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

DYCOTIAM
(Acotiamide Tablets 100 mg)

COMPOSITION
Each film coated tablet contains:
Acotiamide Hydrochloride Hydrate .....100 mg
Colour: Yellow Iron Oxide and Titanium Dioxide I.P.

INDICATION
For the treatment of bloating after meals, epigastric bloating and early satiety in functional Dyspepsia.

DOSAGE FORM
Film coated tablets

POSOLOGY AND METHOD OF ADMINISTRATION
The usual adult dosage of Acotiamide Hydrochloride Hydrate is 100 mg orally three times a day before meals. Strictly follow the instructions.

Note:
If symptoms do not improve after 1 month of treatment with Acotiamide, consideration should be given to treatment discontinuation. If symptoms persist, the possibility of organic disease should be taken into account and consideration should be given to performing other tests in addition to upper gastrointestinal endoscopy, as necessary. When symptoms have remained improved over a sufficiently long period of time, consideration should be given to treatment discontinuation. Acotiamide should not be administered without careful consideration for a long period of time.

CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients.

SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Acotiamide should not be co-administered with other cholinergic drugs. Acotimide is an acetylcholinesterase inhibitor (AChE inhibitor), and since the action of acetylcholine increases, Acotiamide should be used carefully considering this. The safety of Acotiamide when combined with other prokinetic agents commonly used for this condition is not known. As reported in literature, in the carcinogenicity test in rats for 24 months, an endometrial adenocarcinoma was noted in 5/50 cases, 8/50 cases, and 5/50 cases in 200 mg/kg/day group, 600 mg/kg/day group, and 2,000 mg/kg/day group, respectively. There is little evidence to suspect that Acotiamide increased the incidence of endometrial adenocarcinomas observed in the carcinogenicity study in rats, and that it is more appropriate to consider that the cancer occurs spontaneously, as observed usually in rat strain. No genetic toxicity and estrogenic activity was noted with Acotiamide. Furthermore, no effect was seen with Acotiamide using dose up to 2,000 mg/kg/day in the carcinogenicity test in mice for24 months.

DRUG-INTERACTION

Drug Name	Clinical Effects
Drugs having anticholinergic effect such as atropine, butylscopolammonium bromide	Action of Acotiamide might decrease. Since Acotiamide has an AChE inhibitory action, the action of Acotimide is affected by co-administration of anticholinergic drug.
Choline activator and cholinesterase inhibitor such as acetylcholine chloride, neostigmine bromide.	As Acotiamide has acetylcholine receptor stimulation action, Action of Acotiamide and the concomitant drug might increase.

FERTILITY, PREGNANCY AND LACTATION

No apparent toxicity was observed in a standard battery of safety pharmacology studies.

Pregnancy

The safety of Acotiamide in pregnant women has not been established. Acotiamide should be used in pregnant women only if the therapeutic benefits exceed the risks.

Lactation

Acotiamide should not be administered in lactating women as Acotiamide has been reported to be excreted in breast milk in rats in preclinical studies. In unavoidable circumstances, if Acotiamide has to be given, the breast-feeding must be discontinued during administration.

USE IN SPECIAL POPULATION

Pediatric Use

The safety of acotiamide in pediatric population has not been established.

Geriatric Use

Acotiamide should be used with caution in elderly patients who have physiological hypofunction (renal/hepatic).

EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects on the ability to drive and use machines have been performed.

UNDESIRABLE EFFECTS

The most common adverse reactions reported are diarrhoea (2.1%), constipation (1.6%), nausea (0.8%), and vomiting (0.5%), rash and hives. The laboratory test value abnormalities showed increase in serum prolactin (3.6%), ALT (GPT) (1.8%), Y-GTP (1.2%), serum triglycerides (1%), AST (GOT) (1 %), serum bilirubin (0.7%), neutrophil count (0.5%) and ALP (0.5%).1f following adverse reactions are noted, administration should be discontinued and appropriate measures must be taken according to symptoms.

Effect on blood cells: Increase white cells count

Digestive system: Diarrhoea, constipation, Nausea, vomiting

Liver: Increased ALT (GPT), increased AST (GOT), increased GTP, Increased blood bilirubin, increased blood ALP.

Metabolic/Endocrine system: Increased blood prolactin, increased blood triglycerides

If any of these symptoms occur, stop taking this medicine and see your doctor immediately.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Mechanism of action

Acotiamide is a novel gastroprokinetic drug that exerts its activity via muscarinic receptor inhibition, which results in enhanced acetylcholine release, and via inhibition of acetylcholinesterase (AChE) activity in the stomach. Evidence from several preclinical studies showed that Acotiamide inhibited AChE activity, inhibited both the slow (competitively) and fast (noncompetitively) inward currents induced by acetylcholine, enhanced electrically stimulated contraction of gastric fundus and gastric body, facilitated acetylcholine release from enteric neurons, potentiated L-type voltage dependent calcium current and inhibited GABA-induced current in area postrema neurons.

In addition, as reported in literature, in in-vivo animal models, Acotiamide stimulated postprandial gastroduodenal and/or colonic motor activity, and improved delayed but not normal gastric emptying Acotiamide 300 mg/day significantly enhanced the gastric accommodation reflex and accelerated the gastric emptying rate (p =0.012) compared with placebo after 14-18 days of treatment.

Pharmacokinetic properties

Absorption

Plasma Concentration after single-dose administration

Pharmacokinetic parameters after a single oral administration:

Dosage (mg)	$T_{max\ (hr)}$	$C_{max\ (ng/mL)}$	AUC (ng.hr/mL)	$T_{1/2\ (hr)}$
100	2.42±0.97	30.82±13.3	171.3±59.43	13.31±6.91

Repeated-dose administration

After repeated oral administration of 100 mg of Acotiamide hydrochloride hydrate one tablet at a time, given three times a day for 9 days, the plasma concentration steady state is reached mostly from 3rd dose given on the 3rd day. Furthermore, the pharmacokinetics by repeated doses is not altered.

Influence of Meal to Drug Absorption

The C_{max} is the highest in case of administration before meals and increased to 62.7% as compared to administration on empty stomach. C_{max} in case of administration after meals was 59.6% of C_{max} achieved when administered before meals.

Plasma Protein Binding Rate (in vitro)

The plasma protein binding rate obtained by in vitro equilibrium dialysis method showed similar binding rate, which was 84.21% -85.95% in human plasma and 82.64%- 85.10% in human serum albumin; hence, the main binding protein was considered to be albumin.

Distribution

Exhibited moderate plasma protein binding in humans (84%-85%), Had a Cb:Cp ratio of 0.85-0.95 in humans, suggesting moderate penetration into red blood cells.

Metabolism

Following an oral administration of ["C] Acotiamide solution (600 mg/103 µCi) on empty stomach to 6 healthy male adults, 60% of the plasma radioactivity were based on unaltered

substance. Acotiamide is metabolised to deisopropyl by CYP2C8, CYP1Al, or CYP3A4. Furthermore, by the in vitro metabolism test using ahuman UGT expression system microsome, it is thought that this drug is metabolised to the glucuronic acid conjugate of unaltered substance by UGTl A8 or UGTl A9.

Excretion

92.7% and 5.3% of dose of Acotiamide has been reported to be excreted in faeces and in urine, respectively.

PRECLINICAL SAFETY DATA

Reproductive and Developmental Toxicity

Fertility toxicity: The NOAEL was 1000 mg/kg/day for both male and female rats.

Embryo-fetal development toxicity: The NOAEL for maternal was 300 mg/kg/day (13 × MRHD) in rats and 100 mg/kg/day (2.2 × MRHD) in rabbits. The NOAEL for fetus was 1000 mg/kg/day (19 × MRHD) in rats and 300 mg/kg/day (24 × MRHD) in rabbits.

Pre- and postnatal developmental toxicity: The NOAEL was determined as 1000 mg/kg/day for F0 and F1 in rats. Acotiamide can be transferred through placenta and excreted through milk.

Carcinogenicity

Increased incidence of endometrial adenocarcinoma was found in 2-year rat tests, but not in rasH2 transgenic accelerating tests.

EXPIRY DATE

Do not use after expiry date.

PACKAGING INFORMATION

Available in PVC/PVDC Blister.

STORAGE AND HANDLING INSTRUCTIONS

Store at a temperature not exceeding 30°C, protected from light and moisture. Keep all medicines out of reach of children.

MARKETED BY

TORRENT PHARMACEUTICALS LTD.
Torrent House, Off Ashram Road,
Ahmedabad-380 009, INDIA

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