Equfina® 50 mg
Safinamide mesylate
film coated tablets

1. COMPOSITION

Brand name	Equfina FILM COATED TABLETS 50 mg
Active ingredient	Safinamide mesylate 65.88 mg (safinamide 50 mg) 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 round biconvex film-coated tablet
Diameter (mm)	Approximately 7.1
Thickness (mm)	Approximately 3.5
Weight (mg)	Approximately 130.0

3. INDICATIONS
Equfina is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) for improvement of wearing-off phenomenon as add-on therapy to a stable dose of levodopa (L-dopa) alone or in combination with other PD medicinal products in late-stage PD.

4. PRECAUTIONS CONCERNING INDICATIONS
This drug should be used in patients with wearing-off phenomenon despite adjustment of the dose or frequency of levodopa-containing products.

5. CONTRAINDICATIONS
This drug is contraindicated to the following patients:

5.1. Patients using other MAO inhibitors (eg, selegiline hydrochloride, rasagiline mesilate) [See 10.1.].

5.2. Patients using pethidine hydrochloride-containing products, tramadol hydrochloride-containing products, or tapentadol hydrochloride [See 10.1.].

5.3. 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 10.1.].

5.4. Patients with severe hepatic impairment (Child-Pugh C) [See 9.2.1.].

5.5. Patients with a history of hypersensitivity to any of the ingredients of this drug.

5.6. Pregnant women or women suspected of being pregnant [See 9.4].

6. 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.

7. PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION

7.1. Coadministration 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.

7.2. The dose of Equfina should not exceed 50 mg daily for patients with moderate hepatic impairment (Child-Pugh B) [See 9.2.2 and 13.6.2].

8. IMPORTANT PRECAUTIONS

8.1. 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 11.1.2].

8.2. 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 11.1.3].

8.3. 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 11.2].

9. PRECAUTIONS CONCERNING PATIENTS WITH SPECIFIC BACKGROUNDS

9.1. Patients with Complication or History of Diseases, etc.

9.1.1. 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.[1)]

9.2. Patients with Hepatic Impairment

9.2.1. 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 5.4].

9.2.2. Patients with moderate hepatic impairment (Child-Pugh B)

Blood concentration of this drug may increase [See 7.2 and 13.6.2].

9.3. 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.[2)]

9.4. Pregnant Women

Equfina should not be used in pregnant women or women who may possibly be pregnant [See 5.6].

In animal studies, administration of this drug during an organogenetic 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 mothers (rats) 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.[2)]

9.5. Breast-feeding Women

Breastfeeding should be discontinued during treatment with this drug.

In animals (rats), administration of safinamide to breastfeeding mothers was associated with vacuoles in the hepatocyte and reduced glycogen in breastfed offspring. In addition, safinamide was detected in the plasma of breastfed offspring, suggesting excretion of safinamide in milk.[2)]

9.6. Pediatric Use

There was no clinical study conducted in children.

10. INTERACTIONS

10.1. Contraindications for Co-administration (Do not co-administered with the following.)

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
MAO inhibitors Selegiline hydrochloride FP Rasagiline mesilate Azilect [See 5.1]	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 Pethilorfan Tramadol hydrochloride-containing products Tramal Tapentadol hydrochloride Tapenta [See 5.2]	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 Tryptanol Amoxapine Amoxan Imipramine hydrochloride Tofranil Clomipramine hydrochloride Anafranil Dosulepin hydrochloride Prothiaden Trimipramine maleate Surmontil Nortriptyline hydrochloride Noritren Lofepramine hydrochloride Amplit [See 5.3]	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, at least 2 to 3 days should elapse between discontinuation of the drugs in the left column and initiation of this drug.	Additive or synergistic effects may occur, although the mechanism is not known.
Tetracyclic antidepressants Maprotiline hydrochloride Ludiomil Mianserin hydrochloride Tetramide Setiptiline maleate Tecipul [See 5.3]		

Drugs	Signs, Symptoms, and Treatment	Mechanism and Risk Factors
Selective serotonin reuptake inhibitors Fluvoxamine maleate Depromel Paroxetine hydrochloride hydrate Paxil Sertraline hydrochloride Jzoloft Escitalopram oxalate Lexapro [See 5.3]	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 Toledomin Duloxetine hydrochloride Cymbalta Venlafaxine hydrochloride Effexor [See 5.3]	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 Strattera [See 5.3]	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 Reflex [See 5.3]	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 Ritalin Lisdexamfetamine mesilate Vyvanse [See 5.3]	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.

10.2. Precautions for Co-administration (This drug should be administered with caution when co-administered 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 Reserpine	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.

11. 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.

11.1. Clinically Significant Adverse Reactions

11.1.1. Psychiatric symptoms such as hallucination

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

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

Daytime somnolence or sudden onset of sleep with no signs may occur [See 8.1].

11.1.3. Impulse-control disorder (0.2%)

Impulse-control disorder including pathological gambling, pathological hypersexuality, compulsive shopping, or hyperphagia may occur [See 8.2].

11.1.4. 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.

11.1.5. 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.

11.2. 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, nausea
Dermatologic				Erythema, hyperhidrosis, photosensitivity reaction

	≥5%	1 to <5%	<1%	Frequency Unknown
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

12. PRECAUTIONS CONCERNING USE

12.1. Precautions Concerning the Dispensing 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.

13. PHARMACOKINETICS

13.1. Blood Level

13.1.1. 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.[3)]

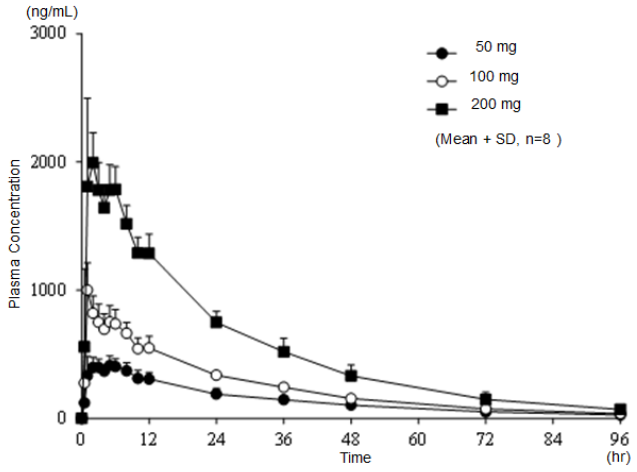


Figure 1 Plasma Concentrations of Safinamide Over Time After Single Oral Administration Under Fasted Condition in Japanese Healthy Adult Subjects

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.

13.1.2. 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.[3)]

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.

13.2. 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[3)] [See 13.1]. In addition, when healthy adult subjects received a single oral dose of safinamide 50 mg, the bioavailability was 95% (non-Japanese data).[4)]

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.[5)]

13.3. Distribution

When healthy adult subjects received a single intravenous dose of safinamide 50 mg, the distribution volume was 165 L (non-Japanese data).[4] The plasma protein binding in humans was 89% (*in vitro*).[6]

13.4. Metabolism

The main elimination pathway of safinamide is metabolism. It was suggested that safinamide is metabolized by nonspecific cytoplasm amidase and CYP3A4, and MAO-A and aldehyde dehydrogenase are involved in the metabolism of 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 13.7].[7), 8)]

13.5. Excretion

When healthy adult subjects received a single oral dose of ^{14}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).[9]

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, 0.22% to 0.25% for benzoate metabolite, and 28.4% to 32.8% for glucuronate conjugate.[3]

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

13.6. Patients with Specific Backgrounds

13.6.1. 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).[10]

13.6.2. 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 7.2 and 9.2.2].[11]

13.7. Drug-Drug Interaction

13.7.1. 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).[8)]

13.7.2. 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).[12)]

13.7.3. 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).[13)]

13.7.4. 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).[14)]

13.7.5. 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).[15)]

13.7.6. 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*).[16)]

14. CLINICAL STUDIES

14.1. Clinical Studies for Efficacy and Safety

14.1.1. 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).[18)]

Table 1 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.[17)]

14.1.2. 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. [18)]

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).[18)]

14.2. Others

14.2.1. 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).[19)]

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

15. PHARMACOLOGY

15.1. 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).

15.2. Pharmacological Effect

15.2.1. 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).[20] MAO-B inhibition of safinamide was reversible (*in vitro, in vivo*).[20]

15.2.2. 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*).[20] In a microdialysis study in the rat hippocampus, safinamide significantly suppressed glutamate release induced by sodium channel agonists (*in vivo*).[20]

15.3. 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.[20]

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.[20]

16. PHYSICOCHEMICAL PROPERTIES

Nonproprietary name : Safinamide Mesylate

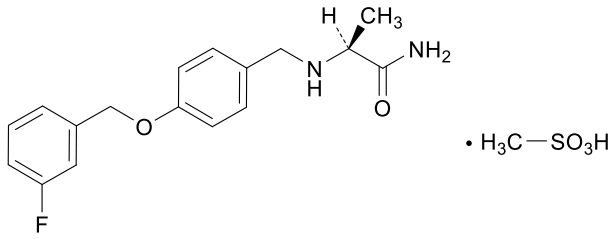
Chemical name : (*S*)-2-[({4-[(3-Fluorophenyl)methoxy]phenyl}methyl)amino]propanamide monomethanesulfonate

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.

17. PRECAUTIONS FOR HANDLING

Equfina should be stored away from moisture after opening of the aluminum pillow or bottle.

18. PACKAGING

Dus, 1 amplop @ 2 blister @ 14 tablet salut selaput

19. EXPIRATION DATE

Do not use after the expiration date indicated on the outer box or label.

20. STORAGE

Do not store above 30°C

21. REFERENCES

1) Data on file. Repeated dose toxicity study, etc. (approved on 20 Sep 2019, CTD 2.6.6.3 and 2.6.6.5) [EQF-0016]
2) Data on file. Reproductive and developmental toxicity study (approved on 20 Sep 2019, CTD 2.6.6.6) [EQF-0017]
3) Data on file. Pharmacokinetic study in healthy adult subjects (approved on 20 Sep 2019, CTD 2.7.6.6) [EQF-0018]
4) Data on file. Bioavailability study (approved on 20 Sep 2019, CTD 2.7.6.2) [EQF-0019]
5) Data on file. Food effect study (approved on 20 Sep 2019, CTD 2.7.6.1) [EQF-0020]
6) Data on file. In vitro plasma protein binding study (approved on 20 Sep 2019, CTD 2.6.4.4.8) [EQF-0021]
7) Data on file. In vitro metabolism study (approved on 20 Sep 2019, CTD 2.6.4.5) [EQF-0022]
8) Data on file. Drug interaction study (ketoconazole) (approved on 20 Sep 2019, CTD 2.7.6.14) [EQF-0023]
9) Data on file. Mass balance study in healthy adult subjects (approved on 20 Sep 2019, CTD 2.7.6.10) [EQF-0024]
10) Data on file. Pharmacokinetic study in subjects with renal impairment (approved on 20 Sep 2019, CTD 2.7.6.11) [EQF-0025]
11) Data on file. Pharmacokinetic study in subjects with hepatic impairment (approved on 20 Sep 2019, CTD 2.7.6.12) [EQF-0026]

12) Data on file. Drug interaction study (midazolam) (approved on 20 Sep 2019, CTD 2.7.6.15) [EQF-0027]
13) Data on file. Drug interaction study (caffeine) (approved on 20 Sep 2019, CTD 2.7.6.15) [EQF-0028]
14) Data on file. Drug interaction study (rosuvastatin) (approved on 20 Sep 2019, CTD 2.7.6.19) [EQF-0029]
15) Data on file. Drug interaction study (levodopa/carbidopa) (approved on 20 Sep 2019, CTD 2.7.6.16) [EQF-0030]
16) Data on file. In vitro enzyme induction study (approved on 20 Sep 2019, CTD 2.6.4.7) [EQF-0031]
17) Data on file. Japanese phase 2/3 study (approved on 20 Sep 2019, CTD 2.7.6.25) [EQF-0032]
18) Data on file. Japanese long-term study (approved on 20 Sep 2019, CTD 2.7.6.35) [EQF-0033]
19) Data on file. QT/QTc evaluation study (approved on 20 Sep 2019, CTD 2.7.6.20) [EQF-0034]
20) Data on file. Pharmacologic study (approved on 20 Sep 2019, CTD 2.6.2.2) [EQF-0035]

Reg. No. : XXXXXXXXXXXXXXX

DO NOT DISPENSE WITHOUT PHYSICIAN'S PRE-SCRIPTION
(HARUS DENGAN RESEP DOKTER)

Manufactured by:
Meiji Seika Pharma Co., Ltd.
ODAWARA, JAPAN

Packaged by:
Bora Pharmaceuticals Co., Ltd.
TAINAN, TAIWAN

Eisai

Imported by:
PT Eisai Indonesia
BOGOR, INDONESIA