

## ACOTIAMIDE – A REVIEW

### ABSTRACT:

Functional dyspepsia (FD) is mainly treated by drugs like H<sub>2</sub> receptors antagonists, Proton pump inhibitors, prokinetics. A novel prokinetic drug to treat FD with 2 subtypes : EPS (Epigastric pain syndrome) & PDS (postprandial distress syndrome), has been introduced recently by the approval of Acotiamide, the first in class, muscarinic receptor antagonist & cholinesterase inhibitor. It has shown improvement in gastric motility in rodents & dogs and reduced PDS symptoms in patients in double blinded multicentric study.

**Keywords:** *Acotiamide, Proton pump inhibitors, dyspepsia.*

### INTRODUCTION:

Functional dyspepsia may change the patient's quality of life. Based on the Rome III classification criteria, the main symptoms of functional dyspepsia consist of bothersome postprandial fullness, early satiety and epigastric burning<sup>1</sup>. The criteria have to be fulfilled by the presence of these symptoms for three months and onset should be at least before six months from diagnosis. The guidelines for functional dyspepsia patients was also provided in Japan, 2014<sup>2</sup>. Functional dyspepsia is primarily treated by: acid inhibitors such as H<sub>2</sub>-receptor antagonists and proton pump inhibitors (PPIs), and prokinetic drugs that accelerate disturbed gastrointestinal (GI) motility by altering visceral sensitivity<sup>1</sup>. The brain-gut axis was acknowledged as an important factor in the causation of functional GI disorders. A Phase III trial was conducted in Europe, and a Phase II trial got over in the USA.

Acotiamide is a novel prokinetic drug approved by PMDA, Japan in June 2013. It is marketed under the trade name of "Acofide" by Zeria pharmaceuticals, Chuo-ku, Tokyo. Zeria has built a pipeline focused on gastrointestinal field & oncology field and has launched numerous pharmaceutical products like Acinon-H2 receptor antagonist & Asacol 400mg-for ulcerative colitis. Molecular formula of acotiamide is C<sub>21</sub>H<sub>30</sub>N<sub>4</sub>O<sub>5</sub>S. HCl .3H<sub>2</sub>O. Molecular weight is 541.06. Chemical name is N-{2-[Bis(1-methylethyl)amino]ethyl}-2-[(2-hydroxy-4,5-dimethoxybenzoyl)amino]thiazole-4-carboxamide monohydrochloride trihydrate. Non-proprietary name: Acotiamide Hydrochloride Hydrate. It is also approved by CDSCO on 06/07/2016.

**Pharmacokinetics:** The maximum plasma levels of Acotiamide are attained in 1-1.5 hours after oral administration, with a plasma t<sub>1/2</sub> of 7-10 hours. Acotiamide was metabolized to M-1 (glucuronide conjugate of acotiamide) by UGT1A8 and UGT1A9. On the other hand, in a separate in vitro metabolic study, acotiamide was metabolized to M-4 (deisopropylacotiamide) in the highest yield by CYP2C8, followed by CYP1A1, and then by CYP3A4<sup>3</sup>. 4% of the drug is eliminated in the faeces. There is no marked CYP inhibition. The recommended dosage is 100mg three times a day before food.

**Pharmacodynamics:** It acts by antagonising the M1 and M2 muscarinic receptors in the enteric nervous system and also by inhibiting the anticholinesterase activity. Hence there is increased availability of ACh at postsynaptic receptors in neuromuscular junctions in enteric nervous system. Acotiamide may also modulate gut-brain interactions through its effects on the afferent vagus nerve, altering the sensory input from the GI tract to the CNS<sup>3</sup>.

**Uses in specific population: Pregnancy** – There is scanty information of safety of drug in the pregnant women. In pregnant rabbits acotiamide administered at oral doses of 100,300,1000mg/kg from gestation day 6 to 18<sup>3</sup>. Decreased body weight, decreased ovary weight, abortion, and an increase in the number of maternal animals with premature labor were observed in the 1000 mg/kg/day group. Decreased food intake was observed in the  $\geq 300$  mg/kg/day dose groups. In fetuses, decreased body weight and increased number of dwarfs were observed in the 1000 mg/kg/day group. The effects observed in fetuses were changes secondary to the decreased body weight of maternal animals caused by decreased food intake. **Geriatric:** The incidence of adverse events was similar between the non-elderly and elderly populations. **Hepatic impairment:** Acotiamide has not been studied in patients with hepatic impairment. It is not recommended for use in such patients<sup>3</sup>.

**Non clinical toxicologies: a) Carcinogenesis:** Acotiamide was administered orally for upto 24 months in mice and rats. No acotiamide-induced neoplastic lesion was noted in mice. **b)Antigenicity:** Acotiamide is not antigenic in mice, rats, or guinea pigs under the experimental conditions used<sup>3</sup>.

**Clinical Trials:** In Europe phase III open label study was conducted to evaluate the efficacy and safety of Acotiamide on postprandial distress syndrome<sup>4</sup>. Patients (defined by ROME III criteria) with active postprandial distress syndrome symptoms and without other symptoms of epigastric pain syndrome and similar GI disorders were recruited and enrolled to receive 100 mg Acotiamide three times daily for one year. 81.6% patients took Acotiamide for >50 weeks, with a mean duration of approximately 320.3 days. There is no deaths or treatment-related severe/serious adverse events, or any clinically significant laboratory test results. Acotiamide showed improvement in the symptoms in larger number of patients. Clinically important minimum differences started to appear from week 1 to week 2 for the postprandial fullness and early satiety<sup>5</sup>.

## CONCLUSION

Acotiamide offers a promising role in functional dyspepsia especially with postprandial distress syndrome. More clinical studies are required which have a larger population size, longer follow up periods, capturing many more clinically relevant parameters to further supplement the earlier clinical studies.

## ETHICAL CLEARANCE:

Ethical Clearance for this study was got approved from the Institutional Human Ethical Committee (IHEC).

## REFERENCES:

1. Yamawaki H, Futagami S, Wakabayashi M, Sakasegawa N, Agawa S, Higuchi K, Kodaka Y, Iwakiri K. Management of functional dyspepsia: state of the art and emerging therapies. *Therapeutic advances in chronic disease*. 2018 Jan;9(1):23
2. Miwa, H., Kusano, M., Arisawa, T. et al. Evidence-based clinical practice guidelines for functional dyspepsia. *J Gastroenterol* 50, 125–139 (2015). <https://doi.org/10.1007/s00535-014-1022-3>.
3. Masuy I, Tack J, Verbeke K, Carbone F. Acotiamide affects antral motility, but has no effect on fundic motility, gastric emptying or symptom perception in healthy participants. *Neurogastroenterol Motil*. 2019 Apr;31(4):e13540. doi: 10.1111/nmo.13540. Epub 2019 Jan 20. PMID: 30663175.
4. Tack J, Pokrotnieks J, Urbonas G, Banciu C, Yakusevich V, Bunganic I, Törnblom H, Kleban Y, Eavis P, Tsuchikawa M, Miyagawa T. Long-term safety and efficacy of acotiamide in functional dyspepsia (postprandial distress syndrome)-results from the European phase 3 open-label safety trial. *Neurogastroenterol Motil*. 2018 Jun;30(6):e13284. doi: 10.1111/nmo.13284. Epub 2018 Jan 8. PMID: 29315999.
5. Narayanan V, Bhargava A, Pallewar S. Real World Efficacy and Tolerability of Acotiamide. Relieving Meal-related Symptoms of Functional Dyspepsia. *J Gastrointest Dig Syst*. 2018;8:1.

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