

▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

XERMELO (telotristat ethyl (as telotristat etiprate)) film-coated tablets

1 NAME OF THE MEDICINE

telotristat ethyl (as telotristat etiprate)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each XERMELO tablet contains 250 mg of telotristat ethyl (free base) equivalent to 327.9 mg telotristat etiprate as the active ingredient.

Each tablet contains 167.91 mg of lactose.

For the full list of excipients, see section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

XERMELO tablets are white to off-white film-coated oval tablets with 'T-E' debossed on one side and '250' debossed on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

XERMELO is indicated for the treatment of carcinoid syndrome diarrhoea in combination with somatostatin analog (SSA) therapy in adults inadequately controlled by SSA therapy.

4.2 DOSE AND METHOD OF ADMINISTRATION

The recommended dose is 250 mg three times daily.

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. It is recommended to reassess the benefit of continued therapy in a patient not responding within this time period.

Based on the high inter-subject variability observed, accumulation in a subset of patients with carcinoid syndrome cannot be excluded. Therefore, intake of higher doses is not recommended (see section 5.2 PHARMACOKINETIC PROPERTIES).

Missed doses

In the event of a missed dose, patients should take their subsequent dose at the next scheduled time point. Patients should not take a double dose to make up for a missed dose.

Special populations

Elderly patients (65 years of age and above)

No dosage adjustments are required in elderly patients (see section 5.2 PHARMACOKINETIC PROPERTIES)

Patients with renal impairment

No specific study has been performed in patients with mild and moderate renal impairment. Patients with mild or moderate renal impairment should be treated with caution.

No specific dose recommendations are available for patients with mild and moderate renal impairment (see section 5.2 PHARMACOKINETIC PROPERTIES).

The use of telotristat is not recommended in patients with severe renal impairment and in patients with end-stage renal disease requiring dialysis (see section 5.2 PHARMACOKINETIC PROPERTIES).

Patients with hepatic impairment

In patients with mild hepatic impairment (Child Pugh score A), it may be necessary to reduce the dose to 250 mg twice daily according to tolerability.

In patients with moderate hepatic impairment (Child Pugh score B), it may be necessary to reduce the dose to 250 mg once daily according to tolerability.

The use of telotristat is not recommended in patients with severe hepatic impairment (Child Pugh score C) as no data are available (see section 5.2 PHARMACOKINETIC PROPERTIES)

Paediatric population

There is no relevant use of telotristat in the paediatric population in the indication of carcinoid syndrome.

Method of administration

Oral use

XERMELO should be taken with food (see section 5.2 PHARMACOKINETIC PROPERTIES).

4.3 CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients (see section 6.1 LIST OF EXCIPIENTS).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hepatic enzymes elevations

Elevations in hepatic enzymes were observed in clinical studies (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)). Laboratory monitoring of hepatic enzymes prior to and during telotristat therapy is recommended as clinically indicated.

In patients with hepatic impairment, continuous monitoring for adverse events and worsening of liver function is recommended.

Patients who develop symptoms suggestive of hepatic dysfunction should have liver enzymes tested and telotristat should be discontinued if liver injury is suspected. Therapy with telotristat should not be resumed unless the liver injury can be explained by another cause.

Constipation

Telotristat reduces bowel movement (BM) frequency. Constipation was reported in patients using a higher dose (500 mg). Patients should be monitored for signs and symptoms of constipation. If constipation develops, the use of telotristat and other concomitant therapies affecting bowel motility should be re-evaluated.

Depressive disorders

Depression, depressed mood and decreased interest have been reported in clinical trials in some patients treated with telotristat or placebo. A causal relationship between depressive disorders and telotristat has not been established. Patients should be advised to report any symptoms of depression, depressed mood and decreased interest to their physicians.

Use in hepatic impairment

See section 4.2 DOSE AND METHOD OF ADMINISTRATION.

Use in renal impairment

See section 4.2 DOSE AND METHOD OF ADMINISTRATION

Use in the elderly

No dosage adjustments are required in elderly patients (see section 5.2 PHARMACOKINETIC PROPERTIES).

Paediatric use

The safety and efficacy of telotristat in children and adolescents aged <18 years have not yet been established. No data are available.

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Effect of other medicinal products on XERMELO

Short-acting octreotide

Concomitant administration of short-acting octreotide with XERMELO significantly decreased the systemic exposure of telotristat ethyl and telotristat, the active metabolite (see section 5.2 PHARMACOKINETIC PROPERTIES). Short-acting octreotide should be administered at least 30 minutes after administration of XERMELO if treatment with short-acting octreotide is needed in combination with XERMELO.

A study examining the effect of short-acting octreotide (3 doses of 200°micrograms given 8°hours apart) on the single dose pharmacokinetics of XERMELO in normal healthy volunteers showed an 83% and 81% decrease in C_{max} and AUC of telotristat ethyl and telotristat, respectively. Reduced exposures were not observed in a 12°week double-blind, placebo-controlled, randomised, multicentre clinical trial in adult patients with carcinoid syndrome on long-acting SSA therapy.

Carboxylesterase (CES) inhibitors

Loperamide caused a <30% decrease in the formation of telotristat (active metabolite) in vitro. In phase 3 clinical trials, telotristat was routinely combined with loperamide with no evidence of safety concerns.

Effect of XERMELO on other medicinal products

CYP2B6 substrates

Telotristat induced CYP2B6 *in vitro* (see section 5.2 PHARMACOKINETIC PROPERTIES). Concomitant use of XERMELO may decrease the efficacy of medicinal products that are CYP2B6 substrates (e.g. valproic acid, bupropion, sertraline) by decreasing their systemic exposure. Monitoring for suboptimal efficacy is recommended.

In vitro telotristat (active metabolite) caused a concentration dependent increase in CYP2B6 mRNA levels (>2-fold increase and > 20% of the positive control, with a maximum observed effect similar to the positive control), suggesting possible CYP2B6 induction.

CYP3A4 substrates

Concomitant use of XERMELO may decrease the efficacy of medicinal products that are CYP3A4 substrates (e.g. midazolam, everolimus, sunitinib, simvastatin, atorvastatin, ethinyloestradiol, amlodipine, nifedipine, felodipine, verapamil, diltiazem, ciclosporin, carbamazepine, topiramate, valproic acid) by decreasing their systemic exposure (see section 5.2 PHARMACOKINETIC PROPERTIES). Monitoring for suboptimal efficacy is recommended.

Telotristat ethyl and its active metabolite were not shown to be inducers of CYP3A4 at systemically relevant concentrations, based on *in vitro* findings. The potential of telotristat ethyl as an inducer of CYP3A4 was not assessed at concentrations expectable at the intestinal level, due to its low solubility *in vitro*. *In vitro* telotristat ethyl inhibited CYP3A4, suggesting a potential interaction with CYP3A4 substrates.

In an *in vivo* clinical drug-drug interaction (DDI) study with midazolam (a sensitive CYP3A4 substrate), following administration of multiple doses of telotristat ethyl, the systemic exposure to concomitant midazolam was significantly decreased. When 3 mg midazolam was co-administered orally after 5-day treatment with telotristat ethyl 500 mg three times daily (twice the recommended dosage), the mean C_{max} , and AUC_{0-inf} for midazolam were decreased by 25%, and 48%, respectively, compared to administration of midazolam alone. The mean C_{max} , and AUC_{0-inf} for the active metabolite, 1'-hydroxymidazolam, were also decreased by 34%, and 48%, respectively.

Other CYPs

Based on *in vitro* findings, no clinically-relevant interaction is expected with other cytochromes P450.

P-glycoprotein (P-gp) and Multi-drug Resistance associated Protein 2 (MRP-2)

Telotristat ethyl and telotristat are not substrates of the transporters P-gp and MRP-2.

Telotristat ethyl is an inhibitor of P-gp (IC₅₀ 2 µM) and it may increase the absorption of co-administered drugs that are substrates of this transporter.

Telotristat ethyl inhibited MRP2-mediated transport (98% inhibition).

In a specific clinical DDI study, the C_{max} and AUC of fexofenadine (a P-gp and MRP-2 substrate) increased by 16% when a single 180 mg dose of fexofenadine was co-administered orally with a dose of telotristat ethyl 500 mg administered tid (twice the recommended dose) for 5 days. Based on the small increase observed, clinically meaningful interactions with P-gp and MRP-2 substrates are unlikely.

Breast Cancer Resistance Protein (BCRP)

In vitro telotristat ethyl inhibited BCRP (IC₅₀ = 20 µM), but its active metabolite telotristat did not show any significant inhibition of BCRP activity (IC₅₀ > 30 µM). The potential for *in vivo* drug interaction via inhibition of BCRP is considered low.

Other transporters

Based on *in vitro* findings, no clinically-relevant interaction is expected with other transporters.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No studies on the effect of telotristat on human fertility have been conducted. Telotristat had no effect on fertility in rats at oral doses up to 500 mg/kg/day of telotristat etiprate (up to 2.5 times the clinical exposure to the active metabolite based on AUC).

Use in pregnancy (Category B3)

There are no data from the use of telotristat in pregnant women. Animal studies have shown reproductive toxicity (described below). XERMELO is not recommended during pregnancy and in women of childbearing potential not using contraception.

Women of childbearing potential should be advised to use adequate contraception during treatment with telotristat.

Telotristat was not teratogenic in rats or rabbits.

Telotristat etiprate administered orally to pregnant rats during organogenesis at up to 750 mg/kg/day (6 times the clinical exposure to the active metabolite based on AUC) did not affect embryofetal development.

In rabbits, maternal toxicity and post-implantation losses were observed at ≥ 250 mg/kg/day telotristat etiprate (>10 times the clinical exposure to the active metabolite based on AUC) and reduced foetal weights at 500 mg/kg/day telotristat etiprate (21 times the clinical exposure to the active metabolite based on AUC).

Use in lactation

It is unknown whether telotristat ethyl and its metabolite are excreted in human breast milk. A risk to newborns/infants cannot be excluded. Patients should not breast-feed during telotristat treatment.

Telotristat etiprate administered to rats at 500 mg/kg/day during from gestation day 6 to lactation day 20 resulted in increased pup mortalities during postnatal days 0 to 4 (no effects at 200 mg/kg/day, exposure similar to the clinical exposure based on AUC), without effect on functional or behavioural development.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Telotristat has a minor influence on the ability to drive and use machines. Fatigue may occur following administration of telotristat (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

Summary of safety profile

The most commonly reported adverse reactions in patients treated with telotristat were abdominal pain (26%), gamma-glutamyl transferase increased (11%) and fatigue (10%). They were generally of mild or moderate intensity. The most frequently reported adverse reaction leading to discontinuation of telotristat was abdominal pain in 7.1% of patients (5/70).

Tabulated list of adverse reactions

Adverse reactions reported in a pooled safety dataset of 70 patients with carcinoid syndrome receiving telotristat ethyl 250 mg three times daily in combination with SSA therapy in placebo-controlled clinical trials are listed in Table 1. Adverse reactions are listed by MedDRA body system organ class and by frequency using the following convention: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), rare ($\geq 1/10,000$ to $< 1/1,000$), very rare ($< 1/10,000$) and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness

Table 1: Adverse Reactions reported in clinical trials

System organ class	Very common	Common
Metabolism and nutrition disorders		Decreased appetite
Nervous system disorders		Headache
Gastrointestinal disorders	Abdominal pain ^a	Abdominal distension, Constipation, Flatulence
Hepatobiliary disorders	Gamma-glutamyltransferase increased ^b	Alanine aminotransferase increased (ALT), Aspartate aminotransferase increased (AST), Blood alkaline phosphatase increased (ALP)
General disorders and administration site conditions	Fatigue	Oedema peripheral, Pyrexia

^a Abdominal pain (including upper and lower abdominal pain)

^b Gamma-glutamyl transferase increased (including preferred terms of gamma-glutamyl transferase increased, gamma-glutamyl transferase, and liver function test abnormal / hepatic enzyme increased for which gamma-glutamyl transferase was increased).

Description of selected adverse reactions

Hepatic enzymes elevations

Elevations in ALT $>3 \times$ upper limit of normal (ULN) or ALP > 2 ULN have been reported in patients receiving therapy with telotristat, most cases being reported at a higher dose (500 mg). These have not been associated with concomitant elevations in total serum bilirubin. The increases were largely reversible on dose interruption or reduction, or recovered whilst maintaining treatment at the same dose. For clinical management of elevated hepatic enzymes, see section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE.

Gastrointestinal disorders

The most frequently reported adverse event in patients receiving telotristat was abdominal pain (25.7%; 18/70) versus placebo (19.7%; 14/71). Abdominal distension was reported in 7.1% of patients (5/70) receiving telotristat ethyl 250 mg tid, versus 4.2% in the placebo group (3/71). Flatulence was seen in 5.7% of patients (4/70) and 1.4% (1/71) in the telotristat ethyl 250 mg and placebo groups, respectively. Most events were mild or moderate and did not limit study treatment.

Constipation was reported in 5.7% of patients (4/70) in the telotristat ethyl 250 mg group and in 4.2% of patients (3/71) in the placebo group. Serious constipation was observed in 3 patients treated with a higher dose (500 mg) in the overall safety population (239 patients).

4.9 OVERDOSE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

Symptoms

There is limited clinical experience with telotristat overdose in humans. Gastro-intestinal disorders including nausea, diarrhoea, abdominal pain and vomiting have been reported in healthy subjects taking a single dose of 1,500 mg in a phase 1 study.

Management of overdose

Treatment of an overdose should include general symptomatic management.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Not yet assigned

Mechanism of action

Both the prodrug (telotristat ethyl) and its active metabolite (telotristat) are inhibitors of L-tryptophan hydroxylases (TPH1 and TPH2, the rate limiting steps in serotonin biosynthesis). Serotonin plays a critical role in regulating several major physiological processes, including secretion, motility, inflammation, and sensation of the gastro-intestinal tract, and is over-

secreted in patients with carcinoid syndrome. Through inhibition of peripheral TPH1, telotristat reduces the production of serotonin, thus alleviating symptoms associated with carcinoid syndrome.

Pharmacodynamic effects

In Phase 1 studies, dosing with telotristat ethyl in healthy subjects (dose range: 100 mg once daily to 500 mg three times daily) produced statistically significant reductions from baseline in whole blood serotonin and 24-hour urinary 5-hydroxyindoleacetic acid (u5-HIAA) compared with placebo.

In patients with carcinoid syndrome, telotristat resulted in reductions in u5-HIAA as shown in Table 3 and Table 4. Statistically significant reductions in u5-HIAA were seen for telotristat ethyl 250 mg three times daily compared with placebo in both Phase 3 studies

Clinical trials

The efficacy and safety of telotristat for the treatment of carcinoid syndrome in patients with metastatic neuroendocrine tumours who were receiving SSA therapy was established in a 12-week double-blind, placebo-controlled, randomised, multicentre phase 3 trial in adult patients, which included a 36-week extension during which all patients were treated with open-label telotristat (TELESTAR Study).

A total of 135 patients in the TELESTAR Study (overall mean age of 63.6 years [range 37-88 years], 52% male, 90% white) were randomized 1:1:1 to receive treatment with placebo or XERMELLO (250 mg or 500 mg three times daily) and were evaluated for efficacy. All patients had well-differentiated metastatic neuroendocrine tumours and carcinoid syndrome. They were on SSA therapy and had ≥ 4 daily bowel movements (BM).

The study included a 12-week double-blind treatment (DBT) period, in which patients initially received placebo (n=45), or XERMELLO 250 mg (n=45) three times daily for one week, or a higher dose (telotristat ethyl 500 mg; n=45). During the study, patients were allowed to use rescue medication (short-acting SSA therapy) and anti-diarrhoeals for symptomatic relief but were required to be on stable-dose long-acting SSA therapy for the duration of the DBT period. XERMELLO was taken within 15 minutes before, or within 1 hour after food.

The primary efficacy endpoint was the reduction in the mean number of daily BM averaged over the 12-week double-blind treatment period. Secondary endpoints included changes from baseline in u5-HIAA at Week 12, daily number of flushing episodes averaged over the 12-week double-blind treatment period and abdominal pain averaged over the 12-week double-blind treatment period. Other endpoints included the proportion of patients with durable response, defined as the proportion of responders with $\geq 30\%$ reduction in daily number of BMs for $\geq 50\%$ of time over the double blind treatment period and the change from Baseline in BM frequency averaged at each study week.

The efficacy of XERMELO was demonstrated through significantly greater reductions in BM frequency averaged over 12 weeks in both doses compared with placebo ($p < 0.001$). Statistically significant differences were also seen in reductions in BM frequency at Week 12, in percentage of patients with durable response, and in reductions in u5-HIAA excretion over 24 hours at Week 12 (Table 2 and Table 3).

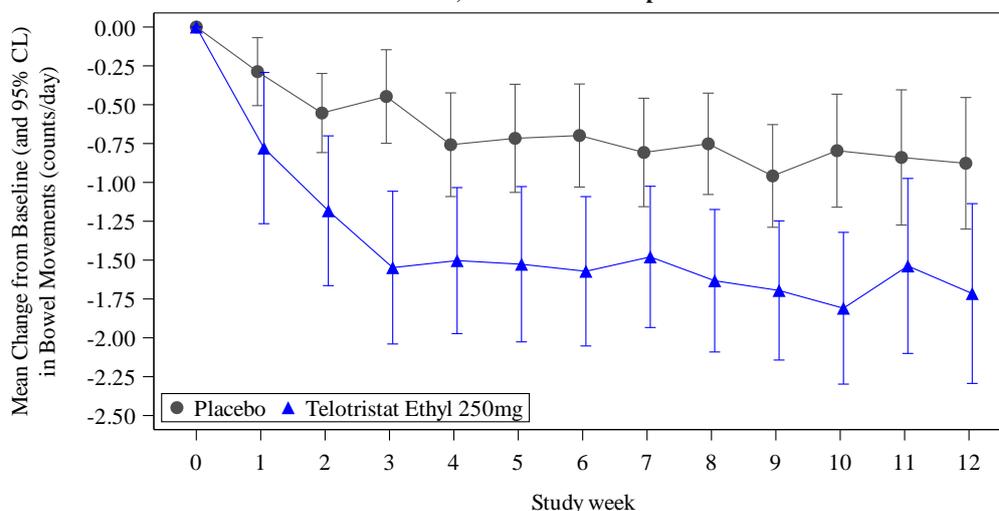
Table 2: BM response (TELESTAR Study)

	Parameter	Placebo	XERMELO 250 mg tid
BMs/day At Baseline	Number of Patients	45	45
	Baseline Mean (SD)	5.2 (1.35)	6.1 (2.07)
Primary Endpoint: Change from Baseline in BMs/day Averaged Over 12 Weeks	Number of Patients	45	45
	Change Averaged over 12 Weeks: Mean (SD)	-0.6 (0.83)	-1.4 (1.37)
	Difference in Arithmetic Means vs Placebo (95% CL)	---	-0.8 (-1.28, -0.34)
	Estimate of Treatment Difference (97.5% CL) ^a	---	-0.8 ^b (-1.26, -0.29)
Change from Baseline in BMs/day at Week 12	Number of Patients	35	36
	Change at Week 12: Mean (SD)	-0.9 (1.23)	-1.7 (1.71)
	Difference in Arithmetic Means vs Placebo (95% CL)	---	-0.8 (-1.55, -0.13)
	Estimate of Treatment Difference (95% CL) ^a	---	-0.7 ^c (-1.40, -0.05)
Percentage of Patients with Durable Response (See text for definition)	Number of Patients	45	45
	Responder, n (%)	9 (20.0)	20 (44.4)
	Odds Ratio ^d (95.0% CL)	---	3.5 ^e (1.33, 9.16)
CL=confidence limit; tid=three times a day; SD=standard deviation.			
a. Statistical tests used a blocked 2-sample Wilcoxon Rank Sum statistic (van Elteren test) stratified by the u5-HIAA stratification at randomization. CLs were based on the Hodges-Lehmann estimator of the median paired difference.			
b. $p < 0.001$			
c. $p = 0.07$			
d. Statistical test, odds ratio, and 95% CL were based on a logistic regression model with responder as the dependent variable, treatment group and u5-HIAA stratification at randomization as fixed effects, and Baseline mean number of BMs (counts/day) as a covariate.			
e. $p = 0.011$			

When the full effect of telotristat is observed (during the last 6 weeks of the DBT period) the proportion of responders with at least 30% BM reduction was 51% (23/45) in the 250 mg group versus 22% (10/45) in the placebo group (post-hoc analysis).

In the 12-week DBT period of the study, average weekly reductions in BM frequency on telotristat were observed as early as 3 weeks, with the greatest reductions occurring during the last 6 weeks of the DBT period, compared with placebo (refer to Figure 1).

Figure 1: Mean change from baseline in bowel movements by study week during the double-blind treatment period, Intent-to-Treat Population



Note: This figure plots the arithmetic mean and 95% confidence limits (CL) (based on normal approximation) of the change from Baseline in the number of daily bowel movements (counts/day) averaged at each week.

The proportions of patients reporting reductions from baseline in daily BM frequency (averaged over 12 weeks) were:

- Patients with a mean reduction of at least 1 BM per day: 66.7% (telotristat ethyl 250 mg) and 31.1% (placebo);
- Patients with a mean reduction of at least 1.5 BM per day: 46.7% (telotristat ethyl 250 mg) and 20.0% (placebo);
- Patients with a mean reduction of at least 2 BM per day: 33.3% (telotristat ethyl 250 mg) and 4.4% (placebo).

Table 3: u5-HIAA excretion at baseline and week 12 (TELESTAR Study)

Parameter		Placebo	XERMELO 250 mg tid
u5-HIAA Excretion (mg/24 hours) At Baseline	Number of Patients	44	42
	Baseline Mean ^a (SD)	81.0 (161.01)	92.6 (114.90)
Percent Change From Baseline In u5-HIAA Excretion (mg/24 hours) At Week 12	Number of Patients	28	32
	Percent Change at Week 12: Mean (SD)	14.4 (57.80)	-42.3 (41.96)
	Difference in Arithmetic Means vs Placebo (95% CL)	---	-56.7 (-82.58, -30.82)
	Estimate of Treatment Difference (95% CL) ^b	---	-53.4 ^c (-69.32, -38.79)

CL=confidence limit; tid=three times a day; SD=standard deviation.

- a. Baseline data based on all patients with data at baseline.
- b. Statistical tests used a blocked 2-sample Wilcoxon Rank Sum statistic (van Elteren test) stratified by the u5-HIAA stratification at randomization. CLs were based on the Hodges-Lehmann estimator of the median paired difference.
- c. $p < 0.001$

There was no significant difference between treatment groups for the endpoints of flushing and abdominal pain.

A post-hoc analysis showed that the average number of daily short-acting SSA injections used for rescue therapy over the 12-week DBT period was 0.3 and 0.7 in the telotristat ethyl 250 mg and placebo groups, respectively.

A pre-specified patient exit interview substudy was conducted to assess relevance and clinical meaningfulness of symptom improvements in 35 patients. Questions were asked to blinded participants to further characterise the degree of change experienced during the trial. There were 12 patients who were “very satisfied”, and all of them were on XERMELO. The proportions of patients who were “very satisfied” were 0/9 (0%) on placebo, 5/9 (56%) on XERMELO 250 mg three times daily, and 7/15 (47%) on a higher dose of XERMELO.

Overall, 18 patients (13.2%) prematurely discontinued from the study during the DBT Period, 7 patients in the placebo group, 3 in the telotristat ethyl 250 mg group and 8 in the higher dose group

At the conclusion of the 12-week DBT period, 115 patients (85.2%) entered the 36-week open-label extension period, where all patients were titrated to receive a higher dose of XERMELO three times daily. Patients then entered an extension study (TELEPATH) to evaluate long-term safety of telotristat. In this study, the maximum duration of exposure was more than 5 years.

In a phase 3 study of similar design (TELECAST), a total of 76 patients were evaluated for efficacy. The mean age 63 years (range 35-84 years), 55% male and 97% white. All patients had well-differentiated metastatic neuroendocrine tumour with carcinoid syndrome. Most patients (92.1%) had fewer than 4 BM per day and all except 9 were treated by SSA therapy.

The primary endpoint was the percent change from Baseline in u5-HIAA at Week 12. The mean u5-HIAA excretion at baseline was 69.1 mg/24hours in the 250 mg group (n=17) and 84.8 mg/24 hours in the placebo group (n=22). The percent change from baseline in u5-HIAA excretion at week 12 was +97.7% in the placebo group versus -33.2% in the 250 mg group (Table 4).

The mean number of daily BM at baseline was 2.2 and 2.5 respectively in the placebo (n=25) and 250 mg group (n=25). The change from baseline in daily BM averaged over 12 weeks was +0.1 and -0.5 in the placebo and 250 mg groups respectively. Telotristat ethyl 250 mg showed that stool consistency, as measured by Bristol Stool Form Scale, was improved compared with placebo (Table 5). There were 40% patients (10/25) with durable response (as

defined in Table 2) in the telotristat ethyl 250 mg group, versus 0% in the placebo group (0/26) (p=0.001).

Table 4: u5-HIAA Excretion at Baseline and Week 12 (TELECAST Study)

	Parameter	Placebo	XERMELO 250 mg tid
u5-HIAA Excretion (mg/24 hours) at Baseline	Number of Patients	22	17
	Baseline Mean ^a (SD)	84.8 (117.14)	69.1 (60.64)
Primary Endpoint: Percent Change from Baseline In u5-HIAA Excretion (mg/24 hours) at Week 12	Number of Patients	22	17
	Percent Change at Week 12: Mean (SD)	97.7 (397.01)	-33.2 (58.48)
	Differences in Arithmetic Means vs Placebo (95% CL)	---	-130.9 (-328.19, 66.43)
	Estimate of Treatment difference (95% CL) ^b	---	-54.0 ^c (-84.96, -25.12)
Change from Baseline in u5-HIAA Excretion (mg/24 hours) at Week 12	Number of Patients	22	17
	Change at Week 12 : Mean (SD)	35.6 (99.54)	-32.2 (43.36)
	Difference in Arithmetic Means vs Placebo (95% CL)	---	-67.8 (-120.32, -15.33)
	Estimate of Treatment Difference (95% CL) ^b	---	-29.8 ^d (-78.80, -9.20)
CL=confidence limit; tid=three times a day; SD=standard deviation.			
a. Baseline data based on patients with data at both Baseline and Week 12.			
b. Statistical tests used a blocked 2-sample Wilcoxon Rank Sum statistic (van Elteren test) stratified by the u5-HIAA stratification at randomization. CLs were based on the Hodges-Lehmann estimator of the median paired difference.			
c. p<0.001			
d. p=0.003			

Table 5: Bowel Movements Response (TELECAST Study)

	Parameter	Placebo	XERMELO 250 mg tid
BMs/Day at Baseline	Number of Patients	25	25
	Baseline Mean (SD)	2.2 (0.67)	2.5 (1.25)
Change from Baseline in BMs/Day Averaged Over 12 Weeks	Number of Patients	25	25
	Change Averaged over 12 Weeks: Mean (SD)	0.1 (0.33)	-0.5 (0.69)
	Difference in Arithmetic Means vs Placebo (95% CL)	---	-0.5 (-0.81, -0.19)
	Estimate of Treatment Difference (95% CL) ^a	---	-0.5 ^b (-0.72, -0.17)
Change from Baseline in BMs/Day At Week 12	Number of Patients	18	16
	Change at Week 12: Mean (SD)	0.1 (0.51)	-0.8 (0.99)
	Differences in Arithmetic Means vs Placebo (95% CL)	---	-0.8 (-1.39, -0.31)
	Estimate of Treatment Difference (95% CL) ^a	---	-0.9 ^c (-1.39, -0.24)
Percentage of Patients with	Number of Patients	26	25

	Parameter	Placebo	XERMELO 250 mg tid
Durable Response (See text for definition)	Responder, n (%) (95% CI) ^e	0 ^d	10 (40.0) ^e (19.0, 61.0)
CL=confidence limit; tid=three times a day; SD=standard deviation; NA= not applicable			
a. Statistical tests used a blocked 2-sample Wilcoxon Rank Sum statistic (van Elteren test) stratified by the u5-HIAA stratification at randomization. 95% CLs were based on the Hodges-Lehmann estimator of the median paired difference.			
b. p=0.004			
c. p=0.002			
d. Statistical test used was the continuity-adjusted chi-square test. 95% CLs were calculated based on normal approximation using a correction for continuity. There were no CLs for the placebo group due to the absence of responders.			
e. p=0.001			

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of telotristat ethyl and its active metabolite have been characterised in healthy volunteers and patients with carcinoid syndrome.

Absorption

After oral administration of XERMELO to healthy volunteers, telotristat ethyl was rapidly absorbed, and almost completely converted to its active metabolite. Peak plasma levels of telotristat ethyl were achieved in 0.53 to 2.00 hours and those of the active metabolite in 1.50 to 3.00 hours after oral administration. Following administration of a single 500 mg dose of telotristat ethyl (twice the recommended dosage) under fasted conditions in healthy subjects, the mean C_{max} and AUC_{0-inf} were 4.4 ng/mL and 6.23 ng•hr/mL, respectively for telotristat ethyl. The mean C_{max} and AUC_{0-inf} were 610 ng/mL and 2320 ng•hr/mL, respectively for telotristat.

In patients with carcinoid syndrome on long-acting SSA therapy, there was also a rapid conversion of telotristat ethyl to its active metabolite. A high variability (% CV range of 18% to 99%) in telotristat ethyl and its active metabolite parameters was observed within the overall PK. The mean PK parameters for telotristat ethyl and the active metabolite appeared unchanged between week 24 and week 48, suggesting the achievement of steady-state conditions at, or prior to, week 24.

Food effect

In a food effect study administration of telotristat ethyl 500 mg with a high-fat meal resulted in higher exposure to the parent compound (C_{max} , $AUC_{0-1last}$, and $AUC_{0-∞}$ being 112%, 272%, and 264% higher, respectively compared with the fasted state) and its active metabolite (C_{max} , $AUC_{0-1last}$, and $AUC_{0-∞}$, 47%, 32%, and 33% higher, respectively compared with the fasted state).

Distribution

Both telotristat ethyl and its active metabolite are > 99% bound to human plasma proteins. From the population modelling, the apparent total volume of distribution for the active metabolite in patients with carcinoid syndrome was estimated at 348.7 L.

Metabolism

After oral administration, telotristat ethyl undergoes hydrolysis via carboxylesterases to its active and major metabolite. The only metabolite of telotristat (active metabolite) representing consistently > 10% of total plasma drug-related material was its oxidative decarboxylated deaminated metabolite, LP-951757. Systemic exposure to LP-951757 was about 35% of the systemic exposure to telotristat in the mass balance study.

LP-951757 was pharmacologically inactive at TPH1 *in vitro*.

Excretion

Following a single 500 mg oral dose of ¹⁴C-telotristat ethyl, approximately 93% of the dose was recovered. The majority was eliminated in the faeces, with less than 1% in the urine.

The apparent half-life of telotristat ethyl in normal healthy volunteers following a single 500 mg oral dose ¹⁴C-telotristat ethyl was approximately 0.6 hour and that of its active metabolite was 5 hours.

Following administration of 500 mg tid, the apparent terminal half-life was approximately 11 hours.

Linearity/non-linearity

In patients treated at 250 mg three times daily, a slight accumulation of telotristat levels was observed with a median accumulation ratio based on AUC_{0-4h} of 1.55 [minimum, 0.25; maximum, 5.00; n=11; week 12], with a high inter-subject variability (%CV = 72%). In patients treated at 500 mg tid (twice the recommended dose), a median accumulation ratio based on AUC_{0-4h} of 1.095 (minimum, 0.274; maximum, 11.46; n=16; week 24) was observed, with a high inter-subject variability (%CV = 141.8%). Based on the high inter-subject variability observed, accumulation in a subset of patients with CS cannot be excluded.

Pharmacokinetics in special patient populations

Elderly

The influence of age on the pharmacokinetics of telotristat ethyl and its active metabolite has not been conclusively evaluated. No specific study has been performed in the elderly population.

Renal impairment

The influence of renal impairment on the pharmacokinetics of telotristat ethyl and its active metabolite has not been conclusively evaluated. No specific study has been performed in patients with renal impairment.

Renal impairment is not expected to affect clearance of the parent drug or its active metabolite because telotristat ethyl has low renal elimination following oral administration (less than 1% of the dose recovered from the urine). Patients with mild and moderate renal impairment should be treated with caution. The use of telotristat is not recommended in patients with severe renal impairment based on the limited data available.

Telotristat was not studied in end-stage renal disease patients requiring dialysis.

Hepatic impairment

In a hepatic impairment study conducted at a single dose of 500 mg, exposures to the parent drug and its active metabolite (based on $AUC_{0-t_{last}}$) were higher in patients with mild hepatic impairment (2.3- and 2.4-fold, respectively) and in patients with moderate hepatic impairment (3.2- and 3.5-fold, respectively) compared with healthy subjects. Administration of a single dose of 500 mg was well tolerated. The use of telotristat is not recommended in patients with severe hepatic impairment as no data are available.

5.3 PRECLINICAL SAFETY DATA

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenicity potential, and reproductive toxicity. A two-year carcinogenicity study is ongoing.

Genotoxicity

Telotristat ethyl was negative in the in vitro Ames test, the in vitro chromosomal aberration test using Chinese hamster ovary cells, and the in vivo rat micronucleus test.

Carcinogenicity

In a 26-week study in transgenic (Tg.rasH2) mice, telotristat ethyl was not tumorigenic at oral doses up to 300 mg/kg/day (exposure to the active metabolite 10 times the clinical exposure based on AUC).

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The inactive ingredients of XERMELO tablets are:

- colloidal anhydrous silica
- croscarmellose sodium
- hypromellose
- lactose
- magnesium stearate

The tablet film-coating contains:

- polyvinyl alcohol
- titanium dioxide (E171)
- macrogol 3350
- purified talc (E553b)

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C

6.5 NATURE AND CONTENTS OF CONTAINER

XERMELO telotristat ethyl (as telotristat etiprate) 250 mg film-coated tablets are supplied in PVC/PCTFE/PVC/Aluminium blister packs packaged in cartons of 90 tablets.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

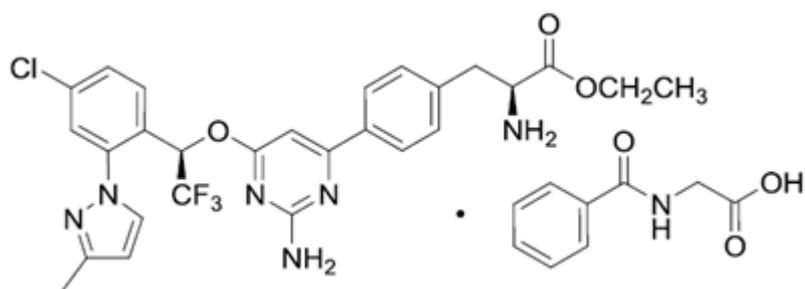
6.7 PHYSICOCHEMICAL PROPERTIES

Telotristat etiprate is a white to off-white solid. The solubility is a function of pH at 25°C; at pH 1 (0.1N HCl), the solubility is greater than 71 mg/mL, at pH 3 phosphate buffer, the solubility is 0.30 mg/mL, at a pH of 5 to 9, the solubility is negligible. In organic solvents, telotristat etiprate is freely soluble in methanol, dimethyl sulfoxide and tetrahydrofuran/water (1:1), soluble in acetone, sparingly soluble in ethanol and slightly soluble in acetonitrile. It is also slightly soluble in water.

Chemical structure

XERMELO tablets contain telotristat ethyl, as telotristat etiprate, a tryptophan hydroxylase inhibitor. Telotristat etiprate is the hippuric acid salt form of telotristat ethyl (the free base). Telotristat is the active metabolite of the prodrug, telotristat ethyl. The chemical name for telotristat etiprate is: [(1S)-1-[[4-[2-amino-6-[(1R)-1-[4-chloro-2-(3-methylpyrazol-1-yl)phenyl]-2,2,2-trifluoro-ethoxy]pyrimidin-4-yl]phenyl]methyl]-2-ethoxy-2-oxo-ethyl]ammonium; 2-benzamidoacetate (IUPAC Name).

The molecular formula of telotristat etiprate is $C_{27}H_{26}ClF_3N_6O_3 \cdot C_9H_9NO_3$ and its molecular mass is 754.2. The molecular formula of telotristat ethyl is $C_{27}H_{26}ClF_3N_6O_3$ and its molecular mass is 575.0.



Telotristat etiprate has two asymmetric centres with absolute configuration as indicated in the structure above (*R*, *S* configuration).

The pKa values of telotristat ethyl are pKa1 = 3.4 (pyrimidine, measured) and pKa2 = 6.7 (amine, measured)

CAS number

CAS Numbers: 1137608-69-5 (telotristat etiprate)

1033805-22-9 (telotristat ethyl free base)

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4

8 SPONSOR

Ipsen Pty Ltd
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 540 Springvale Road
 Glen Waverley Victoria 3150

Telephone: 1800 317 033

9 DATE OF FIRST APPROVAL

14 September 2018

10 DATE OF REVISION

Not applicable