For the use of a Registered Medical Practitioner or Hospital or a Laboratory only

ELOBETRA

1. Generic Name

Elobixibat Tablets 5 mg

2. Qualitative and quantitative Composition:

Elobetra 5

Each film coated tablet contains:

Elobixibat hydrate equivalent to Elobixibat …….5 mg

Excipients …….. q.s.

Colours: Yellow Oxide of Iron and Titanium Dioxide I.P.

The excipients used are Microcrystalline Cellulose (Flocel 102), Mannitol (Mannitol 25), Hypromellose E15 LV, Croscarmellose sodium, Colloidal Silicon Dioxide, Magnesium stearate, Opadry 03K520105 yellow and Purified Water.

3. Dosage form and strength

Dosage form: Film Coated Tablet

Strength: 5 mg Tablets

4. Clinical particulars

4.1 Therapeutic indication

For treatment of chronic constipation (except for constipation associated with organic disease).

4.2 Posology and method of administration

Posology

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.

Method of administration

Tablet should be taken orally.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Patients with medical history of hypersensitivity to the ingredients of Elobixibat. 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

Precaution Concerning Indication: No clinical experience of use in drug-induced and disease-induced constipations.

Precaution Concerning Dosage and Administration: Elobixibat may cause abdominal pain or diarrhea; dose reduction, drug withdrawal, or discontinuation should be considered depending on the patient's symptoms, and the need for continuing treatment with Elobixibat should be carefully evaluated on a regular basis to avoid continuing aimless administration.

Careful Administration (Elobixibat should be administered with care in the following patients): Patient with serious liver disorder. [Elobixibat may fail to achieve its expected efficacy in patients with biliary obstruction or reduced bile acid secretion, etc.]

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 (Press through Package) 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.]

Caution for Usage Drug Compatibility: Because there are no studies on drug compatibility, do not mix this drug with other drugs.

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

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

4.5 Drugs interactions

Elobixibat exerts its inhibitory effects on P-glycoprotein (See the section of Pharmacology and Pharmacokinetics). (See belowTable)

Precautions for Coadministration (Elobixibat 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 Elobixibat on ileal bile acid transporter may interfere with reabsorption of bile acid preparations.
Aluminum-containing antacids Sucralfate hydrate, aldioxa, etc.	These drugs may attenuate the effect of Elobixibat.	These drugs absorb bile acids in the gastrointestinal tract and may attenuate the effect of Elobixibat.
Cholestyramine, colestimide	These drugs may attenuate the effect of Elobixibat.	These drugs absorb bile acids and may attenuate the effect of Elobixibat.
Digoxin, dabigatran etexilate methanesulfonate	The blood levels of these drugs may elevate and possibly enhance their effects.	Because of the inhibitory effect of Elobixibat on P-glycoprotein (See Pharmacology: Pharmacokinetics under Actions).
Midazolam	The blood level of midazolam may decrease, and the effect of midazolam may decrease (See Pharmacology: Pharmacokinetics under Actions).	The mechanism is unknown.

4.6 Use in special populations

Pregnancy

Elobixibat 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).]

Lactation

It is advised that lactating women should avoid Elobixibat. If treatment with Elobixibat 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.]

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

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

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

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 diarrhea in 99 patients (15.7%). Other Adverse Reactions: In the case of the adverse reactions as follows, appropriate measures should be taken according to the patient's symptoms. (See below Table)

Other adverse events:

	≥5%	**1%< - <5%**	**<1%**	**Frequency unknown**
Hepatic Note 1		Liver function test abnormal (ALT(GPT) increased, AST(GOT) increased)		
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		
Hypersensitivity Note 2			Urticaria, rash	
Hematologic			Eosinophil count increased, anaemia, vitamin E increased	
Others		CK (CPK) increased	Dysmenorrhoea	LDL decreased,

	≥5%	1%< - <5%	<1%	Frequency unknown
				LDL/ HDL ratio decreased
Note 1) Patients should be carefully monitored for these symptoms and if any abnormalities are observed, Elobixibat should be discontinued. Note 2) If these symptoms are observed, Elobixibat should be discontinued.				

Reporting of adverse reactions

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via any point of contact of Torrent Pharma available at: https://www.torrentpharma.com/index.php/site/info/adverse_event_reporting By reporting side effects, you can help provide more information on the safety of this medicine.

4.9 Overdose

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 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, Elobixibat induces the therapeutic effects on constipation.

5.2 Pharmacodynamic properties

Effects on Bile Acid Transporters in Transfected Cells: Elobixibat showed strong inhibitory effects on intracellular uptake of C-glycocholic acid (a substrate for bile acid transporters) on human IBAT with IC of 0.53 nmol/L in HEK293 cells transfected with human IBAT gene, while IC for human LBAT (liver bile acid transporter) was 240 nmol/L in HEK293 cells transfected with human LBAT gene. Elobixibat showed inhibitory effects on intracellular uptake of 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.

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. Twentyfour hours later, elobixibat inhibited absorption of ^{75}SeHCAT in a dosedependent manner (ED = 0.274 mg/kg), indicating orally administered elobixibat was shown to inhibit bile acid absorption in the ileum in mice.

Effects on Constipation Induced by Loperamide in Rats: In rats of loperamideinduced constipation model, a single oral administration of elobixibat demonstrated the effects of improving constipation.

5.3 Pharmacokinetic properties

Absorption

A single oral dose of Elobixibat 5 mg, 10 mg or 15 mg was administered to patients with chronic constipation before breakfast and the pharmacokinetic parameters were noted as follows.

Dose	5 mg	10 mg	15 mg
Number of patients	10	10	10
Cmax (pg/ml)	186.8±87.1	386.4±215.4	389.7±103.6
AUCo-ro (pg-h/ml)	837.8±572.9	1272.5±656.2	1632.2±475.8
Tmax (h)	1.8±1.6	1.9±1.6	1.8±0.6
t112(h)	3.3±3.1	2.5±1.5	3.2±1.5
Mean± S.D.			

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 follows.

Parameter	5 mg ^{14}C-elobixibat
Cmax (nmol/L)	0.5±0.3
ALJ,Co-oo(nmol-h/L)	1.2+0.4 (n=3)
Tmax (h)*	0.8 (0.5-2.0)
t112 (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%. A single oral dose of Elobixibat 5 mg, 10 mg or 15 mg was administered to patients with chronic constipation before breakfast and the pharmacokinetic parameters were noted as follows.

Parameter	5mg	10mg	15mg
n	10	10	10
Vd/F (Ukg)	481.1±164.1	535.8±247.2	663.8±360.0
Mean± S.D.			

Lacteal transfer in rat (See Precautions). ^{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.

Metabolism

No metabolites were observed in plasma of healthy adult male subjects (n = 6) following a single oral dose of Celobixibat 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

When a single oral dose of Elobixibat 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. When a single oral dose of 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:

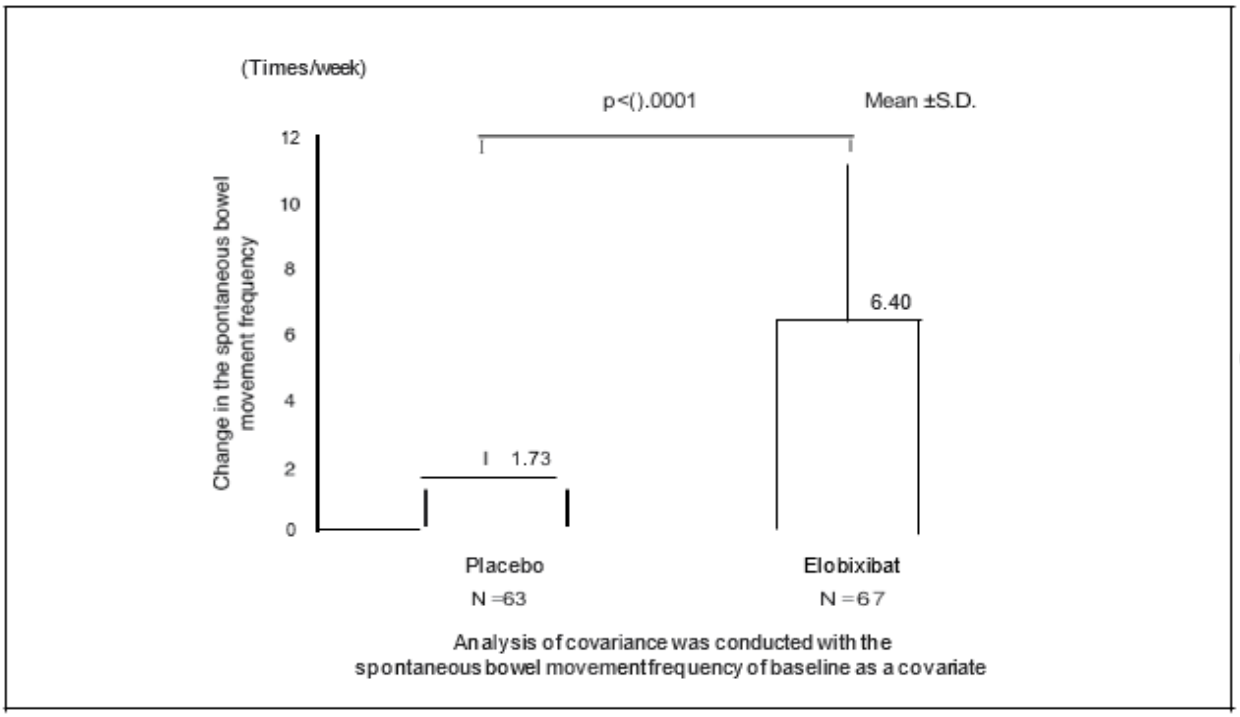
IC_{50} of elobixibat towards digoxin (P-glycoprotein substrate) transport was 2.65 μmol/L in Caco-2 cells, indicating the inhibitory effect of elobixibat on P-glycoprotein. In healthy adult male and female subjects (n = 25), elobixibat 10 mg was orally administered once daily for 5 days with coadministration 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 (Pglycoprotein 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 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-t} was below 0.80 as the reference value.

Food Effects

In patients with chronic constipation (n = 60), the Effects of food intake on pharmacokinetics was evaluated following a single oral dose of Elobixibat in a crossover design. C_{max} and AUC0- ∞ under fed condition were approximately 20 to 30% of those under fasting one.

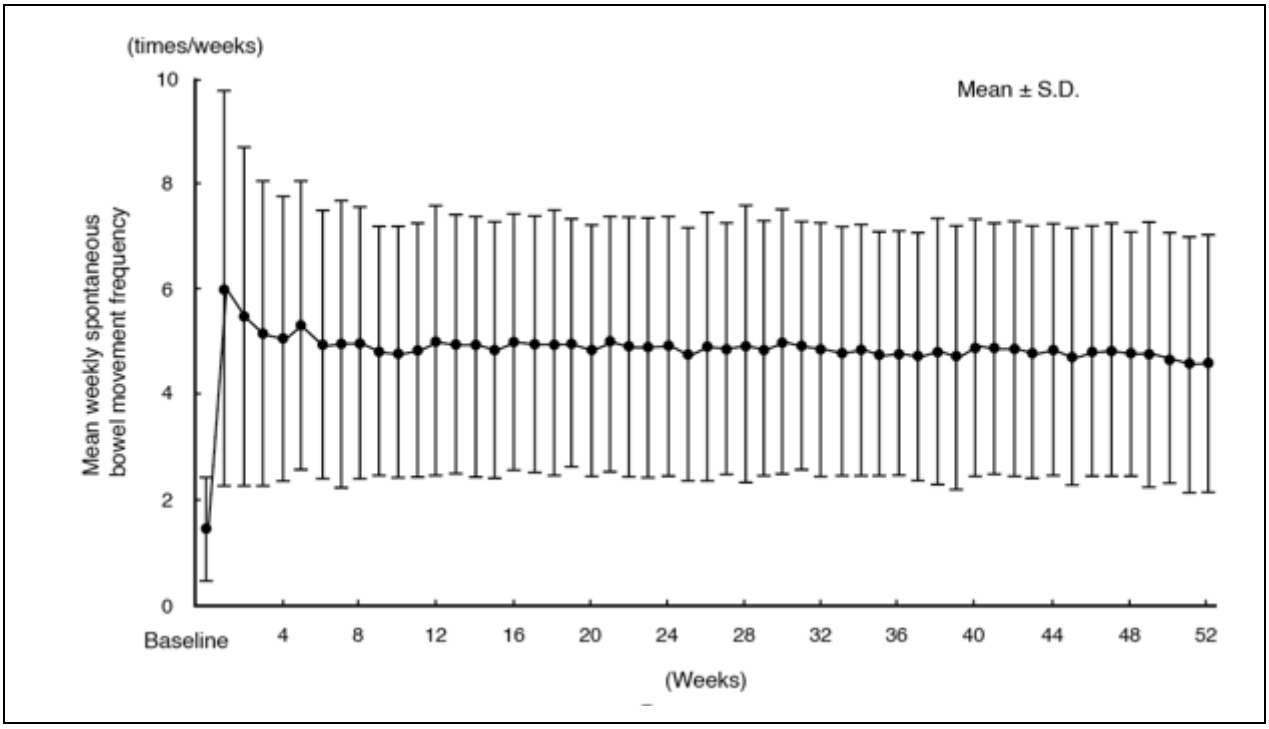
Clinical Studies

Phase III Double-blind, Placebo-controlled Comparative Study: In patients with chronic constipation (n = 132), placebo or Elobixibat 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 Elobixibat was significantly greater than that with placebo, confirming the superiority of Elobixibat to the placebo ($p < 0.0001$).



Long-term Treatment Study

In patients with chronic constipation (n = 340), Elobixibat 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.



6 Nonclinical properties

6.1. Animal Toxicology or Pharmacology

In pharmacodynamic studies, inhibitory effect on bile acid transporters, suppressive effect on bile acid reabsorption, and improving effect of constipation were investigated. In secondary pharmacodynamic studies, selectivity of receptors, etc., other than bile acid transporters was

investigated. In safety pharmacology studies, the effects on the central nervous system, cardiovascular system, respiratory system, gastrointestinal system, and renal/urinary system were investigated.

Bile acids biosynthesized in the liver are secreted into the duodenal lumen and then reabsorbed via the IBAT, a bile acid transporter localized in luminal epithelial cells in the terminal ileum Elobixibat suppresses the reabsorption of bile acids by inhibiting the IBAT from the luminal surface and thereby increases the flow of bile acids into the colon. A resulting increase in bile acids in the colonic lumen enhances the secretion of fluid and electrolytes to the colonic luminal surface and promotes gastrointestinal motility, improving colonic propulsion. With this mechanism of action, elobixibat is assumed to have a therapeutic effect on constipation.

A single intravenous dose of elobixibat at 0.0035 to 3.5 mg/kg to dogs, a significant decrease in coronary blood flow was observed in ≥0.35 mg/kg groups. Based on this result, the non-observed effect level was assumed to be 0.035 mg/kg. The plasma concentrations of elobixibat in dogs following an intravenous dose of 0.35 mg/kg, at which effects were observed on the coronary artery, were 959 to 999 nmol/L, which was approximately 1500-fold the Cmax (0.63 nmol/L) after administration of elobixibat at the maximum clinical dose, 15 mg. Therefore, elobixibat is unlikely to have any adverse effects when used in clinical practice. While a decrease in the level of bicarbonate ion (HCO3−) in the arterial blood was observed in the 3.5 mg/kg group, this was a minor, transient change unaccompanied by changes in arterial blood pH or pCO2 and was considered to be of little toxicological significance.

As toxicity studies of elobixibat, were conducted: single-dose toxicity studies, repeateddose toxicity studies, genotoxicity studies, carcinogenicity studies, and reproductive toxicity studies. In each study, doses of elobixibat are expressed as free base. For vehicle, 1% methylcellulose aqueous solution containing 0.5% Tween 80 was used unless otherwise noted.

Genotoxicity was evaluated in a bacterial reverse mutation assay, a gene mutation assay using the mouse lymphoma L5178Y cell line (L5178Y cells), and a rat bone-marrow micronucleus assay, in none of which elobixibat showed genotoxicity.

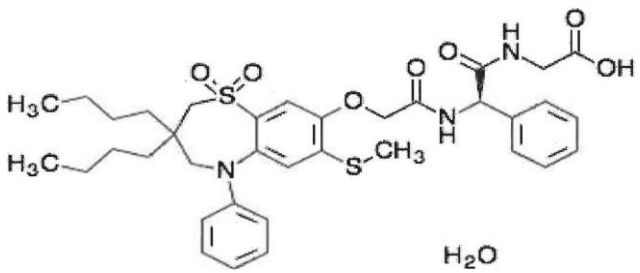
Carcinogenicity was evaluated in studies in mice and rats, in none of which elobixibat showed carcinogenicity.

The exposure (AUC) at the non-carcinogenic doses in mice and rats (125 and 200 mg/kg/day, respectively, for male and female mice, and 285 mg/kg/day for male and female rats) was 395-(male mice), 415-fold (female mice), 831- (male rats), and 621-fold (female rats) the exposure (AUC) at the proposed clinical dose (15 mg/day), respectively.

7 Description

Elobixibat Hydrate:

Elobixibat Hydrate is 2-[(2R)-2-(2-{[3,3-dibutyl-7-(methylsulfanyl)-1,1-dioxo-5-phenyl-2,3,4,5-tetrahydro-1lambda6,5-benzothiazepin-8-yl]oxy}acetamido)-2-phenyl acetamido] acetic acid. It has empirical formula of $C_{36}H_{45}N_3O_7S_2$. H_2O and molecular weight of 713.90 g/mol. The chemical structure is as below:



Elobetra 5

The excipients used are Microcrystalline Cellulose (Flocel 102), Mannitol (Mannitol 25), Hypromellose E15 LV, Croscarmellose sodium, Colloidal Silicon Dioxide, Magnesium stearate, Opadry 03K520105 yellow and Purified Water.

8 Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf-life

12 months.

8.3 Packaging information

Elobixibat Tablets is available in 10 blisters strips of 10 Tablets each.

8.4 Storage and handing instructions

Store at a temperature not exceeding 30°C.

Keep out of reach of children

9 Patient Counselling Information

Ask the patients to inform the treating physicians in case of any of the below:

- Have any allergies
- Have kidney or liver problems
- Are pregnant or plan to become pregnant
- Are breastfeeding or plan to breastfeed
- Have any serious illness
- Are taking any medicines (prescription, over-the-counter, vitamins, or herbal products)

10 Details of manufacturer

Torrent Pharmaceuticals Ltd.

Vill. Bhud & Makhnu Majra,

Teh. Baddi - 173 205,

Dist. Solan (H.P.), INDIA

11 Details of permission or licence number with date

Mfg. Licence No: MNB/05/183 dated.14/02/2025

12. Date of revision

NA

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ELOBETRA 5 mg/Feb-2025/01/PI