Drug for Parkinson's Disease

Equfina® Film-Coated Tablets 50 mg

<Safinamide>

CONTRAINDICATIONS (This drug is contraindicated in the following patients)

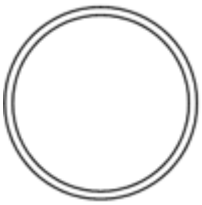
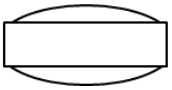
1. Patients using other MAO inhibitors (eg, selegiline hydrochloride, rasagiline mesilate) [see "INTERACTIONS" section]
2. Patients using pethidine hydrochloride-containing products, tramadol hydrochloride-containing products, or tapentadol hydrochloride [see "INTERACTIONS" section]
3. Patients using tricyclic antidepressants (eg, amitriptyline hydrochloride, amoxapine, imipramine hydrochloride, clomipramine hydrochloride, dosulepin hydrochloride, trimipramine maleate, nortriptyline hydrochloride, lofepramine hydrochloride), tetracyclic antidepressants (eg, maprotiline hydrochloride, mianserin hydrochloride, setiptiline maleate), selective serotonin reuptake inhibitors (eg, fluvoxamine maleate, paroxetine hydrochloride hydrate, sertraline hydrochloride, escitalopram oxalate), serotonin–noradrenaline reuptake inhibitors (eg, milnacipran hydrochloride, duloxetine hydrochloride, venlafaxine hydrochloride), selective noradrenaline reuptake inhibitor (atomoxetine hydrochloride), noradrenergic and serotonergic antidepressant (mirtazapine), or central nervous system stimulants (eg, methylphenidate hydrochloride, lisdexamfetamine mesilate) [see "INTERACTIONS" section]
4. Patients with severe hepatic impairment (Child-Pugh C) [see "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" section]
5. Patients with a history of hypersensitivity to any of the ingredients of this drug
6. Pregnant women or women suspected of being pregnant [see "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" section]

COMPOSITION AND PRODUCT DESCRIPTION

1. Composition

Brand name	Equfina Film-Coated Tablets 50 mg
Active ingredient	65.88mg safinamide mesilate (equivalent to 50mg safinamide) per tablet
Inactive ingredients	Lactose hydrate, corn starch, sodium carboxymethyl starch, hydroxypropylcellulose, light anhydrous silicic acid, magnesium stearate, hypromellose, D-mannitol, Macrogol 6000, talc, and carnauba wax

2. Product Description

Description	White film-coated tablets		
Appearance	Surface	Reverse	Side
			
Diameter (mm)	Approximately 7.1		
Thickness (mm)	Approximately 3.5		
Weight (mg)	Approximately 130.0		

INDICATIONS

Improvement of wearing-off phenomenon in idiopathic Parkinson's disease currently treated with levodopa-containing products

DOSAGE AND ADMINISTRATION

This drug is used in combination with levodopa-containing products. The usual adult dosage for oral use is 50 mg of safinamide once daily. The dosage for oral use may be administered at 100 mg once daily according to the patient's condition.

Equfina 100 mg should be tapered by decreasing the dose to 50 mg for one week before discontinuation.

Precautions concerning dosage and administration

1. Co-administration with levodopa-containing products may cause adverse reactions of levodopa origin (dyskinesia, etc.). Therefore, patients should be closely monitored when the dosing of this drug is started or the dose of this drug is increased, and if such adverse reactions occur, the dose of this drug or levodopa-containing products should be adjusted.
2. The dose of Equfina should not exceed 50 mg daily for patients with moderate hepatic impairment (Child-Pugh B) [see "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" and "PHARMACOKINETICS" sections].

IMPORTANT PRECAUTIONS

1. This drug may induce daytime somnolence or sudden onset of sleep with no signs. Therefore, patients should be cautioned against engaging in dangerous activities such as driving a car,

operating machinery, or working at heights under administration of this drug [see "ADVERSE REACTIONS" section].

2. Equfina may induce impulse-control disorder such as pathological gambling (persistent repetition of gambling despite socially adverse consequences including disruption of personal life), pathological hypersexuality, compulsive shopping, and hyperphagia. Therefore, if any of such symptoms is observed, appropriate measures including discontinuation of treatment should be taken. In addition, patients and their family members should be informed of these symptoms of impulse-control disorder [see "ADVERSE REACTIONS" section].

3. Equfina may induce orthostatic hypotension or hypotension. Therefore, if dizziness, lightheadedness, wobble, or any other symptoms which are suspected orthostatic hypotension or hypotension are observed, appropriate measures including discontinuation of treatment should be taken. Patients with Parkinson's disease are at an increased risk of falls associated with motor dysfunction and, if orthostatic hypotension occurs, they may experience fracture and/or trauma due to a fall [see "ADVERSE REACTIONS" section].

PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

1 Patients with complications or history of diseases

Patients with active or a history of retina-related disease

Patients with retinal degeneration, uveitis, hereditary retinopathy, or severe progressive diabetic retinopathy, patients with a history of eye disorders that are highly likely to affect the retina (eg, retinitis pigmentosa, any form of active retinopathy, family history of hereditary retinal disease), and patients with albinism should be regularly monitored for any change in acuity- and field-related symptoms. Such patients were excluded from clinical studies. In animals, a repeated-dose oral toxicity study (rats) and carcinogenicity studies (mice and rats) demonstrated dose- and duration-dependent retinal degeneration and exacerbation due to light exposure in rats. This change was not observed in monkeys.

Patients with hepatic impairment

Patients with severe hepatic impairment (Child-Pugh C)

Equfina should not be administered. Blood concentration of this drug may increase. Such patients were excluded from clinical studies [see "CONTRAINDICATIONS" section].

Patients with moderate hepatic impairment (Child-Pugh B)

Blood concentration of this drug may increase [see "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" and "PHARMACOKINETICS" sections].

2. Patients with reproductive potential

Women of childbearing potential should be instructed to use appropriate contraception during treatment with this drug and for a certain period of time after completion of treatment with this drug.
In animals (rats), a reproductive and developmental toxicity study showed mild decreases in the corpora lutea count and the number of implantation sites in female rats.

3. Pregnant women

Equfina should not be used in pregnant women or women who may possibly be pregnant [see "CONTRAINDICATIONS" section].

In animal studies, administration of this drug during an organogenesis period in pregnant rats induced ectopic testis, urologic changes (ureteric dilatation and renal pelvis dilatation), and skeletal abnormality in fetuses. In addition, coadministration with levodopa/carbidopa resulted in an increase in the incidence of skeletal malformation (bowing of scapula and shortening/bowing/thickening of long bones). In rabbits, coadministration with levodopa/carbidopa resulted in an increase in the incidence of cardiovascular malformation (ventricular septal defect and dilation of 1 blood vessel leading directly to the heart), which was observed with levodopa/carbidopa alone, as well as an increase in the rate of embryonic or fetal death. A study in which rat dams were administered this drug pre- and post-natally showed an increased mortality and changes associated with hepatobiliary disorder (yellow/orange discoloration of the skin and skull bone) in offspring.

4. Breast-feeding women

Breastfeeding should be discontinued during treatment with this drug.
In animals (rats), administration of safinamide to lactating dams was associated with vacuoles in the hepatocyte and reduced glycogen in suckling offspring. In addition, safinamide was detected in the plasma of suckling offspring, suggesting excretion of safinamide in milk.

5. Pediatric use

There was no clinical study conducted in children.

6. Patients with congenital short QT syndrome

Equfina should not be used in patients with congenital short QT syndrome [see "CLINICAL STUDIES" section].

INTERACTIONS

<u>Contraindications for co-administration (Do not co-administer with the following)</u>

Drugs	Signs, symptoms, and treatment	Mechanism and risk factors
MAO inhibitors Selegiline hydrochloride Rasagiline mesilate [see "CONTRAINDICATIONS" section]	Serious adverse reactions including hypertensive crisis and serotonin syndrome may occur. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column. In addition, at least 14 days should elapse between discontinuation of the drugs in the left column and initiation of this drug.	The effect of this drug to inhibit MAO-B may induce an additive effect.
Pethidine hydrochloride-containing products Tramadol hydrochloride-containing products Tapentadol hydrochloride [see "CONTRAINDICATIONS" section]	Serious adverse reactions including serotonin syndrome may occur. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column. In addition, at least 2 to 3 days should elapse between discontinuation of tramadol hydrochloride-containing products and initiation of this drug.	The mechanism is not known.
Tricyclic antidepressants Amitriptyline hydrochloride Amoxapine Imipramine hydrochloride Clomipramine hydrochloride Dosulepin hydrochloride Trimipramine maleate Nortriptyline hydrochloride Lofepramine hydrochloride [see "CONTRAINDICATIONS" section]	Coadministration with other MAO-B inhibitors was associated with adverse reactions including hypertension, syncope, asystole, sweating, epilepsy, altered motor/mental disorder, and rigidity, and the reports of death. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column. In addition, an interval period should elapse between discontinuation of the drugs in the left column and initiation of this drug. The length of the interval is determined based on the half-life of the drug, but should generally be at least 2 to 3 days.	Additive or synergistic effects may occur, although the mechanism is not known.
Tetracyclic antidepressants Maprotiline hydrochloride Mianserin hydrochloride Setiptiline maleate [see "CONTRAINDICATIONS" section]		

Drugs	Signs, symptoms, and treatment	Mechanism and risk factors
Selective serotonin reuptake inhibitors Fluvoxamine maleate Paroxetine hydrochloride hydrate Sertraline hydrochloride Escitalopram oxalate [see "CONTRAINDICATIONS" section]	Serious adverse reactions including serotonin syndrome may occur. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column. In addition, between discontinuation of the drugs in the left column and initiation of this drug, at least 7 days should elapse for fluvoxamine maleate, and at least 14 days should elapse for paroxetine hydrochloride hydrate, sertraline hydrochloride, and escitalopram oxalate.	The effect of these drugs to inhibit serotonin reuptake may increase brain serotonin concentration.
Serotonin–noradrenaline reuptake inhibitors Milnacipran hydrochloride Duloxetine hydrochloride Venlafaxine hydrochloride [see "CONTRAINDICATIONS" section]	Serious adverse reactions including serotonin syndrome may occur. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column. In addition, between discontinuation of the drugs in the left column and initiation of this drug, at least 2 to 3 days should elapse for milnacipran hydrochloride, at least 5 days should elapse for duloxetine hydrochloride, and at least 7 days should elapse for venlafaxine hydrochloride.	The degradation of monoamine neurotransmitters may be suppressed, and the total amount of monoamine in the brain may increase.
Selective noradrenaline reuptake inhibitors Atomoxetine hydrochloride [see "CONTRAINDICATIONS" section]	Serious adverse reactions including serotonin syndrome may occur. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column. In addition, at least 14 days should elapse between discontinuation of the drugs in the left column and initiation of this drug.	
Noradrenergic and serotonergic antidepressant Mirtazapine [see "CONTRAINDICATIONS" section]	Serious adverse reactions including serotonin syndrome may occur. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column. In addition, at least 14 days should elapse between discontinuation of the drugs in the left column and initiation of this drug.	The neurotransmission of noradrenaline and serotonin in the brain may be enhanced, and the total amount of monoamine in the brain may increase.
Central nervous system stimulants Methylphenidate hydrochloride Lisdexamfetamine mesilate [see "CONTRAINDICATIONS" section]	Serious adverse reactions including hypertensive crisis may occur. At least 14 days should elapse between discontinuation of this drug and initiation of the drugs in the left column.	The total amount of monoamine in the brain may increase.

Precautions for co-administration (This drug should be administered with caution with the following)

Drugs	Signs, symptoms, and Treatment	Mechanism and Risk factors
Trazodone hydrochloride	Administration of this drug immediately after discontinuation of trazodone hydrochloride or concomitantly with trazodone hydrochloride may increase brain serotonin concentration.	The effect of this drug to inhibit serotonin reuptake may increase brain serotonin concentration.
Reserpine derivative	The effect of this drug may be reduced.	Brain dopamine is reduced.
Phenothiazines Chlorpromazine Butyrophenones Haloperidol Sulpiride Metoclopramide		The dopamine receptors in the brain are blocked.
Dextromethorphan hydrobromide hydrate	Serotonin syndrome may occur.	The effect of dextromethorphan hydrobromide hydrate to increase brain serotonin concentration may further increase brain serotonin concentration.
Linezolid	Increased blood pressure, etc. including hypertensive crisis may occur.	Coadministration with linezolid, which has a nonselective, reversible MAO inhibitory effect, may induce an additive effect.
Sympathomimetic agents Ephedrine hydrochloride Methylephedrine hydrochloride Pseudoephedrine hydrochloride-containing drugs Phenylpropanolamine-containing drugs	Increased blood pressure including hypertensive crisis may occur.	The sympathomimetic effect of these drugs may be enhanced if the selectivity for MAO-B is lowered.

Interaction with dietary tyramine intake

Dietary tyramine restriction is not required during treatment with recommended doses of Equfina. However, use with certain foods that contain very high amounts (i.e., more than 150 mg) of tyramine could cause severe hypertension, resulting from an increased sensitivity to tyramine in patients taking recommended dosages of Equfina, and patients should be advised to avoid such foods.

ADVERSE REACTIONS

The following adverse reactions may occur. Therefore, patients should be closely monitored, and if any abnormal findings are observed, appropriate measures including discontinuation of this drug should be taken.

1. Clinically significant adverse reactions

Psychiatric symptoms such as hallucination

Visual hallucinations (3.2%), hallucination (1.1%), or other symptoms may occur.

Somnolence (1.9%), sudden onset of sleep (0.4%)

Daytime somnolence or sudden onset of sleep with no signs may occur [see "IMPORTANT PRECAUTIONS" section].

Impulse-control disorder (0.2%)

Impulse-control disorder including pathological gambling, pathological hypersexuality, compulsive shopping, or hyperphagia may occur [see "IMPORTANT PRECAUTIONS" section].

Serotonin syndrome (frequency unknown)

If any of symptoms of serotonin syndrome, such as anxiety, restlessness, excitement, confusion, fever, myoclonus, sweating, and tachycardia, is observed, treatment with this drug should be discontinued, systemic management such as cooling and fluid replacement should be initiated, and appropriate measures should be taken.

Neuroleptic malignant syndrome (frequency unknown)

Rapid dose reduction or discontinuation of this drug may cause high fever, consciousness disorder, severe muscle rigidity, involuntary movement, increased serum CK, or other related symptoms. If any of these symptoms is observed, systemic management such as cooling and fluid replacement should be initiated, and appropriate measures should be taken.

2. Other Adverse Reactions

	≥5%	1 to <5%	<1%	Frequency unknown
Infections			Gingivitis, nasopharyngitis	Pneumonia
Hematologic			Anemia	
Metabolism			Decreased appetite	
Psychoneurologic	Dyskinesia(12.4%)	Insomnia, headache, dizziness	Delirium, REM sleep abnormal, pleurothotonus, Parkinson's disease, restless legs syndrome	Agitation, anxiety, confusional state, depression, restlessness, akinesia, balance disorder, hyperkinesia, tremor
Sensory			Vertigo	Cataract, diplopia, blurred vision, reduced visual acuity, visual impairment
Cardiovascular			Hypotension	Hypertension, orthostatic hypotension
Respiratory				Dyspnea
Gastrointestinal		Nausea, constipation	Dyspepsia, gastritis, vomiting	Abdominal discomfort, abdominal pain, diarrhea, queasy
Dermatologic				Erythema, hyperhidrosis, photosensitivity reaction
Musculoskeletal			Back pain, posture abnormal, spinal osteoarthritis	Arthralgia, muscle rigidity, muscle spasms
General symptom		Fall	Gait disturbance, oedema peripheral, thirst	Asthenia, condition aggravated, fatigue, malaise
Laboratory test		ALT increased	AST increased, ALP increased, γ-GTP increased, blood potassium increased, glucose urine present, decreased blood pressure, weight decreased	Blood pressure increased

Urinary tract infection (frequency unknown)

Urinary tract infection was observed in a long-term open-label study.

OVERDOSE AND TREATMENT

There is no apparent human experience with safinamide overdose.

Of note, 2 patients have taken 200 mg/day of safinamide. Of them, 1 experienced fall, nausea, and freezing phenomenon, and the other experienced confusional state, somnolence, and memory impairment. However, both subjects recovered. In addition, of 12 subjects who continuously received safinamide 300 mg/day for approximately 6 weeks, 4 experienced serious adverse events of macular edema, colitis ulcerative, rib fracture, and eczema, and these events were assessed as not related to safinamide, except for macular edema. All the events, excluding colitis ulcerative, were recovered.

There is no known antidote to safinamide nor any specific treatment for safinamide overdose. If an overdose occurs, safinamide treatment should be discontinued and supportive treatment should be administered as clinically indicated. In cases of overdose with safinamide, dietary tyramine restriction should be observed for several weeks.

PRECAUTIONS CONCERNING USE

Precautions concerning the administration of the drug

For drugs that are dispensed in a press-through package (PTP), instruct patients to remove the drug from the package before use. If the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa and cause a perforation, resulting in severe complications including mediastinitis.

PHARMACOKINETICS

1. Blood Level

   Single dose

   When Japanese healthy adult subjects received single oral doses of safinamide 50, 100, and 200 mg under fasted condition, plasma concentrations of safinamide over time and plasma pharmacokinetic parameters of safinamide were as follows.

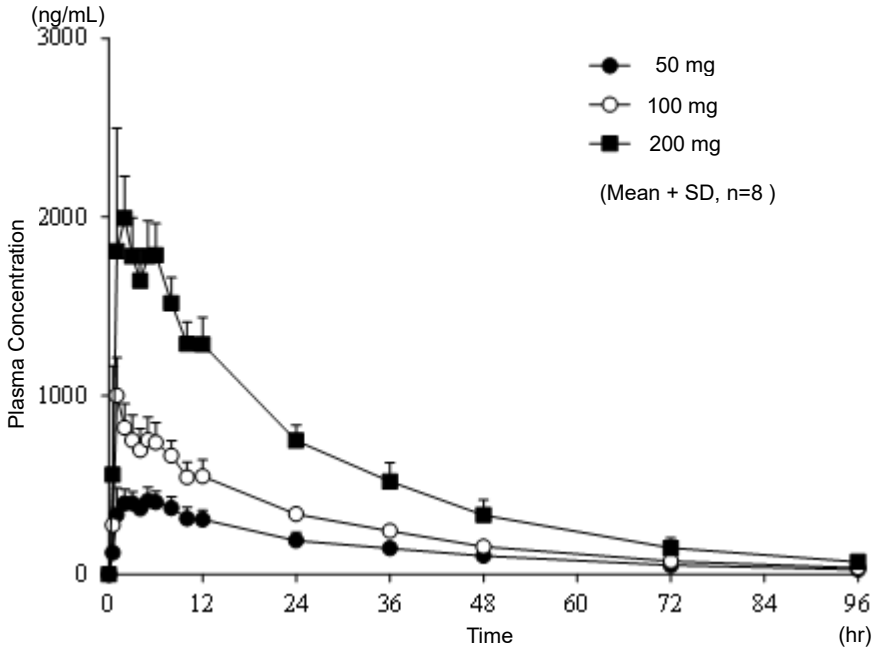


Figure 1 Plasma Concentrations of Safinamide Over Time after Single Oral Administration under Fasted Condition in Japanese Healthy Adult Subjects

Table 1 Plasma Pharmacokinetic Parameters of Safinamide after Single Oral Administration under Fasted Condition in Japanese Healthy Adult Subjects

Dose	Number of Subjects Evaluated	t_{max}[a] (hr)	C_{max} (ng/mL)	$AUC_{0-\infty}$ (ng·hr/mL)	$t_{1/2}$ (hr)
50 mg	8	3.5 (1.0 - 6.0)	463.02 ± 52.54	14343.2 ± 3085.4	24.16 ± 2.37
100 mg	8	1.0 (1.0 - 5.0)	1006.71 ± 209.13	24440.0 ± 2178.2	22.39 ± 2.36
200 mg	8	1.5 (1.0 - 5.0)	2172.88 ± 298.69	53845.3 ± 8751.0	20.44 ± 2.85

a: Median and range (minimum – maximum) Mean ± SD

Note: The approved daily dose of this drug is generally 50 mg and the maximum is 100 mg.

Multiple dose

When Japanese healthy adult subjects received multiple oral doses of safinamide 50, 100, and 200 mg once daily for 7 days under fed condition (under fasted condition on Day 7 only), plasma pharmacokinetic parameters of safinamide after the last dose were as follows. C_{max} and AUC after multiple doses of safinamide increased dose-proportionally. The accumulation ratio for C_{max} and AUC_{0-24} (Day 7/Day 1) ranged 1.9 to 2.0, and no accumulation occurred at any doses, and the steady state was reached by Day 6 of treatment.

Table 2 Plasma Pharmacokinetic Parameters of Safinamide after Multiple Oral Administration in Japanese Healthy Adult Subjects

Dose (Number of Subjects Evaluated)	Day	t_{max}[a] (hr)	C_{max} (ng/mL)	AUC_{0-24h} (ng·hr/mL)	$t_{1/2}$ (hr)
50 mg (8)	1	3.0 (0.5 – 4.0)	398.51 ± 72.98	5647.5 ± 793.8	18.67 ± 2.97
	7	1.0 (1.0 – 6.0)	745.84 ± 93.40	11434.4 ± 1758.3	21.61 ± 1.92
100 mg (7)	1	4.0 (3.0 – 5.0)	936.06 ± 154.02	13989.5 ± 2325.7	18.90 ± 3.52
	7	1.0 (0.5 – 6.0)	1819.01 ± 451.92	28754.7 ± 7215.5	21.56 ± 2.91
200 mg (8)	1	3.0 (2.0 – 4.0)	1842.86 ± 214.24	26595.0 ± 2479.9	18.16 ± 1.45
	7	1.0 (1.0 – 5.0)	3632.43 ± 547.66	53976.0 ± 5553.3	20.39 ± 2.16

a: Median and range (minimum – maximum) Mean ± SD
Note: The approved daily dose of this drug is generally 50 mg and the maximum is 100 mg.

2. Absorption

After single and multiple oral administrations to Japanese healthy adult subjects under fasted condition, safinamide was rapidly absorbed with a t_{max} of 1.0 to 3.5 hours [see "PHARMACOKINETICS" section]. In addition, when healthy adult subjects received a single oral dose of safinamide 50 mg, the bioavailability was 95% (non-Japanese data).

A comparison of plasma pharmacokinetic parameters (C_{max}, t_{max}, $t_{1/2}$, and AUC_{0-t}) in Japanese healthy adult subjects (n=8) who received a single oral dose of safinamide 50 mg under fasted and fed conditions showed no food effect.

3. Distribution

When healthy adult subjects received a single intravenous dose of safinamide 50 mg, the distribution volume was 165 L (non-Japanese data). The plasma protein binding in humans was 89% (*in vitro*).

4. Metabolism

The main elimination pathway of safinamide is metabolism. It was suggested that safinamide is metabolized to NW-1153 by nonspecific cytoplasm amidase and CYP3A4, MAO-A and aldehyde dehydrogenase are involved in the metabolism of safinamide to NW-1689 via intermediate products. It was estimated that the contribution of nonmicrosomal enzymes (cytoplasm amidase/MAO-A) might be greater than that of CYP3A4 to safinamide metabolic capacity (*in vitro*, non-Japanese data) [see "PHARMACOKINETICS" section].

5. Excretion

When healthy adult subjects received a single oral dose of C-safinamide 400 mg, 78% of total radioactivity was excreted (76% in urine and 1.5% in feces). A trace of unchanged safinamide was excreted in urine within 48 hours after administration, indicating that most of the administered safinamide is metabolized (non-Japanese data).

When Japanese healthy adult subjects received single oral doses of safinamide 50, 100, and 200 mg, 4.5% to 4.9% was excreted unchanged in urine by 96 hours after administration, and the cumulative urinary excretion rate of metabolites up to 96 hours after administration was 31.5% to 34.3% for propionate metabolite (NW-1153), 0.22% to 0.25% for benzoate metabolite (NW-1689), and 28.4% to 32.8% for glucuronate conjugate (NW-1689 acyl glucuronide).

Note) The approved daily dose of this drug is generally 50 mg and the maximum is 100 mg.

6 Patients with specific backgrounds

Patients with renal impairment

When subjects with moderate renal impairment (eGFR 30 to 59 mL/min) and subjects with severe renal impairment (eGFR of less than 30 mL/min and not requiring hemodialysis) received a single oral dose of safinamide 50 mg, plasma pharmacokinetic parameters were similar to those of subjects with normal renal function (eGFR of more than 90 mL/min) (non-Japanese data).

Patients with hepatic impairment

When subjects with mild and moderate hepatic impairment (Child-Pugh A and B) received a single oral dose of safinamide 50 mg, AUC0-∞ was increased by 32% and 82%, respectively, compared with subjects with normal hepatic function (non-Japanese data) [see "PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION" and "PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS" sections].

7. Drug-drug interaction

Ketoconazole

When healthy adult subjects (n=14) received a multiple dose of ketoconazole (CYP3A4 inhibitor) 200 mg twice daily for 6 days and a single dose of safinamide 100 mg, C_{max} and $AUC_{0-\infty}$ were increased by 6.6% and 12.9%, respectively, compared with safinamide alone (non-Japanese data).

Midazolam

When healthy adult subjects (n=16) received a multiple dose of safinamide 100 mg once daily for 14 days and a single dose of midazolam (CYP3A4 substrate) 7.5 mg, C_{max} and AUC_{0-t} were decreased by 2% and 20%, respectively, compared with midazolam alone (non-Japanese data).

Caffeine

When healthy adult subjects (n=16) received a multiple dose of safinamide 100 mg once daily for 14 days and a single dose of caffeine (CYP1A2 substrate) 200 mg, C_{max} and AUC_{0-t} were increased by 7% and 13%, respectively, compared with caffeine alone (non-Japanese data).

Rosuvastatin

When healthy adult subjects (n=24) received a multiple dose of safinamide 100 mg once daily for 11 days and a single dose of rosuvastatin calcium (BCRP substrate) 20 mg, C_{max} and AUC_{0-t} were increased by 29% and 21%, respectively, compared with rosuvastatin calcium alone (non-Japanese data).

Levodopa/Carbidopa

When patients with Parkinson's disease (n=24) received multiple dose of safinamide 100 mg once daily for 6 days in combination with levodopa/carbidopa, C_{max} and AUC_{0-6} of levodopa were decreased by 0.6% and 7.2%, respectively, compared with levodopa/carbidopa alone (non-Japanese data).

Induction of CYP

In an enzyme induction study using human hepatocytes, safinamide at concentrations of ≥1 μM led to a ≥2-fold increase in CYP2B6 mRNA expression compared with a control, suggesting possible induction of CYP2B6 by safinamide (*in vitro*).

CLINICAL STUDIES

1. Clinical studies for efficacy and safety

Japanese phase 2/3 study

In a randomized, double-blind study in Japanese patients with Parkinson's disease with wearing-off phenomenon under treatment with levodopa-containing products, there was a statistically significant increase in the change in mean daily "on" time from the baseline to the last evaluation point in the safinamide 50 mg and 100 mg groups compared with the placebo group (P=0.0002 and P<0.0001, respectively).

Table 3 Changes in Mean Daily "On" Time from the Baseline to the Last Evaluation Point

Treatment Group (Number of Subjects Evaluated)	Last Evaluation Point – Baseline[a] (hours)	Comparison With the Placebo Group[b]	
		Difference in Change Between Groups [95%CI, Lower, Upper]	P-value
Placebo (n=136)	–0.17 ± 0.26	—	—
Safinamide 50 mg (n=131)	1.22 ± 0.26	1.39 [0.67, 2.11]	0.0002
Safinamide 100 mg (n=128)	1.49 ± 0.26	1.66 [0.93, 2.39]	< 0.0001

a: LS Mean ± SE
b: Mixed model for repeated measure (MMRM) with changes from the baseline as a response variable, the treatment group, evaluation time point, and an interaction between the treatment group and evaluation point as fixed effects, and the baseline value as a covariate

The incidence of adverse reactions was 31.6% (42/133 subjects) in the 50 mg group and 30.3% (40 /132 subjects) in the 100 mg group. Major adverse reactions were dyskinesia 8.3% (11/133 subjects), visual hallucinations 3.0% (4/133 subjects), headache 2.3% (3/133 subjects), somnolence 2.3% (3/133 subjects), and nausea 2.3% (3/133 subjects) in the 50 mg group, and dyskinesia 10.6% (14/132 subjects), visual hallucinations 4.5% (6/132 subjects), somnolence 2.3% (3/132 subjects), nausea 2.3% (3/132 subjects), decreased weight 2.3% (3/132 subjects), and decreased appetite 2.3% (3/132 subjects) in the 100 mg group.

Japanese phase 3 study

In an open-label, long-term study in Japanese patients with Parkinson's disease with wearing-off phenomenon under treatment with levodopa-containing products, the change in mean daily "on" time from the baseline with safinamide 50 to 100 mg/day (mean ± SD) was 1.05±1.74 hours (n=193) at Week 4 and 1.42±2.72 hours (n=142) at Week 52, showing a persistent effect after long-term treatment.

The incidence of adverse reactions was 38.9% (79/203 subjects). Major adverse reactions were dyskinesia 16.3% (33/203 subjects), fall 3.4% (7/203 subjects), constipation 3.0% (6/203 subjects), visual hallucinations 2.5% (5/203 subjects), insomnia 2.5% (5/203 subjects), and nausea 2.5% (5/203 subjects).

2. Others

Effect on QT interval

When safinamide 100 and 350 mg was administered to healthy adult subjects once daily for 6 days, the QTc interval reached a minimum 1 hour after administration, with a difference from the placebo

group of -5.4 and -15.5 msec, respectively. This effect was correlated with plasma concentrations of safinamide (non-Japanese data).

Note) The approved daily dose of this drug is generally 50 mg and the maximum is 100 mg.

PHARMACOLOGY

1. Mechanism of action

Safinamide has a selective and reversible MAO-B inhibitory effect and increases brain concentrations of intrinsic dopamine and dopamine of levodopa origin. This MAO-B inhibition is considered as the main mechanism of action of safinamide. Safinamide also has a nondopaminergic effect (glutamate release suppressive effect via a voltage-gated sodium channel inhibitory effect).

2. Pharmacological effect

MAO-B inhibition

For inhibitory effect of safinamide on MAO-B, IC_{50} was 79 nM in the human brain and 98 nM in the rat brain, showing that MAO-B inhibition was approximately 1000-fold more potent in the human brain and approximately 6000-fold more potent in the rat brain than MAO-A inhibition (in vitro). MAO-B inhibition of safinamide was reversible (*in vitro, in vivo*).

Voltage-gated sodium channel inhibition

Safinamide inhibited a voltage-gated sodium channel in an activity-dependent manner. In human Nav subtypes (Nav 1.1 - 1.8), IC_{50} was 13 - 82 μM under rest conditions and 1.6 - 4.9 μM in the inactivated state (*in vitro*). In a microdialysis study in the rat hippocampus, safinamide significantly suppressed glutamate release induced by sodium channel agonists (*in vivo*).

Effect in Parkinson's disease model

Although coadministration of levodopa and benserazide to rats with 6-hydroxydopamine (6-OHDA) is associated with rotary motion, multiple dosing of levodopa and benserazide reduces rotary motion (wearing-off phenomenon). Safinamide significantly reversed this reduction in rotary motion.

In a cynomolgus monkey model of Parkinson's disease induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), treatment with safinamide prolonged the duration of the therapeutic effect of levodopa on Parkinson's disease.

PHYSICOCHEMICAL PROPERTIES

Nonproprietary name: Safinamide Mesilate

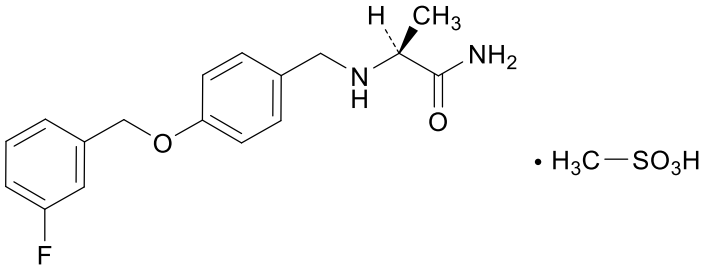
Chemical name: (*S*)-2-[({4-[(3-Fluorophenyl)methoxy]phenyl}methyl)amino]propanamide monomethanesulfonate

Molecular formula: $C_{17}H_{19}FN_2O_2 \cdot CH_4O_3S$

Molecular weight: 398.45

Description: White crystalline powder

Structural formula:



Melting point: Approximately 216 to 217 °C

Partition coefficient (log P): 2.4 (1-octanol/water)

Solubility: Freely soluble in water, methanol, and dimethyl sulfoxide. Very slightly soluble in acetone. Sparingly soluble in ethanol.

STORAGE

Store at or below 30°C.

Store away from moisture after opening of the aluminum pillow.

SHELF LIFE

36 months

PACKAGING

28 film-coated tablets

[PVC/aluminium foil blister, 14 tablets per sheet x 2 sheets in an aluminium pouch with desiccant]

PRODUCT REGISTRANT

Eisai (Singapore) Pte. Ltd.

152 Beach Road,

#15-05 to 08 Gateway East,

Singapore 189721

DATE OF REVISION OF PACKAGE INSERT

August 2022