GOOFICE®

Film-Coated Tablet 5 mg
elobixibat

1. Name of the medicinal product

GOOFICE® Film-coated Tablet 5 mg

2. Qualitative and quantitative composition

Each film-coated tablet contains 5.13 mg of elobixibat monohydrate equivalent to 5 mg elobixibat.
For the full list of excipients, see section 6.1.

3. Pharmaceutical form

GOOFICE® is a light-yellow round-shaped film-coated tablet.

Brand name	Identification code	Appearance			Size Weight
		Face	Reverse	Lateral	
GOOFICE®	EA1				Diameter approx. 6.1 mm Thickness approx. 3.9 mm Weight approx. 110.3 mg

4. Clinical particulars

4.1 Therapeutic indications

GOOFICE® is indicated for the treatment of chronic idiopathic constipation in adults.

4.2 Posology and method of administration

The usual adult dose for oral use is 10 mg once daily as elobixibat before meal. The dosage may be adjusted depending on the patient's symptoms but must not exceed the highest dose of 15 mg per day.

Special populations

Elderly

Since the elderly generally have reduced physiological functions, cautions should be exercised, such as reducing the dose.

Pediatric population

GOOFICE® is not recommended for use in pediatric patients due to a lack of clinical data in this population (see section 4.4).

Discontinuation of treatment

There is no data showing that discontinuation of GOOFICE® does not lead to rebound effects (see section 4.4).

4.3 Contraindications

(1) Patients with medical history of hypersensitivity to the ingredients of GOOFICE®.
(2) Patients with a documented intestinal obstruction associated with a tumor or hernia or with the suspicion of such conditions. [Intestinal obstruction may be aggravated.]

4.4 Special warnings and precautions for use

Abdominal pain or diarrhoea

GOOFICE® may cause abdominal pain or diarrhoea; dose reduction, drug interruption, or discontinuation should be considered depending on the patient's symptoms, and the need for continuing treatment with GOOFICE® should be carefully evaluated on a regular basis.

Serious liver disorder

GOOFICE® may fail to achieve its expected efficacy in patients with biliary obstruction or reduced bile acid secretion, etc., because these patients may not secrete the amount of bile acid enough to show therapeutic effect on constipation. GOOFICE® should be administered with care in these patients (see section 5.1).

Precaution concerning use

Precaution concerning the dispensing of the drug: Patients who are given drugs supplied in PTP package must be instructed to remove the drugs from the PTP sheet before taking drugs. [It has been reported that, if the PTP sheet is swallowed, the sharp corners of the sheet may puncture the esophageal mucosa causing perforation and resulting in serious complications, such as mediastinitis.]

Special populations

Pediatric use

Safety has not been established in low-birth-weight infants, neonates, nursing infants, infants, or pediatric patients (no clinical experience) (see section 4.2).

Discontinuation of treatment

There is no data showing that discontinuation of GOOFICE® does not lead to rebound effects (see section 4.2).

4.5 Interactions with other medical products and other forms of interactions

GOOFICE® exerts its inhibitory effect on P-glycoprotein (see section 5.2).

Precautions for co-administration (GOOFICE® should be administered with care when co-administered with the following drugs)

Individual patients may need to be monitored to determine if a dosage adjustment or discontinuation is necessary when such drugs are taken concomitantly with GOOFICE®.

Drugs	Signs, Symptoms and Treatment	Mechanism and Risk Factors
Bile acid preparations Ursodeoxycholic acid, chenodeoxycholic acid	The effects of these drugs may be attenuated.	The inhibitory effect of GOOFICE® on ileal bile acid transporter (IBAT) may interfere with reabsorption of bile acid preparations.
Aluminum-containing antacids Sucralfate hydrate, aldioxa, etc.	These drugs may attenuate the effect of GOOFICE®.	These drugs absorb bile acids in the gastrointestinal tract and may attenuate the effect of GOOFICE®.
Cholestyramine, colestimide	These drugs may attenuate the effect of GOOFICE®.	These drugs absorb bile acids and may attenuate the effect of GOOFICE®.

Digoxin, dabigatran etexilate methanesulfonate	The blood levels of these drugs may elevate and possibly enhance their effects.	Because of the inhibitory effect of GOOFICE® on P-glycoprotein (see section 5.2).
Midazolam	The blood level of midazolam may decrease, and the effect of midazolam may decrease (see section 5.2).	The mechanism is unknown.

4.6 Pregnancy, delivery or lactation

(1) GOOFICE® should be used in pregnant women and women who may possibly be pregnant only if the expected therapeutic benefits outweigh the possible risks associated with treatment. [The influences of a high dose oral administration of drug in animal studies (in rats) were observed in maternal toxicity (1000 mg/kg/day) and survival, growth and development of offspring (350 mg/kg/day and higher).]

(2) It is advised that lactating women should avoid GOOFICE®. If treatment with GOOFICE® is essential, breast feeding must be discontinued during treatment. [In an animal experiment (in rats) using ^{14}C-elobixibat, transfer of radioactivity into milk has been reported.]

4.7 Effects on ability to drive and use machines

There is no evidence of drug effects on the ability to drive or operate machinery.

4.8 Undesirable effects

Any of the adverse reactions listed below may occur. Therefore, patients receiving GOOFICE® treatment should be carefully monitored, and if any abnormalities are noted, appropriate measures should be taken including discontinuation of GOOFICE® treatment.

Other adverse reactions

	≥ 5%	1% to < 5%	< 1%	Frequency unknown
Hepatic		Hepatic function abnormal (ALT increased, AST increased, γ-GTP increased, Al-P increased, LAP increased)		LDH increased
Central and peripheral nervous system		dizziness		Headache
Cardiovascular				Hot flush
Gastrointestinal	Abdominal pain (23.2%), diarrhoea (14.4%)	Abdominal pain lower, abdominal distension, nausea, abdominal pain upper, abdominal discomfort, faeces soft	Stomatitis, thirst	Flatulence, defaecation urgency, vomiting, gastrointestinal sounds abnormal, constipation, colitis ischaemic,

				haematochezia, frequent bowel movements, faeces discoloured, anal incontinence, decreased appetite
Hypersensitivity			Urticaria	Rash
Hematologic		Anaemia	Vitamin E increased	Eosinophil count increased
Others		CK increased		Dysmenorrhoea

Adverse events related to the study drug reported in clinical studies

Phase III Double-blind, Placebo-controlled Comparative Study (see section 5.1)

In adult Japanese patients with chronic constipation (except for constipation associated with organic diseases, drug-induced and disease-induced constipations), placebo (n = 63) or GOOFICE® 10 mg (n = 69) was orally administered once daily before breakfast for 2 weeks. The frequency of adverse events related to the study drug was 30% (21/69 patients). Major adverse events related to the study drug included abdominal pain 19% (13/69 patients) and diarrhoea 13% (9/69 patients). These adverse events related to the study drug were non-serious and patients recovered from them while using, after interruption or discontinuation of the study drug.

Adverse events related to the study drug

		Placebo (n = 63)	GOOFICE® （n = 69）
Central and peripheral nervous system	Headache	0% (n = 0)	1% (n = 1)
Gastrointestinal	Abdominal pain	2% (n = 1)	19% (n = 13)
	Diarrhoea	0% (n = 0)	13% (n = 9)
	Abdominal pain lower	0% (n = 0)	4% (n = 3)
	Nausea	0% (n = 0)	3% (n = 2)
	Stomatitis	2% (n = 1)	0% (n = 0)
	Thirst	2% (n = 1)	0% (n = 0)
Hepatic	Liver function test abnormal	3% (n = 2)	1% (n = 1)
Others	CK increased	2% (n = 1)	0% (n = 0)

Long-term Treatment Study (see section 5.1)

In adult Japanese patients with chronic constipation (except for constipation associated with organic diseases, drug-induced and disease-induced constipations) (n = 340), GOOFICE® was orally administered once daily before breakfast for 52 weeks. The initial dose was 10 mg, and after 7 days from starting administration, the daily dose could be adjusted to 5 mg, 10 mg or 15 mg depending on symptoms. The frequency of adverse events related to the study drug was 48% (163/340 patients). Major adverse events related to the study drug included abdominal pain 24% (82/340 patients) and diarrhoea 15% (50/340 patients). These adverse events related to the study drug were non-serious and

patients recovered from them while using, after interruption or discontinuation of the study drug.

Adverse events related to the study drug (Occurring at an incidence of ≥ 2%)

		GOOFICE® （n = 340）
Gastrointestinal	Abdominal pain	24% (n = 82)
	Diarrhoea	15% (n = 50)
	Abdominal pain lower	5% (n = 17)
	Abdominal distension	3% (n = 11)
	Nausea	3% (n = 10)
	Abdominal discomfort	2% (n = 7)
Hepatic	Liver function test abnormal	3% (n = 10)

4.9 Overdosage

There is no data on overdose of the drug, do not exceed the dosing indicated of the drug. Actively monitor for timely response.

5. Pharmacological properties

5.1 Pharmacodynamic properties

ATC code: Not applicable

Mechanism of action

Elobixibat inhibits bile acid reabsorption via ileal bile acid transporter (IBAT) expressed on the epithelial cells of the terminal ileum and thereby increases the amount of bile acid passing into the large intestinal lumen. Bile acid promotes the secretion of water and electrolytes into the large intestinal lumen and enhances the colonic motility. Therefore, GOOFICE® induces the therapeutic effect on constipation.

Effect on constipation induced by loperamide in rats

In rats of loperamide-induced constipation model, a single oral administration of elobixibat demonstrated the effect of improving constipation.

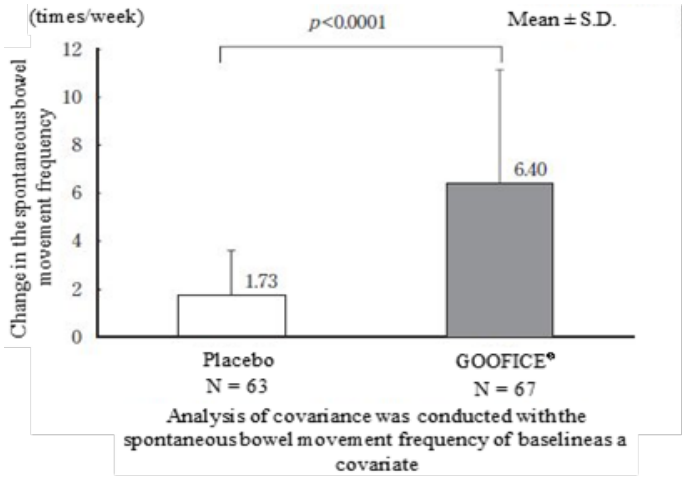
Clinical efficacy *(Japanese)*

Phase III Study and Long-term Treatment Study were conducted in Japanese patients with chronic constipation (except for constipation associated with organic diseases, drug-induced and disease-induced constipations). The diagnosis of chronic constipation was defined as less than three spontaneous bowel movements (SBMs) per week and had at least one of the following 3 symptoms related to SBM: (1) straining during at least 25% of defecations; (2) lumpy or hard stools in at least 25% of defecations; and (3) sensation of incomplete evacuation for at least 25% of defecations.

Phase III Double-blind, Placebo-controlled Comparative Study (Japanese)

A total of 132 patients (female: 82.5% (52/63) in placebo, 82.6% (57/69) in GOOFICE®; age: 43.8 ± 13.0 years in placebo, 43.0 ± 13.7 years in GOOFICE®; BMI: 21.81 ± 2.65 kg/m^2 in placebo, 21.42 ± 2.55 kg/m^2 in GOOFICE®) were orally administered placebo or GOOFICE® 10 mg once daily before breakfast for 2 weeks.

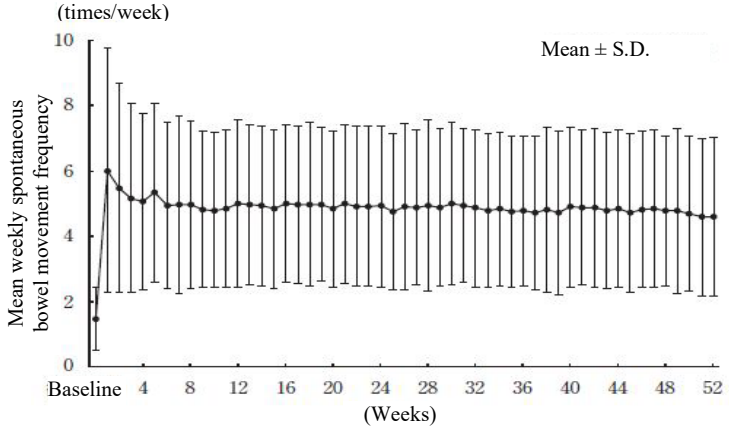
The primary endpoint, the change in SBM frequency at treatment Week 1 from baseline in GOOFICE® was significantly greater than that in placebo (placebo:1.73 ± 1.88, GOOFICE®:6.40 ± 4.73, $p < 0.0001$). The change in SBM frequency at treatment Week 2 from baseline in GOOFICE® was significantly greater than that in placebo (placebo: 1.79 ± 1.78, GOOFICE®: 5.00 ± 3.20, $p < 0.0001$). The median time to the first SBM was 25.5 hours in placebo and 5.2 hours in GOOFICE® ($p = 0.0001$). The changes in complete spontaneous bowel movements (CSBM) frequency at treatment Week 1 and at treatment Week 2 from baseline were also significantly greater in the GOOFICE® than those in the placebo (placebo:0.62 ± 1.44 and 0.86 ± 1.45, GOOFICE® :3.39 ± 3.86 and 2.98 ± 3.10, both $p < 0.0001$).



Long-term Treatment Study (Japanese)

A total of 340 patients (female: 83.2% (283/340), age: 43.9 ± 12.0 years, and BMI: 21.84 ± 3.15 kg/m^2) were orally administered GOOFICE® once daily before breakfast for 52 weeks. The initial dose was 10 mg, and after 7 days from starting administration, the daily dose could be adjusted to 5 mg, 10 mg or 15 mg depending on symptoms.

The change in SBM frequency from baseline was 4.55 ± 3.63, 4.01 ± 3.10, and 3.70 ± 2.92 at treatment Week 1, 2, and 3, respectively. Subsequently, it was stable between 3.12 and 3.88 until Week 52. A significant increase as compared to baseline was observed for all time points that were treatment Week 4, 12, 24, 36, and 52 (1 sample t test, $p < 0.0001$ for all the time points). The estimate of median time to the first SBM by the Kaplan-Meier method was 7.00 hours (95% confidence interval, 5.67 to 7.75 hours). The change in CSBM frequency from baseline was 2.54 ± 3.18 at treatment Week 1 and 2.39 ± 2.93 at treatment Week 2. After treatment Week 2, it was stable between 2.11 and 2.48 until Week 52. A significant increase as compared to baseline was observed for all time points that were treatment Week 4, 12, 24, 36, and 52 (1 sample t test, $p < 0.0001$ for all the time points).



Clinical efficacy *(US)*

Phase IIb study in patients with chronic idiopathic constipation (CIC) was conducted in US. The diagnosis of CIC was defined as less than 3 CSBMs per week and had at least 2 of the following 4 symptoms for the previous 3 months with symptom onset at least 6 months prior to diagnosis: (1) straining during at least 25% of defecations; (2) lumpy or hard stools in at least 25% of defecations; (3) sensation of incomplete evacuation in at least 25% of defecations; (4) sensation of anorectal obstruction/blockage in at least 25% of defecations.

Phase IIb Double-blind, Placebo-controlled Comparative Study (US)

A total of 190 patients (female: 89.5% (170/190), age 48.1 years (range, 20 to 79 years)) were orally administered placebo or 3 doses of GOOFICE® (5, 10 and 15 mg) once daily before breakfast for 8 weeks.

The primary endpoint, change from baseline in SBM frequency at treatment Week 1 was significantly increased in 10 mg and 15 mg as compared to placebo (10mg vs placebo: mean difference = 2.31; 0.89-3.73; p=0.002, 15mg vs Placebo: mean difference = 3.73; 2.33-5.13; p<0.001) in the modified intent-to-treat (mITT) population, excluding patients using rescue medications during Week 1. The change in SBM frequency per week from Week 1 to Week 8 from baseline was significantly greater in 10 mg and 15 mg compared to placebo.

The change in SBM frequency

SBM	Placebo	5 mg	10 mg	15 mg
WEEK 1*				
LS Mean Change from Baseline	1.65	2.50	3.96	5.38
LS Mean Difference	---	0.85	2.31	3.73
95% CI	---	-0.56 - 2.27	0.89 - 3.73	2.33 - 5.13
p-value[#]	---	0.236	0.002	<0.001
WEEKS 1-8**				
LS Mean Change from Baseline	1.51	2.57	3.12	4.61
LS Mean Difference	---	1.06	1.61	3.10
95% CI	---	-0.25 - 2.37	0.29 - 2.92	1.79 - 4.41
p-value[#]	---	0.113	0.017	<0.001

*mITT population, excluding patients using rescue medications during Week 1

**mITT population

[#]analysis of covariance with treatment group as a fixed factor and baseline value as a covariate in the model

The change from baseline in CSBM frequency at week 1 was significantly increased in 5, 10 and 15 mg as compared to placebo. The change in CSBM frequency per week from Week 1 to Week 8 from baseline was significantly greater in all treatment groups compared to placebo.

The change in CSBM frequency

CSBM	Placebo	5 mg	10 mg	15 mg
WEEK 1*				

LS Mean Change from Baseline	0.63	1.90	2.54	3.87
LS Mean Difference	---	1.27	1.91	3.23
95% CI	---	0.06 - 2.47	0.71 - 3.11	2.05 - 4.42
p-value[#]	---	0.040	0.002	<0.001
WEEKS 1-8**				
LS Mean Change from Baseline	1.01	2.43	2.46	4.10
LS Mean Difference	---	1.43	1.46	3.10
95% CI	---	0.22 - 2.64	0.26 - 2.65	1.91 - 4.29
p-value[#]	---	0.021	0.017	<0.001

*mITT population, excluding patients using rescue medications during Week 1
**mITT population
[#]analysis of covariance with treatment group as a fixed factor and baseline value as a covariate in the model

5.2 Pharmacokinetic properties

Absorption

(1) A single oral dose of GOOFICE® 5 mg, 10 mg or 15 mg was administered to patients with chronic constipation before breakfast and the pharmacokinetic parameters were noted as below. Analysis using a power model showed that the slope of the regression equation for C_{max} and $AUC_{0-\infty}$ indicated an increase in exposure with the dose increase.

Dose	5 mg	10 mg	15 mg
Number of patients	10	10	10
C_{max} (pg/mL)	186.8 ± 87.1	386.4 ± 215.4	389.7 ± 103.6
$AUC_{0-\infty}$ (pg•h/mL)	837.8 ± 572.9	1272.5 ± 656.2	1632.2 ± 475.8
T_{max} (h)	1.8 ± 1.6	1.9 ± 1.6	1.8 ± 0.6
$t_{1/2}$ (h)	3.3 ± 3.1	2.5 ± 1.5	3.2 ± 1.5

Mean ± S.D.

The repeated oral dose of GOOFICE® 5 mg, 10 mg or 15 mg was administered to patients with chronic constipation before breakfast and the pharmacokinetic parameters on Day 14 were noted as below. No accumulation potential was observed at dose levels > 5 mg on Day 14 of repeated-dose administration.

Dose	5 mg	10 mg	15 mg
Number of patients	10	8	10
C_{14max} (pg/mL)	178.1 ± 62.3	250.5 ± 86.3	449.9 ± 330.7
$AUC_{14(0-\tau)}$ (pg•h/mL)	860.4 ± 221.5	1435.7 ± 459.6	2120.9 ± 875.6
T_{14max} (h)	1.3 ± 0.5	1.7 ± 0.8	1.4 ± 0.5
$T_{14(1/2)}$ (h)	4.1 ± 2.5	10.5 ± 15.4	7.4 ± 5.5

Mean ± S.D.

(2) A single oral dose of ^{14}C-elobixibat 5 mg (approx. 2.75 MBq) was administered to healthy adult male subjects (n = 6) before breakfast and the pharmacokinetic parameters were noted as below.

Parameter	5 mg ^{14}C-elobixibat
C_{max} (nmol/L)	0.5 ± 0.3
$AUC_{0-\infty}$ (nmol•h/L)	1.2 ± 0.4 (n = 3)
T_{max} (h)*	0.8 (0.5–2.0)
$t_{1/2}$ (h)	0.8 ± 0.2 (n = 3)

Mean ± S.D.

* Median (range)

Distribution
In vitro human plasma protein binding rate of elobixibat was in excess of 99% with human blood to plasma concentration ratio less than 5%.

Metabolism
No metabolites were observed in plasma of healthy adult male subjects (n = 6) following a single oral dose of ^{14}C-elobixibat 5 mg (approx. 2.75 MBq). Unchanged and monohydroxy forms of elobixibat were found in feces pooled over 24 to 48 hours post-dose, while the percentages of radioactivity were 96.06% and 3.16%, respectively, indicating that the majority was unchanged form.

Excretion
(1) When a single oral dose of GOOFICE® was administered to patients with chronic constipation under fasting conditions, the cumulative urine drug excretion rate up to 144 hours post-dose was approximately 0.01% of the amount of dose, indicating that drug excretion into urine was almost absent.
(2) When a single oral dose of ^{14}C-elobixibat 5 mg (approx. 2.75 MBq) was administered to healthy adult male subjects (n = 6), 103.1% of radioactivity dosed was excreted in feces while 0.00 to 0.02% excreted in urine up to 144 hours post-dose.

Drug-drug interactions
(1) IC_{50} of elobixibat towards digoxin (P-glycoprotein substrate) transport was 2.65 μmol/L in Caco-2 cells, indicating the inhibitory effect of elobixibat on P-glycoprotein.
(2) In healthy adult male and female subjects (n = 25), GOOFICE® 10 mg was orally administered once daily for 5 days with coadministration of both dabigatran etexilate 150 mg/dose/day on Day 1 and midazolam 2 mg/dose/day on Day 1 and Day 5 to compare with monoadministration of each drug. The results showed that $AUC_{0\text{-}t}$ and C_{max} of dabigatran (P-glycoprotein substrate) were 1.17 fold greater (90% confidence interval: 1.00-1.36) and 1.13 fold greater (90% confidence interval: 0.96-1.33), respectively, compared with those under monoadministration and both the upper limit of 90% confidence intervals were above 1.25 as the reference value. $AUC_{0\text{-}t}$ and C_{max} of midazolam on Day 5 were 0.78-fold greater (90% confidence interval: 0.73-0.83) and 0.94-fold greater (90% confidence interval: 0.87-1.01), respectively, compared with those under monoadministration and the lower limit of 90% confidence intervals of $AUC_{0\text{-}t}$ was below 0.80 as the reference value.

Food effects
In patients with chronic constipation (n = 60), the effect of food intake on pharmacokinetics was evaluated following a single oral dose of GOOFICE® in a crossover design. C_{max} and $AUC_{0\text{-}\infty}$ under fed condition were approximately 20 to 30% of those under fasting one.

Effect of gender difference
The repeated oral dose of GOOFICE® 5 mg, 10 mg or 15 mg was administered to Japanese patients with chronic constipation before breakfast. When $AUC_{0\text{-}\tau}$ was subjected to analysis of covariance using covariates including gender, no gender difference was observed on Day 8 and Day 14 of repeated-dose administration.

Effect of race difference
Steady-state exposures following repeated doses of GOOFICE® 15 mg or 20 mg once daily before breakfast were compared in Japanese patients with chronic constipation and US

patients with functional constipation. C_{max} for US patients tended to be higher than that for Japanese patients, while AUC was almost the same for both (internal data).

5.3 Pre-clinical safety data

Though the liver-related findings (increase in blood AST and ALT and hepatocyte vacuolar degeneration) were observed in mice (500 mg/kg/day and higher at treatment Week 13) and the frequent vomiting was observed in dogs (139.2 mg/kg/day and higher at treatment Week 4 and 13) in repeated oral dose toxicity studies, wide safety margins were supported by NOAEL, and there seemed to be no concern about safety in clinical practice.
Neither genotoxicity nor carcinogenicity of elobixibat was recognized.

6. Pharmaceutical particulars

6.1 List of excipient

Microcrystalline Cellulose, D-mannitol, Hypromellose, Croscarmellose Sodium, Light Anhydrous Silicic Acid, Magnesium Stearate, Macrogol 6000, Titanium Oxide, Yellow Ferric Oxide, and Carnauba Wax.

6.2 Incompatibilities

Because there are no studies on drug compatibility, do not mix this drug with other drugs.

6.3 Shelf life

36 months from manufacturing date
6 months after opening aluminum pouch

6.4 Special precautions for storage

Store at or below 30ºC. (Store protected from high temperature and moisture after opening the aluminum pouch)

6.5 Nature and contents of container

Polypropylene film/aluminum foil blisters.
Box of 10 blisters x 10 tablets in an aluminium pouch.

7. Product registrant

Eisai (Singapore) Pte. Ltd
152 Beach Road,
#15-07 to 08, Gateway East,
Singapore 189721

8. Date of revision of the text

September 2023