Telotristat ethyl

**Approved indication:** carcinoid syndrome diarrhoea

Xermelo (Ipsen)

250 mg film-coated tablets

Telotristat ethyl is approved for carcinoid syndrome diarrhoea. This is a rare condition which occurs in a minority of people with neuroendocrine tumours. These tumours can produce excess amounts of serotonin which causes severe diarrhoea, flushing, bronchoconstriction and cardiac valvular fibrosis. Serotonin elevations can be tracked by measuring the urinary metabolite 5-hydroxyindoleacetic acid.

Currently, these patients are treated with a somatostatin analogue (e.g. octreotide) which binds to somatostatin receptors on tumour cells and inhibits the release of serotonin. When the somatostatin analogue does not adequately control symptoms, telotristat ethyl can be added to therapy. It works by inhibiting an enzyme required for serotonin synthesis called tryptophan hydroxylase.

Telotristat ethyl is a pro-drug. After oral administration, it is hydrolysed to the active metabolite telotristat. Its terminal half-life is around 11 hours and most of the dose is eliminated in the faeces.

The recommended daily dose of this drug is 250 mg three times daily, taken with food to increase its absorption. Telotristat is not recommended in severe renal or hepatic impairment as there are limited clinical data.

The approval of telotristat is based on a study of 135 patients with carcinoid syndrome (TELESTAR).1 They were experiencing at least four bowel movements a day despite receiving somatostatin analogue therapy for three months or more. The participants were randomised to receive telotristat (250 or 500 mg three times a day) or placebo on top of their somatostatin analogue therapy. After 12 weeks of treatment, daily bowel movements had reduced by significantly more with telotristat (1.7 fewer with 250 mg and 2.1 fewer with 500 mg) compared to placebo (0.9 fewer). A response to treatment was defined as at least a 30% reduction in bowel movements from baseline. Based on this, 44% and 42% of people who received telotristat 250 mg and 500 mg were classified as responders versus 20% who received placebo. There were no statistically significant differences in symptoms such as flushing and abdominal pain between the groups.1

In a supporting placebo-controlled study with a similar design (TELECAST), telotristat was assessed in 76 patients who were having fewer than four bowel movements a day. Most of them were receiving somatostatin analogue therapy. The end point was the change in urinary hydroxyindoleacetic acid, a marker of serotonin levels. After 12 weeks, this had gone up by 98% in the placebo group and down by 33% and 77% in the telotristat 250 mg and 500 mg groups.2

The most common adverse effects with the recommended telotristat dose of 250 mg included nausea, abdominal pain, elevated gamma-glutamyl transferase and fatigue. Constipation also occurs with telotristat. Most of these events were more common with the 500 mg telotristat dose. In an open-label 36-week extension of the TELECAST trial, depression was also more common with telotristat 500 mg and patients should be warned of this risk.2

In terms of drug interactions, concomitant use of short-acting octreotide decreased exposure to telotristat and its pro-drug. If short-acting octreotide is used, it should be taken at least 30 minutes after the telotristat dose. Reduced telotristat exposure has not been observed with long-acting somatostatin analogue therapy. Telotristat may decrease concentrations of cytochrome P450 (CYP) 2B6 substrates (e.g. sertraline, valproate) and CYP3A4 substrates (e.g. atorvastatin, midazolam, valproate).

Adding telotristat to somatostatin analogue therapy for 12 weeks reduced the number of bowel movements per day in patients with carcinoid syndrome. However, treatment is associated with abdominal pain, constipation and altered liver function.

**REFERENCES**


The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.