



# An Open-Label, Multicenter Post Marketing Study to Assess the Symptomatic Efficacy and Safety of Troxipide [Troxip<sup>TM</sup>] in the Management of Acid Peptic Disorders in Indian Patients

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## **Authors' contributions**

*This work was carried out in collaboration between all authors. Author BD designed the study, performed the statistical analysis, reviewed the protocol, and wrote the manuscript for publication. Author DS managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.*

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## **ABSTRACT**

**Aims:** A post marketing study to assess the symptomatic efficacy and safety of Troxipide (TROXIP<sup>TM</sup>) 100mg in the management of acid peptic disorders (APDs) in Indian population.

**Study Design:** An observational, prospective, uncontrolled, open-label, multicenter post marketing study.

**Place and Duration of Study:** Patients were enrolled from 62 centers across 11 states of India, between October 2010 and March 2012.

**Methodology:** Out of 1500 APD patients, 1486 (850 men, 636 women; age range 16-85 years) were prescribed Troxipide 100mg tablet orally thrice daily. The efficacy and safety assessments were performed on day 14 and day 28 after beginning the treatment and recorded in the case report forms. The efficacy of Troxipide was estimated based on the changes from the baseline in the symptom score on a 100 point visual analogue scale (VAS) for individual symptoms. Safety was assessed by adverse events reported with usage of Troxipide on day 14 and day 28 after start of the treatment.

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**Results:** Troxipide monotherapy (n=1427) significantly reduced the mean VAS score from baseline for all major symptoms, viz. nausea, vomiting, belching, heart burn, epigastric pain, acid regurgitation, abdominal bloating & loss of appetite at the end of the study. The global mean VAS score (a sum of individual symptom VAS score) of these patients decreased from  $134.26 \pm 75.31$  to  $21.88 \pm 39.52$  at the end of the study ( $P < .001$ ). All the patients who were previously treated but uncontrolled, with acid inhibitors like proton pump inhibitors (PPIs), histamine 2 receptor antagonists (H2RAs) etc. had a significant reduction in the VAS score from  $164.38 \pm 64.54$  to  $35.56 \pm 54.24$  on day 28 ( $P < .001$ ). Troxipide was well tolerated with overall incidence of adverse events being 1.05% (n=15) and all the events were resolved without any sequel.

**Conclusion:** The present study demonstrates that Troxipide symptomatically controls APDs like gastritis, dyspepsia, gastro-esophageal reflux disease (GERD) and ulcers with good tolerability.

*Keywords: Troxipide; acid peptic disorder; cytoprotective agent; gastritis; ulcer.*

## 1. INTRODUCTION

Acid peptic disorders (APDs) are multifactorial disorders, including number of conditions like gastro-esophageal reflux disease (GERD), gastritis, dyspepsia, gastric ulcer, duodenal ulcer, esophageal ulcer, Zollinger Ellison Syndrome etc. [1] and is highly prevalent among the Asian population [2,3]. Although, increased gastric acid secretion was reported to be primarily associated with the pathogenesis of APD, off late, involvement of diminished mucosal defense or impaired mucosal defensive mechanisms have been revealed. These mucosal defense mechanisms support the gastric mucosa to withstand frequent exposure to damaging factors across a wide range of pH, osmolality and temperature [4]. Owing to the disease chronicity, APDs influence the quality of life and productivity of afflicted patients and are common and important causes of morbidity and mortality [5].

The acute or chronic conditions associated with APDs have been managed successfully for years with gastric antisecretory agents like the histamine 2 receptor antagonists (H2 RAs), proton-pump inhibitors (PPIs), muscarinic antagonists and antacids [2]. While, treatment with these acid suppressants usually gives symptomatic relief but the gastric mucosal damage still remains untreated and thus the role of the cytoprotective agents is gaining importance [6]. Cytoprotective agents are known to stimulate mucus production and strengthen the mucosal barrier which ultimately balances the aggressive factors (acid, pepsin, bile salts etc.) and defensive factors (mucin secretion, cellular mucus, bicarbonate secretion, mucosal blood flow, and cell turnover) in the gastrointestinal tract [7-9].

Troxipide is a new gastric cytoprotective agent with chemical formula 3, 4, 5-trimethoxy-N-(3-piperidyl) benzamide (Fig. 1) its molecular formula is  $C_{15}H_{22}N_2O_4$  and molecular weight is 294.4. [11], It has been clinically proven to treat gastritis and ulcer without inhibiting the gastric acid secretion [10-12]. The gastro protective action of Troxipide includes increase in mucus production [13], cytoprotective prostaglandin secretion in addition to regeneration of collagen fibers [14], reduction in inflammatory mediator induced neutrophil migration and reactive oxygen species generation in gastric mucosa [15]. Troxipide was also found to enhance gastric mucosal metabolism [16] and microcirculation [17], independent of pH and content of the gastric juice [10]. Further, it has been reported to be more efficacious than the

prototype cytoprotectants (gefarnate, cetraxate and sucralfate) [16-19] and acid suppressants (famotidine and ranitidine) in preclinical studies [20].

Troxipide is well absorbed throughout the gastrointestinal tract after administration in humans. It was detected in plasma from 0.05 hr after oral administration of 100 mg of film coated tablets, suggesting a rapid absorption. Bioavailability of Troxipide is 99.40%. A peak serum concentration of  $1052.471 \pm 51.9318$  ng/ml is obtained within  $3.042 \pm 0.1896$  hrs of drug administration and the resultant area under the curve is  $8737.481 \pm 315.4253$  ng/ml.hr. It is found that, at any time, a mean concentration of 5.3- 8.9  $\mu$ g is present per gram of tissue, which is capable of inhibiting the chemotactic migration and superoxide generation in the gastric mucosa. Thus, even 3 hrs after attaining peak serum levels, Troxipide is found in therapeutically active concentrations in the small intestine, liver and stomach. It has a half life of  $7.615 \pm 0.3782$  hrs, and is mainly excreted in the urine (96%) as metabolites (61% after 24hrs and 87% after 48hrs) [11,26].

In previous comparative clinical trials, Troxipide was found to be more effective than Ranitidine (300 mg/day) and Rabepazole (20 mg/day) in controlling the subjective symptoms and improving the endoscopic findings in gastritis and gastric ulcers [21,22]. However, no large scale studies, particularly symptomatic efficacy and safety with Troxip<sup>TM</sup> (Troxipide 100mg) in patients suffering from APDs have been conducted in India. Therefore, an observational, prospective, uncontrolled, open label, multi-centric post marketing study was conducted by Zuventus Healthcare Ltd., through a clinical research organization called Vimta Laboratories limited, to assess the symptomatic efficacy and tolerability of Troxip<sup>TM</sup> in day to day medical practice in India.

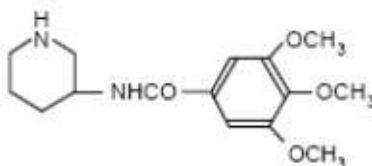


Fig. 1. Chemical structure of troxipide [11]

## 2. MATERIALS AND METHODS

### 2.1 Study Design

This was an observational, prospective, open-label, multicenter post marketing study carried out on 1500 patients with APDs recruited from 62 centers across 11 states of India (Gujarat, Karnataka, Orissa, Tamil Nadu, Delhi, Assam, West Bengal, Andhra Pradesh, Uttar Pradesh, Maharashtra and Chhattisgarh). The study was conducted by gastroenterologist and post graduate physician practicing gastroenterology in accordance with Indian regulatory guidelines for the conduct of clinical trials (schedule Y), and was approved by independent ethics committee. The eligibility criteria for the patient to be enrolled in the study included adult patients of either sex, who had APDs (symptomatic presentation as pain and discomfort by the patients), who had been prescribed Troxipide as per the prescribing information, who were never prescribed Troxipide earlier, and who were not likely to be pregnant or lactating patients. Written informed consent was obtained from each participant before the study.

### **2.1.1 Clinical trial registry of India (CTRI)**

This study has been registered with the Clinical Trial Registry of India (Reg No: REF/2012/10/004106).

### **2.2 Treatment**

Troxip<sup>TM</sup>, (Troxipide 100mg, t.i.d.) marketed by Zuventus Healthcare Ltd, Mumbai, India was prescribed as monotherapy to the patients for a period of 28 days and the assessments were made before initiating the therapy, at day 14 and day 28. The efficacy of Troxipide was assessed based on the change in symptom score from the baseline on the 100 point visual analogue scale (VAS) [21]. The eight symptoms of APD for which VAS scoring was observed were nausea, vomiting, belching, heart burn, epigastric pain, acid regurgitation, abdominal bloating and loss of appetite. Based on the severity of each symptom, a score was given ranging between 0 to 100 on the VAS scale by the investigator. If any other drug treatment was taken by the patient for any pre-existing, co-existing and underlying medical conditions, the same was documented as concomitant drugs in the relevant section of the case report form (CRF) and were considered as a separate subgroup for efficacy analysis. Safety was assessed by the clinical adverse events reported during the study period.

### **2.3 Data Collection and Statistical Analysis**

The demographic data was collected during study and analyzed descriptively by using frequency distribution table. The data obtained from 1486 patients enrolled in the study was divided into different subgroups (monotherapy subgroup, clinical symptoms wise subgroup, indications wise subgroup and previously treated patients) for efficacy analysis based on their therapy, effect on clinical symptoms, indication treated and their history of previous treatment; and analyzed by using paired t-test. The statistical software used for analysis was Microsoft Excel- Analyse it. All data are presented as mean  $\pm$  standard deviation (SD) and percentage. We considered that difference between the groups is statistical significant if  $P \leq 0.05$ .

## **3. RESULTS**

### **3.1 Demographics**

The data was obtained from 1486 patients including 850 (57.20%) males and 636 (42.79%) females, aged 16-85 years. The demographic data of patients who qualified the eligibility criteria and were successfully enrolled in the study is provided in Table 1.

**Table 1. Demographic data of the study population (n= 1486)**

<b>Demographic</b>		
<b>Gender</b>		
Female	n(%)	636 (42.79%)
Male	n (%)	850 (57.20%)
<b>Age (Years)</b>		
	< 18	5 (0.34%)
	18-30	406 (27.32%)
	31-40	405 (27.25%)
	41-50	338 (22.74%)
	51-60	224 (15.08%)
	60<	108 (7.27%)
<b>Previously treated patients</b>		
<b>Comorbid conditions</b>		
	n (%)	287 (19.31%)
	Cardiovascular System	53 (3.56%)
	Central Nervous System	27 (1.81%)
	Respiratory	23 (1.54)
	Genitourinary	8 (0.53%)
	Skeletomuscular	9 (0.60%)
	Hepatobiliary	7 (0.47%)
	Other	65 (4.37)

Troxip<sup>TM</sup> (100 mg oral tablet, thrice daily) was given as a monotherapy in 1427 patients, while remaining 59 were concomitantly treated with rabeprazole, pantoprazole, domperidone, itopride, levosulpiride, drotaverine, ondansetron or other medications for gastrointestinal disorders.

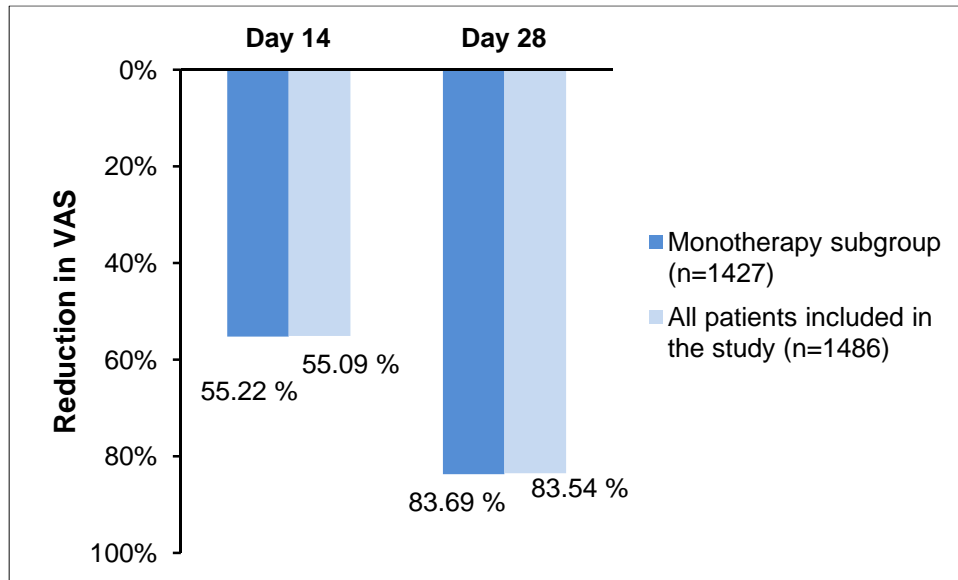
In the monotherapy subgroup (n=1427), Troxip<sup>TM</sup> was majorly prescribed for treating gastritis (n=648) followed by dyspepsia (n=470), GERD (n=279), and ulcer (n=19). In this subgroup there were 287 patients having previous history of treatment with anti-ulcer or antisecretory agents.

### **3.2 Efficacy Analysis**

The collected data was assessed as different subgroups (monotherapy subgroup, clinical symptoms subgroup, indications subgroup and previously treated subgroup). Troxipide therapy effectively controlled the APD symptoms in all patients and none of the patients had shown worsening of the symptoms. In the monotherapy group 718 out of 1427 patients were left with no symptoms at the end of 28 days of treatment. The efficacy assessment results of each subgroup are as follows:

#### **3.2.1 Monotherapy subgroup**

The percentage reduction in the Global VAS score (a sum of individual symptom VAS score) for all the patients included in the study is represented in the Fig. 2. In the monotherapy subgroup, the mean VAS score decreased from  $134.26 \pm 75.31$  to  $60.11 \pm 47.26$  on day 14 and  $21.88 \pm 39.52$  on day 28. The reductions in the Global VAS score for various symptoms were found to be statistically significant in all patients including monotherapy group ( $P < .001$ ).



**Fig. 2. Percentage reduction in Global VAS scores of all patients (n=1486) and Troxipide monotherapy subgroup (n=1427)**

### 3.2.2 Indication subgroup

In the monotherapy subgroup of patients, common indications reported were Dyspepsia (32.93%), Gastritis (45.40%), GERD (39.81%), and Ulcer (1.33%). The mean global VAS score of individual indication is represented in Table 2. A significant reduction of 96.76, 89.31, 78.20 and 78.17% was observed in the Global VAS score in the patients having ulcers, gastritis, dyspepsia and GERD respectively, at the end of the study ( $P < .001$ ).

**Table 2. Mean VAS scores of individual indications at different time points (n=1427)**

Indication	Day 0	Day 14	Day 28	Mean difference between day 0 day 28 (95% CI)	P value
<b>Mean</b>					
Dyspepsia (n=470)	145.40 ± 68.78	74.09 ± 57.04 *	31.64 ± 50.31 *	113.8 (108.1 to 119.4)	<.001
Gastritis (n=648)	134.84 ± 83.91	50.70 ± 39.74 *	14.41 ± 28.88 *	120.4 (113.8 to 127.0)	<.001
GERD (n=279)	111.85 ± 54.63	59.68 ± 40.46 *	24.40 ± 38.25 *	87.5 (80.9 to 94.0)	<.001
Ulcer (n=19)	190.15 ± 96.79	56 ± 35.34 *	6.16 ± 11.82 *	179.6 (228.2 to 130.9)	<.001

\* P Vs baseline < .001

### **3.2.3 Clinical symptom subgroup**

At the end of treatment duration, Troxipide significantly reduced the mean VAS score for all major symptoms (i.e. nausea, vomiting, belching, heart burn, epigastric pain, acid regurgitation, abdominal bloating & loss of appetite) as compared to the baseline values with statistically significant difference ( $P < .001$ ) as shown in the Table 3.

**Table 3. Mean VAS scores individual symptoms of APDs at different time points (n=1427)**

Sr. no.	Symptoms	Day 0	Day 14	Day 28	Mean difference between Day 0 Day 28 (95% CI)	P value
	<b>Mean</b>					
1.	Nausea (n=771)	34.99 ± 18.63	6.92 ± 11.27 *	4.55 ± 10.42 *	30.4 (29.2 to 31.7)	<0.001
2.	Vomiting (n=572)	31.42 ± 17.81	12.49 ± 14.15 *	3.78 ± 10.31 *	27.6 (26.2 to 29.0)	<0.001
3.	Belching (n=697)	35.85 ± 19.13	16.30 ± 16.31 *	6.09 ± 12.71 *	29.8 (28.4 to 31.1)	<0.001
4.	Heart Burn (n=574)	39.42 ± 18.14	17.24 ± 16.43 *	6.68 ± 13.42 *	32.7 (31.5 to 34.0)	<0.001
5.	Epigastric Pain (n=732)	40.82 ± 19.18	19.07 ± 16.48 *	7.86 ± 13.55 *	33.0 (31.6 to 34.3)	<0.001
6.	Acid Regurgitation (n=509)	39.41 ± 19.23	18.06 ± 17.40 *	8.37 ± 14.65 *	31.0 (29.5 to 32.6)	<0.001
7.	Abdominal Bloating (n=527)	39.57 ± 17.62	17.96 ± 15.44 *	7.08 ± 12.96 *	32.5 (31.0 to 34.0)	<0.001
8.	Loss of Appetite (n=580)	36.43 ± 18.74	14.36 ± 13.77 *	3.86 ± 9.79 *	32.6 (31.1 to 34.0)	<0.001

\* P Vs baseline < .001

### **3.2.4 Previously treated subgroup**

There were 287 patients who were previously treated but uncontrolled with PPI (225 patients), H2 RA (38 patients), Sucralfate (3 patients), other miscellaneous drugs and their combinations (21 patients) i.e. PPI with prokinetics, PPI with H2 antagonist, PPI with antacid etc. All the patients in this subgroup had a significant reduction in the VAS score from  $164.38 \pm 64.54$  to  $35.56 \pm 54.24$  at the end of treatment period ( $P < .001$ ). Moreover 103 patients were found to be symptom free (n=287) at the end of 28 days treatment. The percent reduction in the Global VAS score of previously treated patients with PPI, H2RA, Sucralfate and other miscellaneous drugs is depicted in Fig 3.

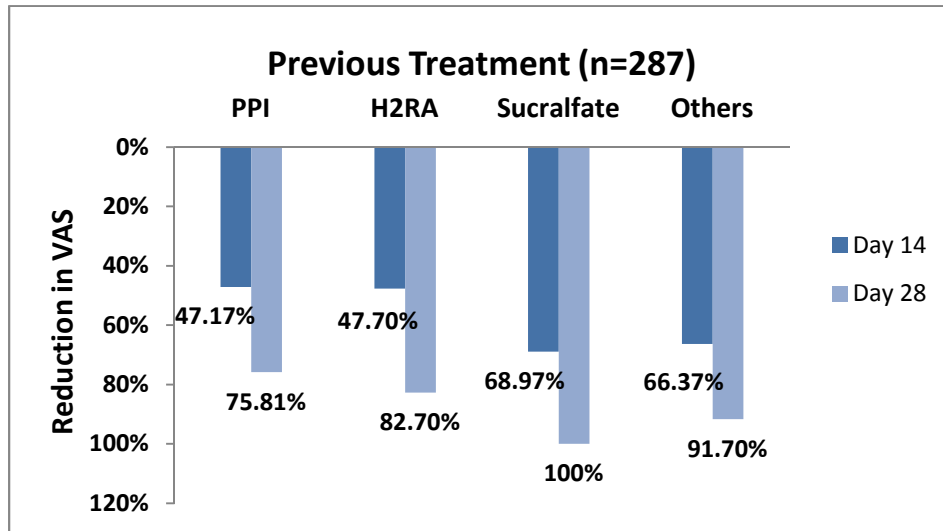


Fig. 3. Percent reduction in the Global VAS score of previously treated patients with PPI, H2RA, Sucralfate and other miscellaneous drugs (n=287)

### 3.3 Safety Assessment

In the current study (n=1486), a total of 15 adverse events (1.05%) were reported in 11 patients (Table 4). Out of the 15 adverse events, the severity was reported to be mild for 9 (60%) and moderate for 6 (40%) events. All the adverse events were resolved without sequelae. No serious adverse events were reported during the study period.

Table 4. Adverse events reported during the study period

Body system	Adverse events	No. (%) of adverse events (n=15)
Nervous system disorders	Fatigue	1 (0.07)
	Headache	1 (0.07)
	Syncope	1 (0.07)
	Malaise	1 (0.07)
Cardiovascular disorder	Chest Pain	1 (0.07)
Gastrointestinal disorders	Belching	2 (0.14)
	Burning	1(0.07)
	Constipation	2 (0.14)
	Fullness	1 (0.07)
	Acidity	1 (0.07)
	Nausea	1 (0.07)
	Vomiting	1 (0.07)
	High levels of SGPT	1 (0.07)

## 4. DISCUSSION

Patients with APDs are mainly associated with diminished mucosal defense [3,24,27], hence it is desirable to correct the defensive factors or mechanisms by administration of cytoprotective agents [7,8]. Troxipide, a cytoprotective agent, is known to have multiple



beneficial mechanism of actions in the treatment of gastritis and gastric ulcers [12]. It promotes the mucus production [13], and increases the synthesis and release of cytoprotective prostaglandins [14], thereby preventing exposure of the apical surface of stomach cells to the gastric acid. These actions of Troxipide are considered to be very important for the management of clinical symptoms in APD patients [24].

Previously, Troxipide had shown good efficacy in the resolution of clinical symptom associated with APDs. The overall amelioration rate observed was 82.9 and 79.4% in acute gastritis/chronic gastritis and gastric ulcer, respectively [11]. In the present study, Troxipide was prescribed in APDs like dyspepsia, GERD, gastritis and ulcer wherein a significant reduction of 78.20, 78.17, 89.31 and 96.76% was observed in the Global VAS score, respectively, at the end of the study ( $P < .001$ ).

Although PPIs and H2 RA had been used as mainstream therapy in the management of APDs [2], our previous studies had proven Troxipide to be superior over ranitidine (300mg/day) and rabeprazole (20mg/day) in reducing the symptom severity of endoscopic gastritis and ulcer. Troxipide provides a higher improvement in symptoms associated with GERD and provides it in a shorter duration as compared to Ranitidine [21,22]. Therefore, Troxipide can be used as an empirical therapy in the treatment of GERD.

We also noted that, Troxipide was effective in treating patients who were previously treated but uncontrolled with PPI and H2 RA as there was a 75.81 and 82.70% reduction in the Global VAS score, respectively, at the end of the study. Collectively these results infer that, Troxipide is more effective than the prototype cytoprotectant (sucralfate) [16,18,19] and acid suppressants (rabeprazole, famotidine and ranitidine) in the amelioration of symptoms associated with APDs [20,21].

The findings of this study suggest that, Troxip<sup>TM</sup> was well tolerated with overall adverse events being reported only in 11 patients (0.74%). Most common adverse events observed with Troxip<sup>TM</sup> were certain gastrointestinal symptoms. The adverse events reported in the study were mild and moderate in nature and resolved without sequelae. The lack of control arm and placebo effect, short duration of treatment period and use of the subjective VAS scale were the limitations of present study. In addition, enrollment of APD patients in the study was based on the previous history and the physician's opinion. Since diagnostic endoscopy was not performed for the confirmation of APD, there might be chances of misdiagnosis. However this study provides a real life treatment scenario of patients' from a large number of centers across India and thus supports the use of Troxipide as an empirical therapy in the management of APD. Further, controlled clinical trials are required in the management of APDs to overcome the above limitations and validate its reliability.

## 5. CONCLUSION

The results of the present study demonstrate that Troxip<sup>TM</sup> (Troxipide 100mg) effectively controls the clinical symptoms associated with APDs and shows good patient tolerability. It is also effective in the symptom resolution of patient pretreated but uncontrolled with PPI and H2 RA treatment. Thus, Troxip<sup>TM</sup> can be regarded as a clinically useful agent in the management of the gastritis, dyspepsia, GERD and ulcers in Indian population.

## CONSENT

Not applicable.

## ETHICAL APPROVAL

All authors hereby declare that the trial has been examined and approved by the independent ethics committee and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

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## COMPETING INTERESTS

Authors are employed at Zuventus Healthcare Limited.

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