Ileal Bile Acid Transporter Inhibitor

GOOFICE®

<Elobixibat Hydrate Tablet>

Keep out of reach of children.
Read instructions carefully before use.

[CONTRAINDICATIONS (GOOFICE® is contraindicated to the following patients)]

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.]

[COMPOSITIONS AND PRODUCT DESCRIPTION, PHARMACEUTICAL DOSAGE 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

GOOFICE® contains the following active ingredient and excipients per tablet:

Active ingredient: 5.13 mg of elobixibat hydrate (5 mg as elobixibat)

Excipients: microcrystalline cellulose, D-mannitol, hypromellose, croscarmellose sodium, light anhydrous silicic acid, magnesium stearate, macrogol 6000, titanium oxide, yellow ferric oxide, and carnauba wax

[INDICATION]

Chronic constipation (except for constipation associated with organic diseases)

[DOSAGE AND 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.

[PRECAUTIONS]

1. Precaution Concerning Indication

No clinical experience of use in drug-induced and disease-induced constipations.

2. Precaution Concerning Dosage and Administration

GOOFICE® may cause abdominal pain or diarrhoea; dose reduction, drug withdrawal, 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 to avoid continuing aimless administration.

3. Careful Administration (GOOFICE® should be administered with care in the following patients.)

Patient with serious liver disorder. [GOOFICE® may fail to achieve its expected efficacy in patients with biliary obstruction or reduced bile acid secretion, etc.]

4. 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.]

5. Effects on Ability to Drive, Operate Machinery

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

6. Drug Interactions

GOOFICE® exerts its inhibitory effect on P-glycoprotein (See section [PHARMACOKINETICS]).

Precautions for Coadministration (GOOFICE® should be administered with care when coadministered with the following drugs.)

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 [PHARMACOKINETICS]).
Midazolam	The blood level of midazolam may decrease, and the effect of midazolam may decrease (See section [PHARMACOKINETICS]).	The mechanism is unknown.

7. Drug Compatibility

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

8. Adverse Reactions

Adverse reactions, including laboratory abnormalities, were reported in 292/631 patients (46.3%) from clinical studies conducted until the approval. Major adverse reactions included abdominal pain in 120 patients (19.0%) and diarrhoea in 99 patients (15.7%).

Other Adverse Reactions

In the case of the adverse reactions below, appropriate measures should be taken according to the patient's symptoms.

	≥5%	1%≤ <5%	<1%	Frequency unknown
Hepatic[Note 1)]		Liver function test abnormal (ALT(GPT) increased, AST(GOT) increased)		

	≥5%	1%≤ <5%	<1%	Frequency unknown
Central and peripheral nervous system			Headache, dizziness	
Cardiovascular			Hot flush	
Gastrointestinal	Abdominal pain (19.0%), diarrhoea (15.7%), abdominal pain lower, abdominal distension	Nausea, abdominal pain upper, abdominal discomfort, faeces soft	Flatulence, thirst, defaecation urgency, vomiting, gastrointestinal sounds abnormal, constipation, stomatitis	
Hypersensitivity[Note 2)]			Urticaria, rash	
Hematologic			Eosinophil count increased, anaemia, vitamin E increased	
Others		CK (CPK) increased	Dysmenorrhoea	LDL decreased, LDL/HDL ratio decreased

Note 1) Patients should be carefully monitored for these symptoms and if any abnormalities are observed, GOOFICE® should be discontinued.
Note 2) If these symptoms are observed, GOOFICE® should be discontinued.

Notify doctor or pharmacist immediately of adverse reactions occurred during use.

9. Use in the Elderly

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

10. Use during 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.]

11. Pediatric Use

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

12. Overdosage and Management

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

[PHARMACOKINETICS]

1. 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.

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.

(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)

2. Distribution

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

(2) 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.

Parameter	5 mg	10 mg	15 mg
n	10	10	10
Vd/F (L/kg)	481.1±164.1	535.8±247.2	663.8±360.0

Mean ± S.D.

(3) Lacteal transfer in rat (See section [PRECAUTIONS] 10. (2))

(4) ^{14}C-Elobixibat was administered to male pigmented (Long Evans) rats at a single oral dose of 2.5 mg/kg, and then, whole-body autoradiograms were prepared. Distribution sites of radioactivity after oral administration were limited, and most of the radioactivity was observed in the gastric mucosa and in small intestinal contents. Radioactivity concentrations in heart blood were less than the detection limit at any time point. Radioactivity was also found in bile, cecum contents, liver, renal cortex, prostate gland, urine and skin by 4 hours after administration but detected only in gastrointestinal contents 24 hours after administration. No radioactivity was detected in the body 2 days after administration.

3. 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.

4. 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.

5. 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-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-t} and C_{max} of midazolam on Day5 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.

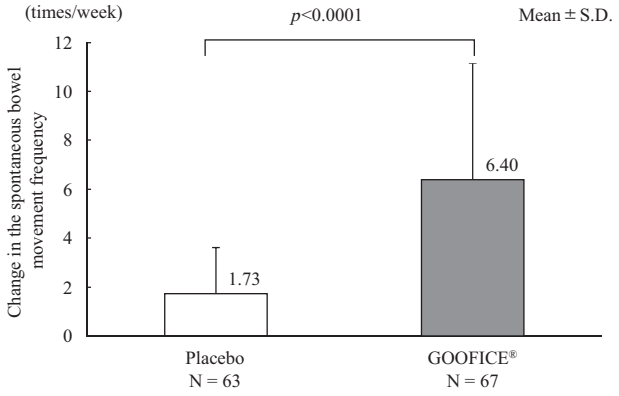
6. Food Effects

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.

[CLINICAL STUDIES]

1. Phase III Double-blind, Placebo-controled Comparative Study

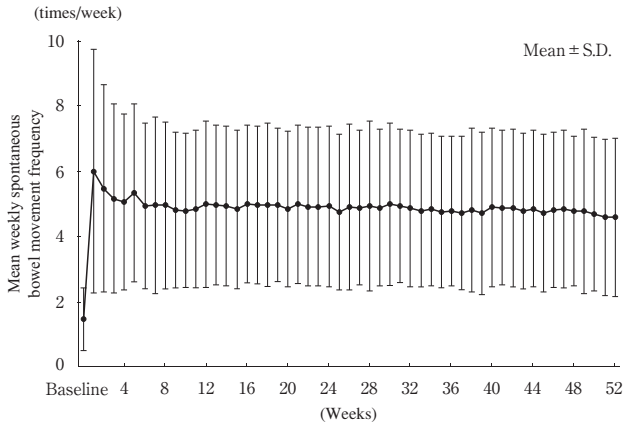
In patients with chronic constipation (n = 132), placebo or GOOFICE® 10 mg was orally administered once daily before breakfast. The change from baseline in the spontaneous bowel movement frequency on treatment period Week 1 with GOOFICE® was significantly greater than that with placebo, confirming the superiority of GOOFICE® to the placebo ($p < 0.0001$).



Analysis of covariance was conducted with the spontaneous bowel movement frequency of baseline as a covariate

2. Long-term Treatment Study

In patients with chronic constipation (n = 340), GOOFICE® 10 mg was orally administered once daily (adjusted in a range of 5 mg to 15 mg depending on the patient's symptoms) before breakfast for 52 weeks. The mean weekly spontaneous bowel movement frequency increased from baseline on treatment period Week 1, and maintained the similar level until Week 52.



[PHARMACOLOGY]

1. 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.

2. Effects on Bile Acid Transporters in Transfected Cells

Elobixibat showed strong inhibitory effect on intracellular uptake of ^{14}C-glycocholic acid (a substrate for bile acid transporters) on human IBAT with IC_{50} of 0.53 nmol/L in HEK293 cells transfected with human IBAT gene, while IC_{50} for human LBAT (liver bile acid transporter) was 240 nmol/L in HEK293 cells transfected with human LBAT gene. Elobixibat showed inhibitory effect on intracellular uptake of ^{14}C-α-aminoisobutyric acid at the human neutral amino acid transporter in HEK293 cells by 35%, 79%, and 93% at 3.125, 12.5, and 50 μmol/L, respectively. These studies showed that elobixibat is a selective inhibitor for IBAT compared to LBAT and neutral amino acid transporter.

3. Effects on Bile Acid Absorption in Mice

Elobixibat was administered orally to ApoE gene knockout female C57BL/6 mice thirty minutes before ^{75}SeHCAT, a tracer of bile acid absorption, was orally given. Twenty-four hours later, elobixibat inhibited absorption of ^{75}SeHCAT in a dose-dependent manner (ED_{50} = 0.274 mg/kg), indicating orally administered elobixibat was shown to inhibit bile acid absorption in the ileum in mice.

4. Effect on Constipation Induced by Loperamide in Rats

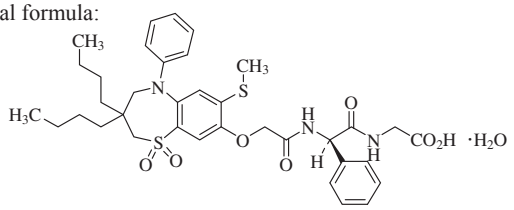
In rats of loperamide-induced constipation model, a single oral administration of elobixibat demonstrated the effect of improving constipation.

[PHYSICOCHEMICAL PROPERTIES]

Nonproprietary name: Elobixibat hydrate (JAN)

Chemical name: [(2*R*)-2-(2-{[3,3-Dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1*H*-1,5-benzothiazepin-8-yl]oxy}acetamido)-2-phenylacetamido]acetic acid monohydrate

Structural formula:



Molecular formula: $C_{36}H_{45}N_3O_7S_2 \cdot H_2O$

Molecular weight: 713.90

Description: Elobixibat hydrate occurs as a white powder. It is freely soluble in N,N-dimethylformamide, sparingly soluble in acetonitrile or methanol, slightly soluble in ethanol (99.5), and practically insoluble in water.

[SHELF-LIFE]

36 months from manufacturing date.

[STORAGE]

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

[PACKAGING]

A box of 10 blisters x 10 tablets in an aluminum pouch

MANUFACTURER

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Plant: Fukushima plant, 103-1, Shirasakaushishimizu, Shirakawa-shi, Fukushima, Japan

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Eisai (Thailand) Marketing Co., Ltd. Bangkok

Manufactured by

EA Pharma Co., Ltd.

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