AUC_{0\text{-}inf}$(ng•hr/mL)
Dotinurad alone (n = 12)	270.77 ± 26.61	3.67 ± 0.78	9.85 ± 1.06	3845.95 ± 578.70
With oxaprozin (n = 11)	266.11 ± 27.01 [0.982;0.945~1.021]	3.64 ± 0.81	11.89 ± 1.33	4487.36 ± 480.21 [1.165;1.114~1.219]

(Mean ± standard deviation)

[ ]: Geometric mean ratio relative to dotinurad alone and the 90% confidence interval

One subject who received oxaprozin and dotinurad together discontinued the study.

Topiroxostat

The pharmacokinetic parameters of dotinurad following once daily oral administrations of dotinurad alone (1 mg) or coadministration of topiroxostat (80 mg) and dotinurad (1 mg) for 7 days in male patients with uric acid-overproduction type and uric acid-underexcretion type hyperuricemia in the fed state on Day 7 are shown below.

Table 2: Pharmacokinetic parameters following the administration of dotinurad alone and co-administration of topiroxostat in the fed state

Treatment group		C_{max}(ng/mL)	T_{max}(hr)	$T_{1/2}$(hr)	$AUC_{0\text{-}inf}$(ng•hr/mL)
Dotinurad alone	overproduction -type group (n = 6)	102.90 ± 21.43	3.67 ± 0.52	11.49 ± 1.49	1688.49 ± 633.70
	underexcretion -type group (n = 6)	101.20 ± 18.28	3.17 ± 0.98	10.44 ± 0.66	1561.90 ± 257.42
With topiroxostat	overproduction -type group (n = 6)	108.33 ± 15.49	3.67 ± 0.52	10.83 ± 0.96	1688.15 ± 354.21

(Mean ± standard deviation)

The pharmacodynamic parameters of serum uric acid levels following once daily oral administrations of dotinurad alone (1 mg) or coadministration of topiroxostat (80 mg) and dotinurad (1 mg) for 7 days in male patients with uric acid-overproduction type and uric acid-underexcretion type hyperuricemia in fed state are shown below.

Table 3: Pharmacodynamic parameters of serum uric acid levels following the administration of dotinurad alone and co-administration of topiroxostat in the fed state

Treatment group		ΔEC_{max} (mg/dL)	Maximum percent reduction (%)	$\Delta AUEC_{0-24}$ (mg•hr/dL)
Dotinurad alone	overproduction -type group (n = 6)	-4.60 ± 0.53	56.86 ± 6.80	99.73 ± 8.70
	underexcretion-type group (n = 6)	-4.83 ± 0.35	55.75 ± 4.48	107.37 ± 9.38
With topiroxostat	overproduction -type group (n = 6)	-5.88 ± 0.50	68.19 ± 7.70	127.98 ± 16.55

(Mean ± standard deviation)
$\Delta AUEC_{0-24}$ values were shown following Day 7 administration.

4.6 Fertility, pregnancy and lactation

Pregnant Women

URECE should be administered to women who are or may be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. Skeletal variations were observed at doses equivalent to approximately 1053 and 174 times the clinical exposure in animal studies (rats and rabbits).

Breast-feeding Women

Continuation or discontinuation of breast-feeding should be considered in view of the therapeutic benefits and the benefits of breast-feeding. It has been reported in animal studies (rats) that dotinurad was excreted in breast milk.

4.7 Effects on ability to drive and use machines

No data available

4.8 Undesirable effects

Since the following adverse reactions may occur, patients should be carefully monitored, and if any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Table 4: Other Adverse Reactions

	≥ 5%	1% to < 5%	< 1%	Frequency unknown
Gastrointestinal			Soft feces	Diarrhoea, Nausea
Hepatobiliary			γ-GTP increased	ALT increased, AST increased
Musculoskeletal	Gouty arthritis	Arthritis, limb discomfort	Arthralgia	

	≥ 5%	1% to < 5%	< 1%	Frequency unknown
Renal and urinary			Nephrolithiasis, nephrocalcinosis, β_2-microglobulin urine increased, blood creatinine increased, urinary albumin/ creatinine ratio increased, albumin urine present	
Skin				Rash, Pruritus
Others				Malaise

4.9 Overdose

There is no experience with unintentional dotinurad overdosage. There is no available specific antidote to an overdose of dotinurad. In the event of overdose, standard medical practice for the management of any overdose should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Antihyperuricemic drug

Selective uric acid reabsorption inhibitor

i) Mechanism of Action

Dotinurad selectively inhibits URAT1, which is a transporter involved in uric acid reabsorption in the kidney, and enhances urinary excretion of uric acid filtered by the glomeruli and thereby reduces blood uric acid levels.

ii) Inhibition of URAT1

Dotinurad inhibited uric acid uptake in cells expressing human URAT1 with an IC_{50} of 0.0372μmol/L. In addition, inhibition of BCRP (ABCG2), OAT1, and OAT3, which are transporters involved in uric acid secretion from blood into the small intestine or renal tubules, was evaluated using cells expressing human ABCG2, OAT1, or OAT3. The IC_{50} values were 4.16, 4.08, and 1.32μmol/L, respectively, suggesting that dotinurad is a uric acid reabsorption inhibitor that is highly selective for URAT1 (*in vitro*).

iii) Reduction in Blood Uric Acid Levels

After single oral administration to capuchin monkeys at doses of 1, 5, and 30mg/kg, dotinurad reduced the plasma uric acid levels and increased the fractional excretion of uric acid in a dose-dependent manner (*in vivo*).

5.2 Pharmacokinetic properties

Blood Level

i. Single administration

The time course of the plasma unchanged drug concentration and the pharmacokinetic parameters after single oral administration of dotinurad to healthy adult males (36 subjects) in the fasted state at doses of 0.5, 1, 2, 5, 10, or 20mg are shown below. C_{max} and $AUC_{0\text{-inf}}$ increased in a dose-dependent manner and linearity was observed. The approved maximum dose of this product is 4mg of dotinurad once daily.

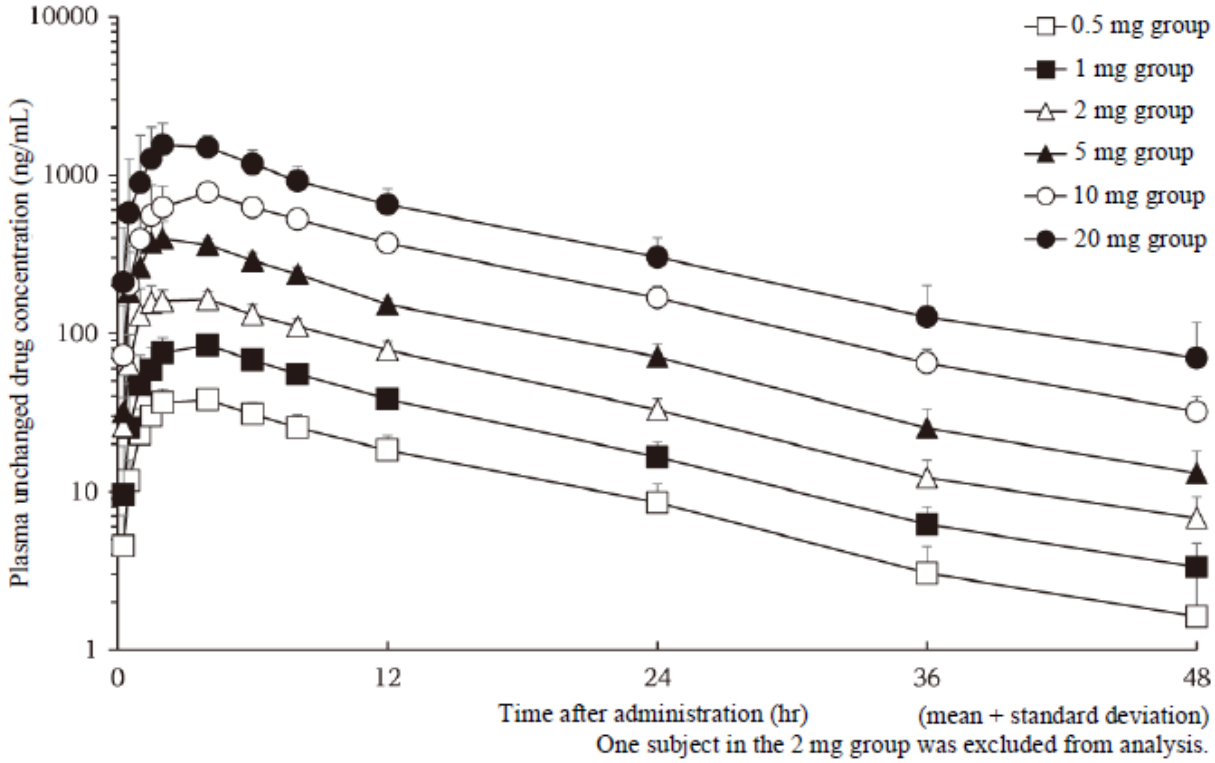

Figure 1: Time course of the plasma unchanged drug concentration after single oral administration of dotinurad

Table 5: Pharmacokinetic parameters after single oral administration of dotinurad

Dose	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-inf}}$ (ng•hr/mL)
0.5mg (n = 6)	41.53 ± 4.51	2.67 ± 1.03	9.67 ± 1.77	612.53 ± 134.12

Dose	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-inf}}$ (ng•hr/mL)
1mg (n = 6)	89.18 ± 10.78	3.33 ± 1.03	9.60 ± 1.27	1276.01 ± 189.17
2mg (n = 5)	175.22 ± 33.01	3.10 ± 1.24	9.53 ± 1.11	2599.01 ± 381.12
5mg (n = 6)	447.82 ± 72.63	2.00 ± 1.10	9.27 ± 1.10	5525.68 ± 419.02
10mg (n = 6)	858.18 ± 136.26	3.25 ± 1.17	9.87 ± 0.83	12126.04 ± 1204.32
20mg (n = 6)	1783.63 ± 351.53	2.25 ± 1.41	10.65 ± 2.85	23397.97 ± 7054.80

(Mean ± standard deviation)
One subject in the 2mg group was excluded from analysis.

ii. Repeated administration

Pharmacokinetic parameters following repeated oral administration of dotinurad to healthy adult males (6 subjects) in the fed state at a dose of 4mg once daily for 7 days are shown below. Plasma unchanged drug concentrations reached the steady state on Day 4 without accumulation.

Table 6: Pharmacokinetic parameters following repeated oral administration of dotinurad

Dosing day	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-24hr}}$ (ng•hr/mL)	Accumulation factor
1	366.50 ± 81.19	3.33 ± 0.52	11.14 ± 1.56	4024.16 ± 758.92	-
4	416.33 ± 77.74	2.67 ± 1.21	11.27 ± 1.22	5052.31 ± 1073.14	-
7	420.67 ± 54.21	3.17 ± 0.75	9.87 ± 1.20	4871.26 ± 890.21	0.97 ± 0.07

Accumulation factor ($AUC_{0\text{-24 hr}}$ on Day 7/$AUC_{0\text{-24 hr}}$ on Day 4)
(Mean ± standard deviation)

Absorption

i. Food effect

After single oral administration of dotinurad to healthy adult males (12 subjects) in the fed state at a dose of 4mg, the C_{max} was slightly decreased and the T_{max} was prolonged compared to those in the fasted state, but $AUC_{0\text{-t}}$ was not affected by food.

Table 7: Pharmacokinetic parameters after single oral administration of dotinurad in the fasted and fed state

Condition	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	AUC_{0-t} (ng•hr/mL)
Fasted (n = 12)	296.48 ± 37.26	2.58 ± 0.87	9.35 ± 0.89	3722.65 ± 654.35
Fed (n = 11)	261.59 ± 52.19	3.91 ± 1.51	9.05 ± 1.09	3672.00 ± 689.34

(Mean ± standard deviation)

Distribution

i. Volume of distribution

After single oral administration of ^{14}C-dotinurad to healthy adult males (6 subjects) in the fasted state at a dose of 1mg, the volume of distribution was 14.75L.

ii. Protein binding rate

The human plasma protein binding rate of dotinurad was 99.2 to 99.4%, with no distribution to human blood cells (*in vitro*).

Metabolism

Dotinurad was mainly metabolized by UGT and SULT to glucuronic acid conjugates and sulfate conjugates.

After single oral administration of ^{14}C-dotinurad to healthy adult males (6 subjects) in the fasted state at a dose of 1mg, the major metabolites were glucuronic acid conjugates and sulfate conjugates.

Multiple isoforms including UGT1A1, 1A3, 1A9, and 2B7 were involved in the formation of glucuronic acid conjugates and SULT1B1 and 1A3 were involved in the formation of sulfate conjugates (*in vitro*).

Dotinurad inhibited CYP2C9 (Ki value: 10.4μmol/L), but no other isoforms (CYP1A2, 2A6, 2B6, 2C19, 2D6, 2E1, and 3A4) (IC_{50} > 100μmol/L). Dotinurad also inhibited UGT1A1 and 2B15 (Ki value: 10.0 and 16.6μmol/L), but no other isoforms (UGT1A3, 1A4, 1A6, 1A7, 1A8, 1A9, 1A10, 2B4, 2B7, 2B10, and 2B17) (IC_{50} > 50μmol/L) (*in vitro*). Dotinurad induced the mRNA expression of CYP2B6, but not for CYP1A2 or 3A4 in human hepatocytes (*in vitro*). None of these effects are likely to cause interactions at clinical doses.

Excretion

After single oral administration of ^{14}C-dotinurad to healthy adult males (6 subjects) in the fasted state at a dose of 1mg, 86.38% and 7.93% of the administered radioactivity was excreted in the urine and feces within 168 hours, respectively, and 5.02% was excreted in exhaled air within 72 hours.

Dotinurad inhibited BCRP (ABCG2), OAT1, OAT3, and OATP1B1 with IC_{50} values of 74.7, 1.87, 2.61, and 11.5μmol/L, respectively, but did not inhibit MDR1, OCT2, OATP1B3, MATE1, or MATE2-K. Dotinurad is unlikely to affect any drug transporters at the clinical dose (*in vitro*).

Patients with Specific Backgrounds

i. Patients with renal impairment

Pharmacokinetic parameters following single oral administration of dotinurad to subjects with mild renal impairment (6 subjects), moderate renal impairment (6 subjects), and normal renal function (6 subjects) in the fasted state at a dose of 1mg are shown below.

Table 8: Pharmacokinetic parameters following single oral administration of dotinurad to subjects with mild and moderate renal impairment and normal renal function

Renal function	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-}inf}$ (ng•hr/mL)
Normal (n = 6)	85.67 ± 10.65	3.50 ± 0.55	8.75 ± 1.80	1157.32 ± 269.46
Mild impairment (n = 6)	88.73 ± 22.74 [1.01;0.79~1.28]	3.00 ± 1.67	10.29 ± 1.50	1366.57 ± 427.94 [1.15;0.84~1.59]
Moderate impairment (n = 5)	88.38 ± 14.39 [1.03;0.87~1.21]	2.60 ± 0.55	10.95 ± 2.17	1428.54 ± 379.58 [1.22;0.90~1.66]

(Mean ± standard deviation)

[ ]: Geometric mean ratio to normal and 90% confidence interval

One subject with moderate impairment was excluded from analysis.

Normal: eGFR ≥ 90 mL/min/1.73 m^2, mild impairment: 60 ≤ eGFR < 90 mL/min/1.73 m^2, moderate impairment: 30 ≤ eGFR < 60 mL/min/1.73 m^2

ii. Patients with hepatic impairment

Pharmacokinetic parameters following single oral administration of dotinurad to subjects with mild hepatic impairment (6 subjects), moderate hepatic impairment (9 subjects), severe hepatic impairment (3 subjects), and normal hepatic function (6 subjects) in the fasted state at a dose of 4mg are shown below.

Table 9: Pharmacokinetic parameters following single oral administration of dotinurad to subjects with mild, moderate and severe hepatic impairment and normal hepatic function

Hepatic function	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-}inf}$ (ng•hr/mL)
Normal (n = 6)	339.15 ± 28.57	2.67 ± 1.03	10.80 ± 0.55	4761.81 ± 369.35
Mild impairment (n = 6)	289.88 ± 65.03 [0.840;0.674~1.047]	2.17 ± 1.17	10.50 ± 2.42	4234.01 ± 950.16 [0.872;0.684~1.112]

Hepatic function	C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-}inf}$ (ng•hr/mL)
Moderate impairment (n = 9)	280.34 ± 87.91 [0.798;0.653~0.976]	2.44 ± 1.01	10.75 ± 2.28	4327.09 ± 1249.48 [0.879;0.704~1.098]
Severe impairment (n = 3)	255.23 ± 46.06 [0.747;0.570~0.979]	1.33 ± 0.58	9.82 ± 2.47	3757.37 ± 1343.74 [0.758;0.563~1.021]

(Mean ± standard deviation)

[ ]: Geometric mean ratio to normal and 90% confidence interval

Mild impairment: Child-Pugh A (Child-Pugh score: 5 to 6), moderate impairment: Child-Pugh B (Child-Pugh score: 7 to 9), severe impairment: Child-Pugh C (Child- Pugh score: 10 to 15)

iii) Geriatric use

Pharmacokinetic parameters following single oral administration of dotinurad to non-elderly males (6 subjects aged between 20 and 35 years), elderly males (6 subjects aged 65 years or older), non-elderly females (6 subjects aged between 20 and 35 years), and elderly females (6 subjects aged 65 years or older) in the fasted state at a dose of 1mg are shown below.

Table 10: Pharmacokinetic parameters following single oral administration of dotinurad to elderly and non-elderly

Treatment group		C_{max} (ng/mL)	T_{max} (hr)	$T_{1/2}$ (hr)	$AUC_{0\text{-}inf}$ (ng•hr/mL)
Male	Elderly (n = 6)	93.30 ± 16.07 [0.93;0.76~1.15]	2.00 ± 0.63	9.28 ± 1.05	1209.38 ± 290.88 [0.84;0.67~1.06]
	Non-elderly (n = 6)	100.92 ± 21.20	2.17 ± 0.75	10.31 ± 1.27	1424.76 ± 242.34
Female	Elderly (n = 6)	112.07 ± 12.66 [0.98;0.80~1.21]	2.17 ± 0.75	10.92 ± 1.19	1797.95 ± 357.84 [0.98;0.80~1.21]
	Non-elderly (n = 6)	116.15 ± 26.67	2.83 ± 0.98	10.47 ± 0.31	1832.67 ± 345.74

(Mean ± standard deviation)

[ ]: Geometric mean ratio (elderly males or females/non-elderly males or females) and the 90% confidence interval

CLINICAL STUDIES

i. Clinical Studies for Efficacy and Safety

a) Japanese phase III study (Benzbromarone-controlled)

A benzbromarone-controlled, double-blind, parallel-group comparative study was conducted in 201 patients with hyperuricemia including gout (excluding uric acid overproduction hyperuricemia). Treatment with dotinurad was started at a dose of 0.5mg/day, followed by a gradual dose increase to 1mg/day after 2 weeks of treatment and then to 2mg/day after 6 weeks of treatment, which was then maintained until 14 weeks after the start of treatment. Treatment

with benzbromarone was started at a dose of 25mg/day, followed by a dose increase to 50mg/day after 2 weeks of treatment, which was then maintained until 14 weeks after the start of treatment. The percent reduction in serum uric acid level from baseline at the final visit (primary endpoint) is shown in the table below. The non-inferiority of dotinurad 2mg/day to benzbromarone 50mg/day was shown in terms of percent reduction in serum uric acid level at the final visit (noninferiority margin: -10%). The proportion of subjects achieving a serum uric acid level of ≤ 6.0mg/dL at the final visit (secondary endpoint) was 86.27% (88/102 subjects) in the dotinurad group and 83.67% (82/98 subjects) in the benzbromarone group.

Table 11: Percent reduction (%) in serum uric acid level at the final visit

Treatment group	Serum uric acid level at baseline (mg/dL)	Percent reduction in serum uric acid level (%)	Between-group difference in percent reduction [95% confidence interval] (%)
Dotinurad 2mg/day (n = 102)	8.90 ± 1.16	45.92 ± 11.94	2.05 [-1.27~5.37]
Benzbromarone 50mg/day (n = 98)	8.92 ± 1.28	43.87 ± 11.84	

(Mean ± standard deviation)
One subject in the benzbromarone group was excluded from analysis.

The incidence of adverse reactions was 14.7% (15/102 subjects) in the dotinurad group and 15.2% (15/99 subjects) in the benzbromarone group. Common adverse reactions were gouty arthritis (7.8%, 8/102 subjects) and arthritis (2.9%, 3/102 subjects) in the dotinurad group, and gouty arthritis (5.1%, 5/99 subjects), AST increased (2.0%, 2/99 subjects), and ALT increased (2.0%, 2/99 subjects) in the benzbromarone group. The incidence of gouty arthritis in each treatment period is shown in the table below. [See 4.4]

Table 12: Incidence (%) of gouty arthritis (number of subjects with an event/number of subjects evaluated)

Treatment group	0 to ≤ 2 weeks	> 2 to ≤ 6 weeks	> 6 to ≤ 14 weeks
Dotinurad 2mg/day	1.0 (1/102) (0.5mg/day)	2.9 (3/102) (1mg/day)	4.0 (4/100) (2mg/day)
Benzbromarone 50mg/day	0.0 (0/99) (25mg/day)	2.0 (2/99) (50mg/day)	3.1 (3/98) (50mg/day)

b) Japanese phase III study (febuxostat-controlled)

A febuxostat-controlled, double-blind, parallel-group comparative study was conducted in 201 patients with hyperuricemia including gout (excluding uric acid overproduction hyperuricemia). Treatment with dotinurad was started at a dose of 0.5mg/day, followed by a gradual dose increase to 1mg/day after 2 weeks of treatment and then to 2mg/day after 6 weeks of treatment, which was then maintained until 14 weeks after the start of treatment. Treatment with febuxostat was started at a dose of 10mg/day, followed by dose increase to 20mg/day after 2 weeks of

treatment and then to 40mg/day after 6 weeks of treatment, which was then maintained until 14 weeks after the start of treatment. The percent reduction in serum uric acid level from baseline at the final visit (primary endpoint) is shown in the table below. The non-inferiority of dotinurad 2mg/day to febuxostat 40mg/day was shown in terms of percent reduction in serum uric acid level at the final visit (noninferiority margin: -10%). The proportion of subjects achieving a serum uric acid level of ≤ 6.0mg/dL at the final visit (secondary endpoint) was 84.8% (84/99 subjects) in the dotinurad group and 88.0% (88/100 subjects) in the febuxostat group.

Table 13: Percent reduction (%) in serum uric acid level at the final visit

Treatment group	Serum uric acid level at baseline (mg/dL)	Percent reduction in serum uric acid level (%)	Between-group difference in percent reduction [95% confidence interval] (%)
Dotinurad 2mg/day (n = 99)	8.61 ± 1.05	41.82 ± 11.47	-2.17 [-5.26~0.92]
Febuxostat 40mg/day (n = 100)	8.67 ± 1.06	44.00 ± 10.63	

(Mean ± standard deviation)
One subject in the dotinurad group and 1 subject in the febuxostat group were excluded from analysis.

The incidence of adverse reactions was 17.2% (17/99 subjects) in the dotinurad group and 19.8% (20/101 subjects) in the febuxostat group. Common adverse reactions were gouty arthritis (5.0%, 5/101 subjects) and β_2-microglobulin urine increased (4.0%, 4/101 subjects) in the febuxostat group. In the dotinurad group, the incidence rate of all adverse reactions was 1% or less (1/99 subjects). The incidence of gouty arthritis in each treatment period is shown in the table below. [See 4.4]

Table 14: Incidence (%) of gouty arthritis (number of subjects with an event/number of subjects evaluated)

Treatment group	0 to ≤ 2 weeks	> 2 to ≤ 6 weeks	> 6 to ≤ 14 weeks
Dotinurad 2mg/day	0.0 (0/99) (0.5mg/day)	1.0 (1/99) (1mg/day)	1.0 (1/97) (2mg/day)
Febuxostat 40mg/day	0.0 (0/101) (10mg/day)	3.0 (3/99) (20mg/day)	2.1 (2/96) (40mg/day)

c) Japanese phase III long-term treatment study

A long-term treatment study was conducted in 330 patients with hyperuricemia including gout (excluding uric acid overproduction hyperuricemia). Treatment with dotinurad was started at a dose of 0.5mg/day, followed by a gradual dose increase to 1mg/day after 2 weeks of treatment and then to 2mg/day after 6 weeks of treatment. If the serum uric acid level was more than 6.0 mg/dL after 14 weeks of treatment, the dose was further increased to 4mg/day after 18 weeks of treatment, which was then maintained until 34 or 58 weeks after the start of treatment.

The percent reduction in serum uric acid level from baseline was 46.73% at 2mg/day and 54.92% at 4mg/day after 34 weeks of treatment, and 47.17% at 2mg/day and 57.35% at 4mg/day after 58 weeks of treatment. The proportion of subjects achieving a serum uric acid level of ≤ 6.0mg/dL was 89.11% (229/257 subjects) at 2mg/day and 97.50% (39/40 subjects) at 4mg/day after 34 weeks of treatment, and 91.30% (84/92 subjects) at 2mg/day and 100.00% (13/13 subjects) at 4mg/day after 58 weeks of treatment.
The incidence of adverse reactions was 21.8% (72/330 subjects). Common adverse reactions were gouty arthritis (12.7%, 42/330 subjects), arthritis (2.1%, 7/330 subjects), and limb discomfort (2.1%, 7/330 subjects). [See 4.4]

5.3 Preclinical safety data

Toxicity

Repeated dose toxicity

In the 13- and 26-week repeated oral dose toxicity studies in rats (0, 30, 100, and 300 mg/kg/day, and 0, 12, 60, and 300 mg/kg/day, respectively) lower body weight, suppression of body weight gain, decreased food consumption, and reduced hematological parameters including erythrocyte count, hemoglobin concentration, and hematocrit were observed and these changes were found to be reversible at the end of the recovery period. Additionally, an increase of trabecula in the femur was observed in a female of the 300 mg/kg/day group in the 26-week study. Based on in vitro and in vivo investigations of induction effects of dotinurad on hepatic drug metabolizing enzymes, it was concluded that the higher liver weight and associated changes observed in rat toxicity studies were adaptive changes with no toxicological significance. The systemic exposures at the no observed adverse effect level (NOAEL) of 60 mg/kg/day in the 26-week study were approximately more than 216 times the maximum recommended human dose (MRHD) based on AUC.
In the repeated-dose toxicity studies in monkeys (up to 39 weeks), dotinurad caused toxicologic changes in various organs and tissues. Increased lymphocytes were observed in the thymus, spleen, lymph node, bone marrow, and liver of the 300 and 1000 mg/kg/day groups in the 4-week oral dose range finding study (0, 10, 100, 300, and 1000 mg/kg/day). In the 13-week oral dose toxicity study (0, 10, 30, and 100 mg/kg/day) in monkeys, at 100 mg/kg/day dose level, lower erythrocyte count, hemoglobin concentration, hematocrit, higher large unstained cell count, and/or leukocyte count, platelet count and low or high cellularity of bone marrow cells were observed. These findings were found to be reversible at the end of recovery period. In the 39-week oral dose toxicity study (0, 3, 12, and 50 mg/kg/day) in monkeys, no histopathological changes were noted in the bone marrow up to 50 mg/kg/day. The systemic exposure at NOAEL of 12 mg/kg/day in the 39-week pivotal monkey toxicity study was more than 17 times the MRHD based on AUC. In vitro, dotinurad demonstrated lymphocyte blastogenic effect in untreated monkey peripheral whole blood, but not in human or rat whole blood. This is consistent with the absence of associated histopathological changes in the repeat dose toxicity studies in rats.

Genotoxicity

Dotinurad was negative in the in vitro reverse mutation assay in bacteria (Ames) and the in vivo micronucleus and unscheduled DNA synthesis tests in rats. In the in vitro chromosomal

aberration test in cultured mammalian cells, dotinurad showed the potential to induce structural chromosomal aberration at higher concentrations (512-800 μg/mL). Based on the in vitro and in vivo genotoxicity study results, there was less concern of genotoxic potential for dotinurad.

Carcinogenicity

In the 104-week oral dose carcinogenicity studies in mice and rats (0, 3, 10, and 30 mg/kg/day), no treatment-related increases of neoplastic and non-neoplastic lesions were observed.

Reproductive and developmental toxicity

In the fertility and early embryonic development study in rats by oral administration (0, 30, 100, and 300 mg/kg/day), lower food consumption, suppression of body weight gain, and/or lower body weight were observed in male and female parental animals at 300 mg/kg/day. Additionally, lower numbers of corpora lutea, implantations, and live embryos were observed at 300 mg/kg/day. The NOAEL was estimated to be 100 mg/kg/day for general toxicity and reproductive functions of parental animals and early embryonic development. The systemic exposure at the NOAEL is more than 366 times the MRHD based on AUC.
Dotinurad was administered orally to pregnant rats during the period of organogenesis at doses of 30, 100, and 300 mg/kg/day. Dotinurad caused maternal toxicity that consisted of lower food consumption, suppression of body weight gain, and lower body weight and higher incidences of skeletal variations (short supernumerary rib, full supernumerary rib, and supernumerary lumber vertebra) in fetuses at 300 mg/kg/day. The NOAEL of 100 mg/kg/day for maternal toxicity and embryo-fetal development is approximately 542 times the MRHD based on AUC.
Dotinurad was administered orally to pregnant rabbits during the period of organogenesis at doses of 10, 30, 100, and 300 mg/kg/day. Lower food consumption, suppression of body weight gain, and scant and no feces were observed in dams at the 300 mg/kg/day. Higher or tendency to higher incidences of skeletal variations (full supernumerary rib and supernumerary lumber vertebra) were observed in fetuses of the 100 and 300 mg/kg/day groups. The NOAEL for general toxicity and reproductive functions of dams was estimated to be 100 mg/kg/day. The NOAEL of 30 mg/kg/day for embryo-fetal development is approximately 55 times the MRHD based on AUC.
In the pre- and postnatal development study in rats by oral administration (0, 30, 100, and 300 mg/kg/day), prolonged gestation period was observed in dams at 300 mg/kg/day. Delayed vaginal opening, incomplete fusion of cutaneous midline in the external genitalia, and lower copulation rate and fertility rate were observed in F1 female offspring at 100 mg/kg/day and/or 300 mg/kg/day. The NOAEL was estimated to be 100 mg/kg/day for general toxicity and reproductive function of dams and 30 mg/kg/day for F1 animals. The systemic exposures at the NOAEL for F1 animals was approximately 112 times the MRHD based on AUC.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

URECE Tablets 0.5mg and URECE Tablets 1mg:
Lactose hydrate, D-mannitol, microcrystalline cellulose, hypromellose, carmellose, magnesium stearate

URECE Tablets 2mg: Lactose hydrate, D-mannitol, microcrystalline cellulose, hypromellose, carmellose, magnesium stearate, red ferric oxide

Note: Magnesium stearate is sourced from plant and animal (bovine and porcine).

6.2 Incompatibilities

Not applicable

6.3 Special precautions for storage

Do not store above 30°C.

6.4 Nature and contents of container

PVC/Aluminum blister packs of 28 tablets [14 tablets (PTP) × 2].

7. MANUFACTURER:

Manufactured by: FUJI YAKUHIN CO., LTD. Toyama Plant
682, Fuchuu-Machi Itakura, Toyama-Shi, Toyama, Japan

Repacked by: Bora Pharmaceuticals Co., Ltd.
No.54, Gong-Yeh W. Road, Guan-Tyan District, Tainan City, Taiwan

8. PRODUCT REGISTRATION HOLDER:

Eisai (Malaysia) Sdn Bhd
Unit 701D, Level 7, Tower D, Uptown 5,
No. 5, Jalan SS21/39, Damansara Uptown,
47400 Petaling Jaya, Selangor, Malaysia

9. DATE OF REVISION

June 2025