Telotristat ethyl: a novel agent for the therapy of carcinoid syndrome diarrhea

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Carcinoid syndrome (CS), characterized by diarrhea and flushing, is present in 20% of patients with neuroendocrine tumors at diagnosis and becomes more frequent with progression. The diarrhea of CS is caused mainly by tumoral secretion of serotonin. It may not be fully controlled by somatostatin analogs, the currently indicated drugs for symptomatic relief. Telotristat ethyl is a novel inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in serotonin biosynthesis. Administration of the drug decreases diarrhea in patients with CS. Telotristat ethyl was approved in February 2017 (USA) and September 2017 (European Commission) for the treatment of CS diarrhea in adults inadequately controlled by somatostatin analog alone. This drug is expected to greatly improve the health and quality of life of patients with CS diarrhea.

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Neuroendocrine cells are widely distributed throughout the body and secrete regulatory peptides and biogenic amines, in response to neural, chemical and other stimuli. Neuroendocrine tumors (NETs) can arise from these cells throughout the intestine (particularly ileum), lung, pancreas and elsewhere. The incidence of NETs is low (~7/100,000 per year) [1], although the estimated prevalence (171,321 cases in the USA in 2014) exceeds that of esophageal cancers and gastric and pancreatic adenocarcinomas combined [2], because of their relatively slower growth and longer overall survival. The incidence has increased over sixfold in the last 40 years. It is unclear how much of the apparent increase in incidence is due to improved diagnostic modalities [1]. These tumors are generally slow growing, although the growth rate is variable and is related to tumor pathology and grade, site of origin and other features. There has been a clear improvement in prognosis, partially attributed to newer therapies, and this improvement is expected to continue based on recently approved and upcoming therapies [1].

The clinical presentation of NETs may be: incidental (e.g., on imaging for other issues or on routine colonoscopy); associated with local symptoms of the tumor (e.g., abdominal pain, chest pain, cough); associated with systemic symptoms related to hormonal secretions of these tumors (e.g., the carcinoid syndrome [CS] of flushing, diarrhea, wheeze or right heart valve disease), or other specific hormone-related symptoms (e.g., insulin-induced hypoglycemia from pancreatic NET). About 20% of patients with NET present with features of CS [3]. However, the prevalence of CS increases with tumor progression (e.g., 56% of jejuno-ileal NET patients with distant disease have CS) [3].

Therapeutic options for NETs and CS include aggressive surgical resection and debulking, even with widespread metastatic disease [4]. Somatostatin analogs (SSAs; Sandostatin LAR[®] or Somatulline[®]) are first-line agents for inhibition of low-grade tumor progression [5,6] and for CS [7,8]. The novel SSA, pasireotide, was initially shown to improve CS in patients who were refractory to Sandostatin LAR [9]. However, a subsequent Phase III trial failed to confirm superiority over Sandostatin LAR for CS [10] and pasireotide is not yet approved for NET therapy. Additionally, IFN- α 2B is registered in Europe for treatment of NETs with CS, but is not approved in the USA for this indication. It is rarely prescribed by US NET experts [11], though it is used in Europe as an add-on to SSA in refractory CS, if SSAs are not appropriate (somatostatin receptor negative tumors), or are not tolerated [12,13]. Various other agents have been used off-label for therapy of CS, including histamine receptor 1

and 2 antagonists [14,15], clonidine [16], ondansetron [17], verapamil [18], glucocorticoids [19] and even aspirin [20], perhaps attesting to the diverse hormonal pathophysiology underlying the features of CS.

Newer tumor-directed inhibitors of mechanistic target of rapamycin and receptor tyrosine kinase inhibitors (Affinitor® and Sutent®) have been approved recently for progressive pancreatic NET (Affinitor and Sutent) [21,22] and nonfunctional gastrointestinal (GI) and lung NETs (Affinitor) [23,24]. Other chemotherapy agents (e.g., capecitabine and temozolomide) have been reported to have clinical benefit in off-label use for progressive, well-differentiated NET lesions [25], while platinum-based regimens are thought to be more effective in high-grade tumors with K-i67 proliferation index greater than 55% [26]. The role of cytotoxic regimens in the treatment of progressive nonpancreatic NETs is less well established than in pancreatic NETs [27,28]. Liver-directed therapies (bland, chemo- and radio-embolization) are used for liver metastatic disease [29]. Peptide radioreceptor therapy with lutetium-177 or yttrium-90-labeled SSAs has been used extensively outside of the USA for decades and Lu-177DOTATATE is anticipated to be approved worldwide by 2018 on the basis of the successful Phase III LU-TATHERA trial [30]. While all of these therapies, directed primarily at control of NET tumor bulk or proliferation, may have an effect on the disease symptoms [31], only SSAs were available for disease symptom control until the approval of telotristat ethyl in 2017. Unfortunately, up to 30% of patients with CS continue to have debilitating symptoms despite initiation of SSA [32] and more lose responsiveness to SSA therapy over time [33], by a process of tachyphylaxis or by tumor growth, despite use of an SSA at indicated doses.

Diarrhea can be associated with severe impact on quality of life [34] as it may be associated with severe urgency to defecate, nocturnal diarrhea and fecal incontinence. It is also associated with significant increases in health complications and healthcare costs, and is associated with a decrease in overall survival [3,35]. While NETs can secrete multiple peptide and nonpeptide hormones, many of which can have motility effects on the GI tract, the effect of serotonin appears to be the predominant cause of diarrhea in the majority of NETs. Serotonin secretion is particularly prominent with tumors originating in the midgut but can also be seen in foregut (pancreatic and lung), though rarely in hindgut tumors. In some pancreatic and duodenal NETs, diarrhea may be caused by gastrin, vasoactive intestinal polypeptide or glucagon.

Serotonin has complex actions on the GI tract that are mediated by multiple serotonin receptors. Effects include alteration of bowel motility, mediated via activation of vagal nerve and actions to inhibit water absorption and increase electrolyte secretion [36]. SSAs reduce the secretion of serotonin and other NET hormones via its action mediated by the G-protein-coupled somatostatin 2 receptor and may also have a direct effect on the small intestinal mucosa to inhibit mucosal ion secretion. However, SSAs may not normalize serotonin secretion [33] or their effect may be lost over time [32] and thus patients may have persistent or recurrent diarrhea despite the use of high-dose SSA therapy.

Prior studies confirmed the value of inhibiting serotonin synthesis to decrease diarrhea in individuals with CS [37]. Engelman *et al.* reported that use of the tryptophan hydroxylase (TPH) inhibitor parachlorophenylalanine dose-dependently decreased 24-h urinary 5-hydroxyindole acetic acid (u5-HIAA) by up to 88% [37]. This was associated with a consistent improvement in diarrhea and a variable effect on flushing; however, the treatment was associated with unacceptable side effects (mainly psychiatric). The psychiatric side effects were thought to relate to a central action of parachlorophenylalanine to decrease brain serotonin, since parachlorophenylalanine crosses the blood–brain barrier.

Understanding the basis of serotonin synthesis and enzyme-specific effects has led to the development of a specific TPH inhibitor, telotristat ethyl, which is rapidly metabolized to the active molecule, telotristat. Serotonin is formed from tryptophan under the rate-limiting control of TPH, followed by the action of aromatic amino acid decarboxylase (Figure 1). TPH is encoded by two genes with 90% homology in the catalytic domains – TPH1 is expressed in serotonin-producing enterochromaffin cells of the GI tract and in the pineal gland; TPH2 is expressed in the hypothalamus and in the myenteric plexus. Animal data from mice with selective *TPH1* or *TPH2* gene knockouts confirm that TPH1 knockout mice have decreased peripheral serotonin but normal CNS serotonin [38]. *In vivo*, telotristat acts as a TPH1 inhibitor because, like serotonin, it does not cross the blood–brain barrier. The differential access of parachlorophenylalanine and telotristat across the blood–brain barrier may relate to the greater molecular weight of telotristat (547 vs 200) [38]. Consistent with the *in vivo* selectivity for TPH1, Margolis *et al.* found that oral telotristat etiprate, the hippurate salt of telotristat ethyl, depletes jejunal serotonin by 95% by 4 days, with no effect on brain or myenteric plexus serotonin in mice [39]. Additionally, analysis of tissue distribution of carbon-14 (C^{14})-labeled telotristat etiprate revealed no measurable radioactivity in the rat brain [40].

Figure 1. Tryptophan metabolism pathway noting tryptophan hydroxylase, the target enzyme of telotristat ethyl.

5HIAA: 5-Hydroxyindoleacetic acid; AAAD: Aromatic amino acid decarboxylase; AD: Aldehyde dehydrogenase; MAO: Monoamine oxidase.

Overview of the market

The initial use of SSA therapy successfully controls diarrhea in over 60% of patients with NET-related diarrhea [41]; however, the proportion that is controlled by SSA decreases over time, related possibly to tumor growth or somatostatin receptor downregulation [42]. Additionally, it is important to recognize that persistent diarrhea in patients with NETs on optimal SSA therapy may have complex causation. The mechanism of diarrhea in these patients might include persistent hormonal secretion from NETs, postoperative factors related to partial bowel resection, biliary diarrhea related to cholecystectomy (which is frequently performed with initial bowel resection for NET), effects of small bowel obstruction related to resections and the desmoplastic reactions that are characteristic of these tumors, small bowel bacterial overgrowth and side effects of SSAs that decrease pancreas enzyme production. Telotristat ethyl is only expected to be functional with one of these mechanisms, that is, serotonin secretion from residual/metastatic NETs.

Telotristat ethyl is the first TPH inhibitor to market. At present, there are no other agents of this class in clinical trials listed at clinicaltrials.gov site. There are other selective TPH1 inhibitors being studied although clinical data are not yet available for these [43]. Other agents have been used off-label for control of symptoms of CS, including diarrhea and flushing. Some of their effects may be mediated by their serotonin receptor antagonism, (e.g., ondansetron, a 5-HT₃ receptor inhibitor). Other agents may have antidiarrheal mechanisms that are unrelated to serotonin (e.g., loperamide, an opioid receptor agonist). Therapy directed at the tumor also has effects on diarrhea related to secretions of the tumor [31].

Introduction to the compound

Telotristat is available as 250-mg tablets of telotristat ethyl, delivered as a hippurate salt (telotristat etiprate), which is rapidly hydrolyzed by carboxylesterases to the active metabolite, telotristat ((S)-2-amino-3-(4-(2-amino-6-((R)-1-(4-chloro-2-(3-methyl-1H-pyrazol-1-yl)phenyl)2,2,2-trifluoroethoxy)pyrimidin-4-yl)phenyl)propanoic acid). Solubility of telotristat etiprate is pH dependent (>71 mg/ml at pH 1, negligible at pH ≥5 at room temperature) [44].

Pharmacodynamics

Three published studies are available for analysis of dose response data. These include studies with the administration of telotristat ethyl 150–500 mg three-times daily (t.i.d.) [45,46] or 250 and 500 mg t.i.d. [47]. Details of the studies are summarized in Table 1. The approved dosage of telotristat ethyl is 250 mg t.i.d. in patients with carcinoid-related diarrhea, which is inadequately controlled on SSA therapy.

Effects on stool frequency

Dose–response studies in humans, using between 150 and 500 mg t.i.d. in a Phase II trial, reveal a significant 22% decline in stool frequency by 2 weeks at 150 mg t.i.d. ($p < 0.001$) [46]. There was a further decline in stool

Table 1. Summary of clinical studies of telotristat ethyl.

Study	Study design	Efficacy findings	Safety findings
NCT00853047 [45]	Phase II, double-blind, placebo-controlled, dose-escalation, multicenter trial in patients with NETs and ≥ 4 BM daily despite stable SSA, n = 23. Placebo, 150, 250, 350, 500 mg t.i.d. for 28 days	<ul style="list-style-type: none"> – 28% clinical response in diarrhea (0% in placebo) – 56% decline in u5-HIAA (0% in placebo) – 56% adequate relief of diarrhea (0% in placebo) 	<ul style="list-style-type: none"> – All doses well tolerated – SAE in 2/18 (hospitalization for vomiting with history of same and recurrent skin cancer) – Most AEs transient, mild, GI-related (nausea, abdominal pain, vomiting) – Transient, $\leq$twofold transaminases elevation in 17% on TE and 40% on placebo
NCT01104415 [46]	Phase II, open-label, dose-escalation, multicenter trial in patients with NETs and ≥ 4 BM daily despite stable SSA, n = 15. Dose escalations 2 weekly from 150–250, 350 and 500 mg t.i.d., with the highest tolerated dose up to 12 weeks	<ul style="list-style-type: none"> – 80% escalated to 500 mg t.i.d. – 100% had some decrease in BM frequency – 43% had $\geq 50\%$ decline in BM frequency – Mean BM/day: 5.9 (baseline), 2.6 (12 weeks) – Improved stool consistency from loose to soft – 74% decline in u5-HIAA by 12 weeks – Flushing episodes decreased by 27% – Adequate relief of diarrhea in 75% 	<ul style="list-style-type: none"> – No drug-related SAE – Most frequent AEs were GI (pain, nausea, vomiting) – AEs were usually early and resolved on continued TE
TELESTAR NCT01677910 [47]	Phase III, double-blind, multicenter, placebo-controlled trial in patients with NET and ≥ 4 BM daily despite stable SSA, n = 135. 250 or 500 mg t.i.d. for 12 weeks. Primary end point: change in BM frequency	<ul style="list-style-type: none"> – Mean decrease in daily BM frequency: -0.9 (placebo), -1.7 (250 mg), -2.1 (500 mg) – BM frequency reduction of $\geq 30\%$ from baseline for $\geq 50\%$ of double-blind period: 20% (placebo), 44% (250 mg), 42% (500 mg) – Decrease in u5-HIAA of $\geq 30\%$ at 12 weeks: 10% (placebo), 78% (250 mg), 87% (500 mg) – No change in flushing or abdominal pain – Some improvement in stool consistency, urgency and use of short-acting octreotide – Improved diarrhea subscale of EORTC QLQ-C30 	<ul style="list-style-type: none"> – Mild nausea and asymptomatic increases in GGT in some patients on 250 mg t.i.d. – Increased nausea, abdominal pain, vomiting and constipation in patients on 500 mg t.i.d.

AE: Adverse event; BM: Bowel movement; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GGT: Gamma glutamyl transferase; GI: Gastrointestinal; NETs: Neuroendocrine tumors; SAE: Serious adverse event; SSA: Somatostatin analog (octreotide or lanreotide); TE: Telotristat ethyl; t.i.d.: Three-times daily; u5-HIAA: 24-h urinary 5-hydroxyindole acetic acid.

frequency to 44% at 500 mg t.i.d. by 12 weeks [46]. In the Phase III TELESTAR trial, the effects of 250 and 500 mg t.i.d. did not significantly differ (44 and 42% responders, defined as those with a decrease of $\geq 30\%$ in stool frequency for $\geq 50\%$ of the 12-week double-blind trial period) [47]. Mean reduction in bowel movement (BM) frequency was 0.9, 1.7 and 2.1 from a baseline of 5.2, 6.1 and 5.8 movements per day in the placebo, 250 and 500 mg t.i.d. groups, respectively. There were some additional benefits in stool consistency and urgency in the 500 mg t.i.d. group, but this was balanced by increased side effects (mainly nausea and abdominal pain). There were also cases of severe constipation with 500 mg t.i.d.; 2/45 patients treated with telotristat ethyl 500 mg t.i.d. for 12 weeks reported constipation and one required hospitalization. During the 36-week extension period, ten of 115 patients on 500 mg t.i.d. reported constipation: one developed intestinal perforation, and one developed obstruction (although these events are relatively common in patients with disseminated NETs). There was no overall difference in GI side effects between placebo and telotristat ethyl 250 mg t.i.d. While these side effects occurred with higher than approved doses of telotristat ethyl, careful monitoring for constipation and abdominal pain is recommended, with drug discontinuation if these symptoms develop or worsen.

Effects on serotonin production

Urinary 5-HIAA decreased by 25–45% by 2 weeks in Phase I studies of healthy subjects reported by the manufacturer [40]. The u5-HIAA was significantly decreased by 3–4 weeks ($\sim 28\%$ decrease at dose of 250 mg t.i.d.) in a Phase II dose escalation study [46]. By 12 weeks of study (at twice the recommended dosage, 500 mg t.i.d., in most patients), the u5-HIAA was decreased by 74% [46]. No biochemical response (defined as $\geq 50\%$ decline of u5-HIAA, or normalization if initially elevated) was observed in a placebo group versus 56% in treatment groups between 150 and 500 mg t.i.d. [47].

Pharmacokinetics

Pharmacokinetic (PK) data from unpublished Phase I studies are described in the 'prescribing information' [44] and in a review manuscript [40]. Peak plasma concentrations of telotristat occur in 1–3 h of taking telotristat etiprate orally. There was no significant plasma accumulation when taken three-times daily. Telotristat is 99% plasma protein bound and has an apparent half-life of 5 h. Over 90% of a dose of C¹⁴-labeled telotristat ethyl is recovered in feces with 0.4% in urine.

Age and sex do not affect the PK of telotristat. Clinical trials of telotristat ethyl excluded pregnant or lactating females and children younger than 18 years and thus there are no data pertaining to these groups. Neither were the PK influenced by renal dysfunction (down to eGFR 20 ml/min) or mild hepatic dysfunction (total bilirubin ≤ 1.5 -times upper limit of normal). The effects of dialysis dependence or more severe liver dysfunction are unknown.

Data on drug interactions *in vivo* are limited. Importantly, concurrent administration of short-acting octreotide with telotristat ethyl significantly decreased the systemic exposure of telotristat. Coadministration of octreotide 200 μ g subcutaneously and telotristat ethyl 500 mg decreased $C_{\max}$ and area under the plasma concentration–time curve (AUC)_{0–inf} by 79 and 68%, respectively, in healthy control subjects. It is recommended that short-acting octreotide be given at least 30 min after administration of telotristat ethyl. Other data from preclinical *in vitro* and *in vivo* studies suggest that telotristat ethyl may decrease midazolam exposure by a glucuronidation effect ($C_{\max}$ and AUC_{0–inf} of alprazolam decreased by 25 and 48%, respectively). No other drug interaction data are available; however, there is a significant effect of food to increase the $C_{\max}$ and AUC_{0–inf} of telotristat by 47 and 33%, respectively. It is recommended that telotristat ethyl be administered within 15 min before or within 1 h after a meal or snack.

Clinical efficacy

The pivotal TELESTAR study [47] included 135 adults with well-differentiated metastatic NETs, documented CS and 'refractory diarrhea' (≥ 4 BMs per day during the 3–4-week run-in period, despite being on minimum of octreotide LAR 30 mg or lanreotide 120 mg every 4 weeks). Patients were randomized to placebo, or telotristat ethyl at 250 or 500 mg t.i.d. Patients with causes of diarrhea other than CS were excluded, as were those with severe (> 12 BMs per day) diarrhea. Use of additional subcutaneous octreotide was recorded. Use of stable doses of other prescription or nonprescription antidiarrheal medication was acceptable during the trial, although changes in these drugs were not tracked. The primary end point was change in BM frequency, averaged over 12 weeks. Secondary end points included change in u5-HIAA, flushing, abdominal pain, quality of life, use of subcutaneous octreotide, stool consistency and urgency to defecate. Responders were defined as patients experiencing $\geq 30\%$ reduction in BM frequency for $\geq 50\%$ of the 12-week double-blind period. Baseline BM frequency was 5.2–6.1 stools per day. Mean baseline u5-HIAA was over fivefold elevated overall, although levels were normal in almost a third of patients with available data.

A response in the primary end point was seen in 43% of the telotristat ethyl groups, with little difference between the two doses, whereas 20% of patients on placebo responded. The mean reduction in daily BM frequency from baseline to week 12 was 0.9 on placebo, 1.7 on telotristat ethyl 250 mg t.i.d. and 2.1 on 500 mg t.i.d. Mean change in u5-HIAA (mg/24 h) from baseline to week 12 was +11.5 on placebo, -40.1 on 250 mg t.i.d. and -57.7 on 500 mg t.i.d. The study was not powered for assessment of changes in flushing or abdominal pain, with only 38% of patients having ≥ 2 flushes per day or having severe abdominal pain. No statistically significant changes were noted in these parameters. Urgency to defecate was improved ($p = 0.006$) and stool consistency trended toward improvement ($p = 0.052$) on telotristat ethyl 500 mg t.i.d.

Telotristat ethyl appeared to be generally well tolerated with excellent tablet use compliance ($\geq 86\%$) and completion of the double-blind phase ($\geq 83\%$), with no major differences between placebo or telotristat ethyl groups in these parameters. Study discontinuation due to treatment emergent adverse effect was not increased in the active drug groups (7% in the telotristat ethyl groups and 13% in placebo group). The most-frequent side effects described were related to the GI system. Nausea and abdominal pain were reported more frequently in the telotristat ethyl 500 mg t.i.d. group (31 and 22%, respectively), with no increase in the 250 mg t.i.d. group over placebo. Increased gamma glutamyl transferase or alanine aminotransferase was seen in 7–9% of patients taking telotristat ethyl 500 mg t.i.d. and gamma glutamyl transferase was elevated in 9% of patients taking 250 mg t.i.d. (no increases noted in placebo).

Importantly, in view of the clear psychiatric disturbances that were associated with the use of older, blood–brain barrier permeable, TPH inhibitors [37], there was no difference between placebo and telotristat ethyl 250 mg t.i.d.

Figure 2. Role of telotristat ethyl in management of carcinoid syndrome diarrhea.

CS: Carcinoid syndrome; SSA: Somatostatin analog; t.i.d.: Three-times daily.

Outline based on recommendations from [11].

groups in depression-related symptoms (7% in each group), or confusion (0 in each group). However, 16% of patients taking telotristat ethyl 500 mg t.i.d. had depression-related symptoms and 7% reported confusion. Fatigue was noted in 16% of patients on telotristat ethyl 500 mg t.i.d. with no increase in 250 mg t.i.d. over placebo (9%).

Based on these and other data documenting a significant improvement in the debilitating symptom of carcinoid diarrhea, refractory to best available therapy and a low side effect profile when given at 250 mg t.i.d., telotristat ethyl was approved by the US FDA in February 2017 and by the European Commission in September 2017.

Current practice guidelines

Since the approval of telotristat ethyl, clinical practice guidelines have been modified. The 2017 US National Comprehensive Cancer Network Clinical Practice Guidelines for NETs now recommend use of telotristat ethyl, in combination with octreotide or lanreotide, for persistent carcinoid diarrhea (category 2A) and state that it may be continued for persistent diarrhea with any other subsequent treatment options as the disease progresses. Recent consensus guidelines from the North American Neuroendocrine Tumor Society (NANETS) support the use of telotristat ethyl for patients with stable disease but suboptimal control of diarrhea due to CS [11]. A suggested approach to the use of telotristat ethyl in carcinoid-related diarrhea, based on the expert panel discussion, is noted in Figure 2. The NANETS panel also suggested that telotristat ethyl could be considered in patients with significantly elevated circulating serotonin and evidence of carcinoid heart valvular damage, but did not recommend its initiation purely to lower serotonin levels in patients lacking evidence of valvular damage. These suggestions go beyond the current indications, and the role of telotristat ethyl in CS features beyond diarrhea requires further evaluation.

Discussion

Telotristat ethyl represents a unique new approach to decreasing symptoms related to serotonin secretion in patients with NETs, by a specific mechanism of inhibiting the rate-limiting step for serotonin biosynthesis in the intestines. Results of Phase II and III trials indicate that the medication was well tolerated and resulted in ‘adequate relief’ of diarrhea in 56–75% of patients.

Given the important role of serotonin in other manifestations of CS (e.g., fibrosis affecting heart valves and intra-abdominal viscera [48,49]), it is possible that telotristat ethyl will have other benefits in patients with NETs, beyond its proven role in uncontrolled diarrhea. These potential indications will require specific clinical research assessment in future. The role of telotristat ethyl in other symptoms of CS (e.g., flushing) and in carcinoid crisis also deserves further study. In both flushing and carcinoid crisis, serotonin is just one of the circulating hormones which may contribute to these features [50]. The available studies of telotristat ethyl were not powered to detect changes in flushing though there was a statistically significant improvement in flushing in a Phase II trial [46] and a statistically nonsignificant, dose-dependent, trend to improved flushing in a Phase III trial [47].

Besides the pathophysiological roles of serotonin in patients with NETs, it is evident from preclinical studies, including studies of the TPH1 knockout mouse model, that serotonin may play a role in other pathology as diverse as Type 2 diabetes [51], obesity [52], steatohepatitis [52], hepatic fibrosis [48], osteoporosis [51], irritable bowel syndrome [36] and inflammatory bowel disease [39,53]. However, intestinal serotonin may also have important beneficial effects. Thus, local pancreatic islet serotonin appears to be important in the β -cell proliferation that occurs to facilitate pregnancy [54]. Additionally, liver regeneration after resection is decreased in mice deficient in TPH1 enzyme [55]. These findings raise the possibility of additional indications for telotristat ethyl, beyond CS,

but also suggest the high degree of complexity of the intestinal serotonergic system and underscore the need for careful preclinical and clinical research to explore additional potential indications for the drug.

Phase II and III studies, published up to now, have shown an excellent safety profile over the 12–20-week durations of these studies. Given the complex and broad effects of serotonin, continued surveillance will be required, as with every new drug, to ensure longer-term safety. The apparent increases in psychiatric and GI side effects on higher doses of telotristat ethyl do raise concern over whether additional duration of exposure at the approved dose may have similar effects. Data from open-label extension phases of prior trials should be available soon which may help to clarify this issue.

Conclusion

The use of telotristat ethyl, in addition to SSA, can significantly improve the quality of life of patients suffering from SSA-resistant diarrhea related to CS. Therapeutic guidelines have been modified since its widespread approval, to incorporate its use in these patients. Available studies demonstrate a low side effect profile, mainly related to the gastrointestinal system. Given the broad range of serotonin effects, both in patients with NETs and also in other human pathophysiology, there may be additional indications for telotristat ethyl in future (e.g., inhibition of cardiac valve dysfunction in CS) but careful analysis of long term safety profiles of this entirely novel agent will be extremely important.

Executive summary

Telotristat ethyl pharmacokinetic properties

- Telotristat ethyl is rapidly absorbed and metabolized to the active form, telotristat, which has an apparent half-life of 5 h. There is no significant effect of mild-to-moderate renal or hepatic dysfunction on the drug kinetics. Coadministration of telotristat ethyl with food increases systemic exposure, whereas octreotide coadministration decreases this parameter.

Phase II efficacy & safety evidence for telotristat ethyl

- Two studies with dosages ranging from 150–500 mg three-times daily (t.i.d.) for 4–12 weeks revealed that: 28% of patients had $\geq 30\%$ decline in bowel movement (BM) frequency for ≥ 2 of 4 weeks and 56% had $\geq 50\%$ decline or normalization of 24-h urinary 5-hydroxyindole acetic acid (u5-HIAA) by 4 weeks, with no responders in the placebo group; and 86% of subjects had $\geq 30\%$ decline in BM frequency and 58% had $\geq 50\%$ decline in u5-HIAA by 12 weeks (mostly at 500 mg t.i.d.). Telotristat ethyl was well tolerated in both studies with some mild and transient nausea, vomiting and abdominal pain.

Phase III evidence for telotristat ethyl in carcinoid-related diarrhea

- There was a reduction of BM frequency of $\geq 30\%$ from baseline for $\geq 50\%$ of the double-blind period in 20, 44 and 42% of patients taking placebo, telotristat ethyl 250 mg and telotristat ethyl 500 mg t.i.d. ($n = 45$ per group, 12-week double-blind treatment period). Urinary 5-HIAA was reduced by $\geq 30\%$ at 12 weeks in 10, 78 and 87% in the same three groups. Mild nausea and asymptomatic increases in gamma glutamyl transferase occurred in some patients on telotristat ethyl 250 mg t.i.d., with increased nausea, abdominal pain, vomiting and constipation in patients on 500 mg t.i.d.

Discussion

- This novel agent targets the elevated serotonin that is a major cause of diarrhea in carcinoid syndrome (CS). Elevated serotonin may also cause some of the other manifestations of CS and possibly other noncarcinoid-related conditions. The role of serotonin reduction by telotristat ethyl in other carcinoid and noncarcinoid-related conditions requires further study.

Conclusion

- Telotristat ethyl is an important new therapy for common symptoms affecting patients with neuroendocrine tumors. It is approved in the USA and Europe for the treatment of CS diarrhea in combination with somatostatin analog therapy, in adults inadequately controlled by somatostatin analog therapy.

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Regulatory affairs

Telotristat ethyl is FDA-approved in the USA and registered by the European Commission for treatment of adults with carcinoid-related diarrhea, in combination with somatostatin analog, where that diarrhea is not adequately controlled by somatostatin analog alone. Approval for the medication is being sought by Ipsen, Inc and Lexicon Pharmaceuticals, Inc, in other markets.

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Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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