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New Drug Update

Tenapanor: new approach to counter irritable bowel syndrome with constipation

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ABSTRACT

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder chronic in nature and characterized predominantly by abdominal pain or discomfort associated with altered bowel habits, diagnosis requires characteristic symptoms during the last 3 months and onset ≥6 months ago. Symptom-based approaches for functional bloating, constipation and diarrhea are best utilised to identify IBS. IBS with constipation exerts significant impairment on work productivity by hampering quality of life. Inadequate relief by existing modalities, persistent hard stools and visceral abdominal pain demanded further clinical research. Tenanapor a novel molecule acts locally on gastrointestinal sodium/hydrogen exchanger isoform 3 (NHE3), an antiporter a counter transporter and exert antinociceptive effects on visceral sensation thereby decreases the frequency of abdominal pain. Action on NHE3 receptors located on small intestine and colon's apical surface reduces the absorption of sodium and phosphate, with minimal systemic exposure. NHE3 Inhibition induced sodium absorption results in increase in water secretion into intestinal lumen resultant an accelerated intestinal transit time and softer stool consistency. Most common adverse reactions (≥2%) are diarrhea, abdominal distension, flatulence and dizziness. The drug is metabolised mainly by CYP3A4/5 and excreted in feaces (70%) and urine (7%). Tenapanor's minimal systemic absorption is likely to be associated with a relatively inert safety and tolerability profile. Based on positive results from the phase III T3MPO trial program, tenapanor demonstrated promising results for IBS-C management and received US Food and Drug Administration approval as IBSRELA @ Ardelyx Pharma in September 2019 and augment existing modalities for management of IBS-C.

Keywords: Tenapanor, Inflammatory bowel syndrome, NHE3 antagonist, Constipation

INTRODUCTION

Irritable bowel syndrome (IBS) is an idioathic gastrointestinal (GI) disorder chronic in nature and characterized predominantly by abdominal pain or discomfort associated with altered bowel habits. Currently followed guidelines for clinical diagnosis of IBS have been formulated by many organisations, as Rome's foundation, American Society of Gastroenterologists, American Gastroenterological Association. IBS also called as functional bowel disease has been associated with clinical spectrum of abdominal pain or discomfort associated with altered bowel habits and duration for more than 3 months and onset at least >6 months prior (Figure 1). The classification is done into subtypes on basis of bristol stool forms. Alarming symptoms suggest the possibility of structural disease, but do not necessarily negate a diagnosis of a functional bowel disorder. IBS is

best identified with symptom based approaches for functional bloating, functional constipation, and functional diarrhea.[1] The prevalence of IBS globally is 7-21% and amongst these, one third of the cases are constipation-predominant IBS (IBS-C).[2-4] According to stool consistency IBS is sub classified as: IBS with constipation (IBS-C); IBS with diarrhea (IBS-D); mixed IBS (IBS-M) and un subtyped IBS (IBS-U). IBS though not associated with mortality but it does greatly hamper quality of life.[5]

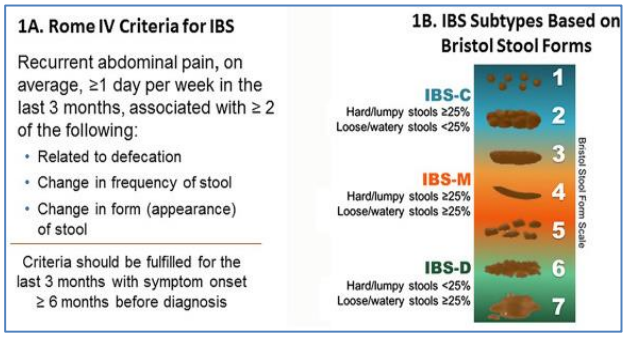

Figure 1: Rome foundation and Bristol stool forms criteria to diagnose IBS and sub types.[4]

There has been comparison of IBS-C with respect to negative impact and concluded impact being often similar or even worse than observed in chronic diseases as diabetes mellitus, rheumatoid arthritis.[7-9] IBS-C diagnosis and formulation of treatment plan presents significant challenge due to the dynamic and diverse symptoms associated with clinical presentation.[10] Historically management of IBS-C by laxatives, dietary fiber, and stool softeners lacked substantial evidences for their efficacy and low treatment satisfaction has been reported.[10,11] The latest available modalities targeting IBS-C symptoms include the guanylate cyclase-C receptor agonist linaclotide and the selective chloride channel activator lubiprostone, both drugs display least systemic absorption and target the GI tract.[12-14] Inspite of achievement of primary end point of treatment for IBS-C, that is improvement in stool consistency and abdominal pain by lubiprostone and linaclotide, scope for therepeutic options still remains unachieved in patients with residual symptoms.[12-14]

Tenapanor is a novel, small-molecule inhibitor of the GI sodium/hydrogen exchanger isoform 3 (NHE3) and may exert antinociceptive effects on visceral sensation.[15-17] Tenapanor acts on the receptors located on apical surface of the GI tract with resultant reduction in the absorption of sodium and phosphate, with minimal systemic drug exposure.[15] Enhanced intestinal fluid volume and transit is demonstrated due increased sodium retention in gut, evident by softer stools and an increase in the frequency of bowel movements. The US Food and Drug Administration (FDA) has approved Ardelyx's IBSRELA (tenapanor) in September 2019 for the treatment of IBS-C.

MECHANISM OF ACTION

Tenapanor tablets contain tenapanor hydrochloride as an active ingredient. Tenapanor hydrochloride is a sodium/hydrogen exchanger 3 (NHE3) inhibitor for oral use.[15-17] The chemical name for Tenapanor hydrochloride is 12,15-Dioxa-2,7,9-triazaheptadecanamide, 17-[3-[(4S)-6,8dichloro-1,2,3,4-tetrahydro-2-methyl-4-isoquinolinyl]phenyl]sulphonyl] amino]-N-[2-[2-[2-[3[(4S)-6,8-dichloro-1,2,3,4-tetrahy-dro-2-methyl-4isoquinolinyl]phenyl]sulphonyl]amino] ethoxy] ethoxy]ethoxy]ethyl]-8-oxo-, hydrochloride (1:2).[15-17]

Tenapanor hydrochloride has with molecular formula of C50H68Cl6N8O10S2, the molecular weight of 1218 Daltons, and the chemical structure as depicted in (Figure 2).[17]

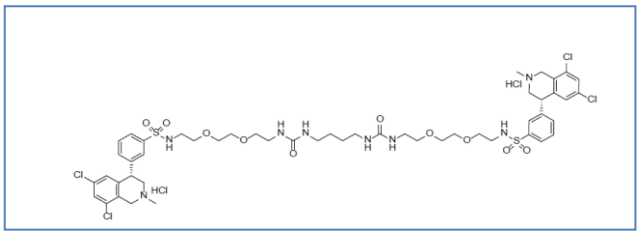

Figure 2: Chemical structure of Tenapanor.

The sodium/hydrogen exchanger (NHE) family of proteins facilitates the electro-neutral exchange of sodium ions for intracellular protons across membranes throughout the GI tract.[18] Tenapanor is a locally acting inhibitor of the sodium/hydrogen exchanger 3 (NHE3), an antiporter, which is expressed on the apical surface of the small intestine and colon primarily responsible for the absorption of dietary sodium.[15] Inhibition of NHE3 in the gut by tenapanor reduces absorption of gastrointestinal sodium, resulting in an increase in stool fluid content.[15,18] The studies conducted in vitro and on animals indicated its major metabolite, M1, is inactive against NHE3. NHE3 receptor inhibition on the apical surface of the enterocytes due to tenapanor, reduces absorption of sodium from the small intestine and colon, consequently increases water secretion into the intestinal lumen, which accelerates intestinal transit time and results in a softer stool consistency. Tenapanor has been effective in reducing abdominal pain, by regulating visceral hypersensitivity.[15]

CLINICAL PHARMACOLOGY

Tenapanor twice daily oral dosage regimen is minimally absorbed. tenapanor and its major metabolite, M1, is bound to plasma protein, 99% and 97%, respectively, in vitro.[16] With high bioavailability following single or repeated oral dosage of tenapanor 50 mg twice daily, Tenapanor plasma concentrations remained below the limit of quantitation (less than 0.5 ng/ml) in the majority of samples from under evaluation subjects.[17]

Tenapanor is metabolized primarily by CYP3A4/5 and low levels of its major metabolite, M1, are detected in plasma.[17] The Cmax of M1 is approximately 13 ng/ml after single dose of Tenapanor 50 mg and 15 ng/ml at steady state following repeated dosing of Tenapanor 50 mg twice daily in subjects.[17] Following administration of a single 15 mg radiolabeled C-Tenapanor dose to healthy subjects, approximately 70% of the radioactivity was excreted in feces within 120 hours post-dose and 79% within 240 hours post-dose, mostly as the parent drug accounting for 65% of dose within 144 hours post-dose.[14,18] Approximately 9% of the administered dose was recovered in urine, primarily as metabolites. M1 is excreted in urine unchanged accounting for 1.5% of dose within 144 hours post-dose.[17]

Further to its pharmacodynamic effects Tenapanor's minimal systemic absorption is likely to be associated with a relatively inert safety and tolerability profile.[19,20]

Cross-study comparison, patients on hemodialysis (eGFR less than 15 ml/min/1.73m^2) plasma concentrations of M1 in end-stage renal disease was not notably different from plasma concentrations of M1 in those of healthy subjects given comparable doses of tenapanor.[19,20]

DRUG DOSAGE AND FORMULATION

Tenapanor tablets contain 50 mg of tenapanor (equivalent to 53.2 mg of tenapanor hydrochloride). Inactive ingredients in the tablet includes colloidal silicon dioxide, hypromellose, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, propyl gallate, stearic acid, tartaric acid powder, Titanium dioxide and Triacetin.[20]

The recommended dosage of tenapanor in adults is 50 mg orally twice daily.[20,21] Tenapanor has to be taken in adherence to meals regimen, immediately prior to breakfast or the first meal of the day and immediately prior to dinner, since the 24 hour Na+ excretion in study subjects taking tenapanor 5-10 minutes prior to meal was higher than taking same dosage in fed condition.[19,21] If a dose is missed, skip the missed dose and take the next dose at the regular time. Taking commulative dosage to compensate missed dose must not be taken in any scenario.[19,21]

DRUG INTERACTION

Tenapanor is metabolised primarily by CYP3A4/5 and and its active matabolite is M1 and excreted mainly in faeces predominantly and amller fraction in Urine.[22] Studies Tenapanor and M1 did not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 in vitro. Tenapanor and M1 did not induce CYP1A2 and CYP2B6 in vitro.[22] CYP3A4 enzyme was unaffected and demonstrated no inhibition or induction using Midazolam as a substrate when Tenapanor 50 mg was administered twice a day for 13 days in healthy subjects.[22]

Tenapanor 50 mg single dose co administration with repeated doses of Itraconazole 200 mg, a CYP3A4 inhibitor, mean AUC and Cmax of M1 was decreased 50% in healthy subjects. And plasma concentrations of Tenapanor mostly remained below the limit of quantitation (less than 0.5 ng/ml).[23]

Tenapanor and M1 did not inhibit P-gp, BCRP, OATP1B1, and OATP1B3. M1 did not inhibit OAT1, OAT3, OCT2, MATE1, and MATE2-K.[24] M1 is a substrate of P-gp. Tenapanor is not a substrate of P-gp, BCRP, OATP1B1, and OATP1B3 and M1 is not a substrate of BCRP, OAT1, OAT3, OCT2, MATE1 and MATE2-K.[24] PepT1 activity had no significant change using cefadroxil as a substrate when Tenapanor 50 mg was administered twice a day for 12 days in healthy subjects.[25]

SPECIAL CONSIDERATION AND SIDE EFFECTS

Pregnancy

Tenapanor is least absorbed systemically on oral administration, and plasma concentrations remain below the limit of quantification (less than 0.5 ng/ml).[22] Maternal use henceforth is not expected to result in fetal exposure. Tenapanor exposure data obtained from a small number of pregnant women have documented drug associated risk for major birth defects, miscarriage, or adverse maternal or fetal outcomes.[22]

Lactation

Tenapanor secretion in either human or animal milk, its effects on milk production or its effects on the breastfed infant is still not being observed and there's paucity of data on said subject. In view of minimal systemic absorption, the drug will not yield clinically relevant exposure to breastfed infants.[23]

Pediatric use

Tenapanor is contraindicated in patients less than 6 years of age.[25] Tenapanor is to be avoided in age group of patients, less than 6 years to 12 years. The safety and effectiveness of tenapanor in patients less than 18 years of age needs to be established and backed by clinical trials and evidences.[25]

ADVERSE EFFECTS

Tenapanor overdose may cause gastrointestinal adverse effects such as diarrhea as a result of exaggerated pharmacology and compounded risk for dehydration if diarrhea is severe or prolonged.[26] The most common side effects involving more than 2% exposed population of tenapanor, include diarrhoea, abdominal distension, flatuelence and dizziness.[26] In patients of chronic kidney disease, hyperkalemia was noted. Incidence rate of less

than 2% mainly rectal bleeding and abnormal gastrointestinal sounds are not a rare possibility. [20]

CONTRAINDICATION

Tenapanor is contraindicated in patients of pediatric age group age less than 6 years, owing to higher risk of dehydartion and patients with known or suspected gastrointestinal obstruction.[1]

CLINICAL TRIALS

The safety data obtained and tabulated below depict data from 1203 adult patients with IBS-C in two randomized, double-blind, placebo-controlled clinical trials (trial 1 and trial 2). Patients were randomized and observed for period of 52 weeks, formulated to placebo or Tenapanor 50 mg twice daily. Demographic profile of both the trial group were comparable.[26]

Double-blind, placebo-controlled, randomized, multicenter trials in adult patients was conducted to evaluate the clinical efficacy of Tenapanor for IBS-C: Trial 1 (TEN-01-302; NCT02686138) and Trial 2 (TEN-01-301; NCT02621892).[26] The population under study included 620 patients in trial 1 and 606 patients in trial 2 with mean age of 46 years (range 18 to 75 years), 80% females, 64% White and 31% Black/African American.[26] Protocol under trial in these studies included, Tenapanor administration immediately prior to breakfast or the first meal of the day and immediately prior to dinner.[26]

Inclusion criteria

Rome III criteria for IBS-C for all patients. Clinical criteria during the 2-week was abdominal pain score of at least 3 on a 0-to-10-point numeric rating scale where a score of 0 indicates no pain and 10 indicates very severe pain, less than 3 complete spontaneous bowel movements (CSBMs) per week and less than or equal to 5 SBMs per week.[26] Identical trial designs were followed in both trials till 12 weeks thereafter in trial one additional 14 week treatment (26 week double blind trial) and trial 2 included 4 week randomised withdrawal.[26] Primary endpoint was the proportion of responders, where a responder was defined as a patient achieving both the stool frequency and abdominal pain intensity responder criteria in the same week for at least 6 of the first 12 weeks of treatment.[26]

The stool frequency (CSBM) and abdominal pain responder criteria for weekly assessment were formulated.[26]

CSBM responder: increase by least 1 CSBM in weekly average from baseline.

Abdominal pain responder: 30% reduction in the weekly average score compared with baseline.

The responder rates for the primary endpoint and components of the primary endpoint (CSBM and abdominal pain), which were pre-specified key secondary end points, are shown in (Table 1).[26]

Table 1: Efficacy responder rates in placebo-controlled trials (trial 1 and trial 2) in adults with IBS-C: responder for at least 6 of the first 12 weeks of treatment.

Responder rates			
Trial 1	**Tenapanor (%) (n=293)**	**Placebo (%) (n=300)**	**Treatment difference (95% CI[a])**
Responder[b] components of responder endpoint	37	24	13% (6%, 20%)
CSBM responder[c]	47	33	
Abdominal pain responder[d]	50	38	
Trial 2	**Tenapanor (%) (n=307)**	**Placebo (%) (n=299)**	
Responder[b] components of responder endpoint	27	19	8% (2%, 15%)
CSBM responder[c]	34	29	
Abdominal pain responder[d]	44	33	

[a]CI: Confidence Interval; [b]a responder for these trials was defined as a patient who met both the abdominal pain and CSBM weekly responder criteria for at least 6 of the first 12 weeks; [c]a CSBM responder was defined as a patient who achieved an increase in at least 1 CSBM per week, from baseline, for a least 6 of at least 12 weeks; [d]an abdominal pain responder was defined as a patient who met the criteria of at least 30% reduction from baseline in weekly average of the worst daily abdominal pain, for at least 6 of the first 12 weeks.

In both trails the proportion of responders for 9 out of the first 12 weeks, including at least 3 of the last 4 weeks, was greater in Tenapanor treated patients compared to placebo-treated patients.[26] There was considerable improvement noted in both trials by week with reference to CSBMs and the effect maintained till end of treatment.[26]

In trial 2 patients were re randomised and on average of 4 weeks observation CSBM and abdominal pain severity worsened.[26] Patients continued on Tenapanor maintained their response to therapy and patients re randomised to Tenapanor had average increase in CSBM frequency and decreased abdominal pain.[26]

APPROVAL

Based on positive results from the phase III T3MPO trial program, Tenapanor has shown positive results for IBS-C management and received US FDA approval in September 2019 and soon will add to the existing modalities for management of IBS-C.[26]

CONCLUSION

With limited options for management of IBS-C, there was a definitive need for exploration of modalities for managing patients stressed due to residual symptoms, thereby hampering their social and mental productivity. Tenapanor, a novel molecule has shown promising results and would be of extreme morale boosting to the patients and clinician managing IBS-C with improved efficacy with least side effects and residual symptoms.

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