▼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.

Excipients with known effect: sugars as lactose. 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 change in dosage is required in patients with mild, moderate or severe renal impairment; who are not requiring dialysis (see section 5.2 PHARMACOKINETIC PROPERTIES).

The efficacy and safety of XERMELO in patients with end-stage renal disease who require dialysis (eGFR < 15 mL/min/1.73 m^2) has not been established.

The use of XERMELO is not recommended 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 class 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 class 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 class C) (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 and from post-marketing in some patients treated with telotristat (see section 4.8 ADVERSE EFFECTS (UNDESIRABLE

EFFECTS)). 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 interaction

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 2 (CES2) inhibitors

The IC_{50} of the inhibition of loperamide on the metabolism of telotristat ethyl by CES2 was 5.2 µM. In phase 3 clinical trials, telotristat was routinely combined with loperamide with no evidence of a change in exposure of telotristat or 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, ethinylestradiol, 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 $AUC_{0\text{-}inf}$ for midazolam were decreased by 25%, and 48%, respectively, compared to administration of midazolam alone. The mean C_{max}, and $AUC_{0\text{-}inf}$ 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.

Carboxylesterase 2 (CES2) substrates

Concomitant use of XERMELO may change the exposure of medicinal products that are CES2 substrates (e.g. prasugrel, irinotecan, capecitabine and flutamide). If co-administration is unavoidable, monitor for suboptimal efficacy and safety events.

In vitro, telotristat ethyl inhibited CES2 with an IC_{50} approximately of 0.56 µM.

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 (IC_{50} 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 (IC_{50} = 20 µM), but its active metabolite telotristat did not show any significant inhibition of BCRP activity (IC_{50} > 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 embryofoetal 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 (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥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 patients treated with XERMELO

System organ class	Very common	Common	Uncommon
Metabolism and nutrition disorders		Decreased appetite	
Psychiatric disorders		Depression, depressed mood	
Nervous system disorders		Headache	
Gastrointestinal disorders	Abdominal pain[a], nausea	Abdominal distension, Constipation, Flatulence	Faecaloma[c], intestinal obstruction
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).

[c] Faecaloma has only been observed in a clinical study at a dosage of 500mg tid (twice the recommended dose).

Description of selected adverse reactions

Hepatic enzymes elevations

Elevations in ALT >3 × 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).

Long-term safety study

In a long-term open-label, extension study (TELEPATH) a total of 124 patients were enrolled with 22 patients receiving telotristat etiprate 250 mg tid and 102 receiving 500 mg tid. The mean duration of exposure was approximately 103 weeks. No new adverse effects were identified from this study.

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: Other alimentary tract and metabolism products: Various alimentary tract and metabolism products

ATC code: A16AX15

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 XERMELO (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 XERMELO 250 mg (n=45) three times daily for one week, or a higher dose (telotristat ethyl 500 mg; n=45) tid (the 500 mg results are not presented as 500 mg tid is not a recommended dose). 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. XERMELO 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 ≥30% reduction in daily number of BMs for ≥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

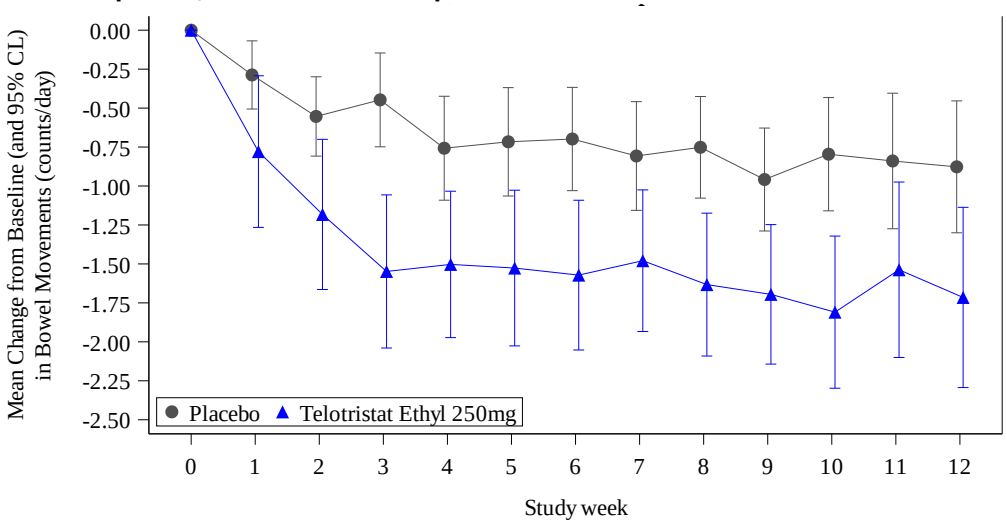
d. Statistical test, odds ratio, and 95% CL were based on a logistic regression model with responder as the dependent variable, treatment group and u5-HIAA stratification at randomization as fixed effects, and Baseline mean number of BMs (counts/day) as a covariate.

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 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 9 -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 Table2) 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 Durable Response (See text for definition)	Number of Patients	26	25
	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 dose) under fasted conditions in healthy subjects, the mean C_{max} and $AUC_{0\text{-}inf}$ were 4.4 ng/mL and 6.23 ng•hr/mL, respectively for telotristat ethyl. The mean C_{max} and $AUC_{0\text{-}inf}$ 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}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ being 112%, 272%, and 264% higher, respectively compared with the fasted state) and its active metabolite (C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$, 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 ^{14}C-telotristat ethyl, approximately 93% of the dose was recovered. The majority was eliminated in the faeces, with less than 1% in the urine.

Following a single oral 250 mg dose of telotristat ethyl to heathy volunteers, urine concentrations of telotristat ethyl were close to or below the limit of quantification (<0.1 ng/mL). The renal clearance of telotristat was 0.126 L/h, confirming that renal elimination is not a significant route of elimination for telotristat ethyl or the active metabolite (telotristat).

The apparent half-life of telotristat ethyl in normal healthy volunteers following a single 500 mg oral dose ^{14}C-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 $AUC_{0\text{-}4h}$ 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 $AUC_{0\text{-}4h}$ 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.

Pharmacokinetic/pharmacodynamic relationship(s)

Acid Reducers

Concomitant use of telotristat etiprate (XERMELO, the hippurate salt of telotristat ethyl) with acid-reducers (omeprazole and famotidine) showed that the AUC of telotristat ethyl was increased 2-3 fold, while the AUC of the active metabolite (telotristat) was not changed. Since telotristat ethyl is rapidly converted to its active metabolite, which is > 25 times more active than telotristat ethyl, no dose adjustments are required when using XERMELO with acid reducers.

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

A study was conducted at a single dose of 250mg telotristat ethyl in eight subjects with severe renal impairment and eight healthy subjects. All renally impaired subjects had severely decreased renal function (eGFR < 30 mL/min/1.73 m² not requiring dialysis).

An increase in C_{max} of telotristat ethyl (1.3-fold) was observed in subjects with severe renal impairment compared with healthy subjects.

An increase (<1.52 fold) in plasma exposure (AUC) and C_{max} of the active metabolite (telotristat) was observed in subjects with severe renal impairment.

As the C_{max} increase in telotristat ethyl and the total and unbound exposure increase (C_{max} and AUC) in its active metabolite (telotristat) was less than 2-fold in subjects with severe renal impairment compared to healthy subjects, there is no expected clinical significance of the increase in exposure in subjects with severe renal impairment.

Overall, severe renal impairment, does not result in a clinically meaningful change in the PK profile of telotristat ethyl or its active metabolite (telotristat). A single oral dose of 250 mg telotristat ethyl was well tolerated in subjects with severe renal impairment and therefore it is not necessary to alter the dose in patients with mild, moderate or severe renal impairment; who are not requiring dialysis.

The efficacy and safety in patients with end-stage renal disease who require dialysis (eGFR < 15 mL/min/1.73 m² requiring dialysis) has not been established.

Hepatic impairment

A hepatic impairment study was conducted in subjects with mild and moderate hepatic impairment and in healthy subjects. At a single dose of 500 mg, exposures to the parent drug and its active metabolite (based on $AUC_{0\text{-last}}$) 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. A reduction in dose may be necessary in patients with mild or moderate hepatic impairment (respectively Child Pugh class A and B) based on tolerability (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

A further hepatic impairment study was conducted in subjects with severe hepatic impairment and in healthy subjects. At a single dose of 250 mg, exposure to the parent compound (AUC_t and C_{max}) was increased 317.0% and 529.5%, respectively, and to the active metabolite ($AUC_{0\text{-last}}$, AUC_{inf}, and C_{max}) 497%, 500%, and 217%, respectively, for subjects with severe hepatic impairment compared to subjects with normal hepatic function. In addition, the half-life of the active metabolite was increased, i.e. the mean half life was 16.0 hours in subjects with severe hepatic impairment compared to 5.47 hours in healthy subjects. Based on these findings, the use of telotristat etiprate is not recommended in patients with severe hepatic impairment (Child Pugh class C) (see section 4.2 DOSE AND METHOD OF ADMINISTRATION).

5.3 Preclinical safety data

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

The carcinogenic potential of telotristat etiprate was studied in transgenic (Tg.rasH2) mice (26 weeks) and rats (85-90 weeks). Telotristat etiprate was not tumourigenic in mice at oral doses up to 300 mg/kg/day (8-12 times the clinical exposure to the active metabolite based on AUC) or rats at oral doses up to 170 mg/kg/day (1-4 times the clinical exposure to the active metabolite based on AUC).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The inactive ingredients of XERMELO tablets are:
colloidal anhydrous silica
croscarmellose sodium

hyprolose
lactose
magnesium stearate

The tablet film-coating contains:
polyvinyl alcohol
titanium dioxide
macrogol 3350
purified talc

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.

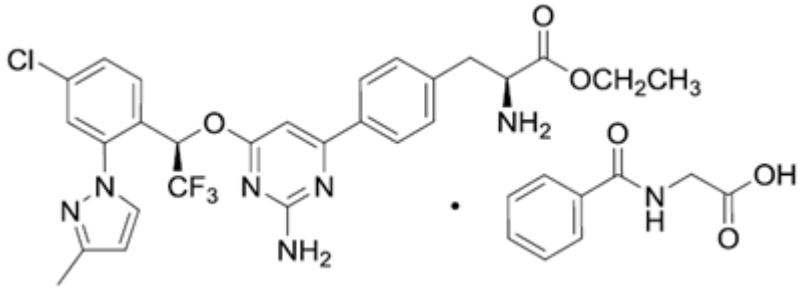
6.7 Physicochemical properties

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: [(1*S*)-1-[[4-[2-amino-6-[(1*R*)-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 $C_{27}H_{26}ClF_3N_6O_3 \bullet C_9H_9NO_3$ 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

Clinect Pty Ltd,

120-132 Atlantic Drive,

Keysborough, VIC 3173,

Australia

Free Call Australia: 1800 899 005

9. DATE OF FIRST APPROVAL

14 September 2018

10. DATE OF REVISION

18 April 2023

Summary Table of Changes

Section Changed	Summary of New Information
All	Font style changes and minor editorial changes throughout PI
2	Addition of excipient with known effects statement.
8	Updated with new sponsor details