PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrXERMELO™

Telotristat Ethyl Tablets

250 mg telotristat ethyl (as telotristat etiprate)

Tryptophan hydroxylase inhibitor

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RECENT MAJOR LABEL CHANGES

4 Dosage and Administration, 4.2 Recommended Dose and Dosage Adjustment	11/2020
7 Warnings and Precautions	12/2021

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

XERMELO (telotristat ethyl) is indicated for the treatment of refractory carcinoid syndrome diarrhea, in combination with somatostatin analogue (SSA) therapy, in patients inadequately controlled by SSA therapy alone.

1.1 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (>65 years of age): Evidence from clinical studies suggests that use in the geriatric population is associated with no differences in safety or effectiveness, but greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

XERMELO is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see **DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING**.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

Available data suggest that clinical response is usually achieved within 12 weeks of treatment. After 12 weeks of treatment with XERMELO, patients should be reassessed to determine the appropriateness of ongoing treatment with XERMELO.

Concomitant use with Short-acting Octreotide

When short-acting octreotide is used in combination with XERMELO, administer short-acting octreotide at least 30 minutes after administering XERMELO (see **DRUG INTERACTIONS**).

4.2 Recommended Dose and Dosage Adjustment

The recommended dose of XERMELO is 250 mg three times a day (tid), taken orally.

Renal impairment
No change in dosage is required in patients with mild, moderate or severe renal impairment; who are not requiring dialysis (see **ACTION AND CLINICAL PHARMACOLOGY**). As a precautionary measure, it is recommended that patients with severe renal impairment will be monitored for signs of reduced tolerability.

The use of XERMELO is not recommended in patients with end-stage renal disease requiring

dialysis (eGFR < 15 mL/min).

Hepatic impairment
In patients with mild hepatic impairment (Child Pugh score A), the recommended dose of XERMELO is 250 mg **twice daily,** based on tolerability. In patients with moderate hepatic impairment (Child Pugh score B), the recommended dose of XERMELO is 250 mg **once daily,** based on tolerability.

The use of XERMELO is not recommended in patients with severe hepatic impairment (Child Pugh score C) (see **ACTION AND CLINICAL PHARMACOLOGY**).

Elderly patients (65 years of age and above)
No dosage adjustments are required in elderly patients, but greater sensitivity of some older individuals cannot be ruled out (see **ACTION AND CLINICAL PHARMACOLOGY**).

Pediatrics
Health Canada has not authorized an indication for pediatric use.

4.4 Administration

Take XERMELO with food (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, *Food Effect).*

4.5 Missed Dose

If a dose is missed, take the next dose at the regular time. Do not take 2 doses at the same time to make up for a missed dose.

5 OVERDOSAGE

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

Management of overdose
Treatment of an overdose should include general symptomatic management.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 Dosage Forms, Strengths, Composition and Packaging.

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients

Oral	tablet 250 mg	Tablet core: Croscarmellose sodium, Hydroxypropylcellulose, Lactose anhydrous, Magnesium stearate, Silica, colloidal anhydrous Film-coating: Macrogol 3350, Polyvinyl alcohol - partially hydrolysed, Talc, Titanium dioxide

XERMELO telotristat ethyl 250 mg film-coated tablets are supplied in blister packs packaged in cartons of 90 tablets.

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.

7 WARNINGS AND PRECAUTIONS

Driving and Operating Machinery
Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery. Fatigue may occur following administration of XERMELO.

Gastrointestinal
Constipation and Intestinal Obstruction
XERMELO reduces bowel movement (BM) frequency. Constipation, in some cases severe, has been reported in patients using a higher dose, i.e., telotristat ethyl 500 mg tid (see **ADVERSE REACTIONS**, Gastrointestinal Disorders). Patients should be monitored for signs and symptoms of constipation. If constipation develops, the use of XERMELO and other concomitant therapies affecting bowel motility should be re-evaluated.

Cases of intestinal obstruction have been reported during post-approval use of XERMELO (see ADVERSE REACTIONS, Post-Market Adverse Reactions). In the majority of cases where time to onset was reported, intestinal obstruction occurred within 3 months. Patients with known or suspected gastrointestinal obstruction (e.g., constipation, bowel obstruction, strictures) or any diseases/conditions that affect bowel transit (e.g., ileus of any type) may also be at higher risk of intestinal obstruction. If intestinal obstruction develops, dose reduction, interruption, or discontinuation of XERMELO should be considered.

Hepatic/Biliary/Pancreatic
Hepatic Enzyme Elevations
Elevations in hepatic enzymes were observed in clinical studies (see **ADVERSE REACTIONS**, Hepatic Enzyme Elevations). Laboratory monitoring of hepatic enzymes prior to and during XERMELO therapy is recommended as clinically indicated. In patients with hepatic impairment, continuous monitoring for adverse events related to worsening of liver function is recommended.

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

Psychiatric
Depressive Disorders
Depression, depressed mood and decreased interest have been reported in clinical studies and post-marketing experience in some patients treated with XERMELO, especially at higher doses,

i.e., telotristat ethyl 500 mg tid (see **ADVERSE REACTIONS**, Depression). Patients should be advised to report any symptoms of depression, depressed mood and decreased interest to their physicians.

Reproductive Health
Fertility
No studies on the effect of Xermelo on human fertility have been conducted.

7.1 Special Populations

7.1.1 Pregnant Women

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

Pregnancy
XERMELO is not recommended during pregnancy and in women of childbearing potential not using contraception. Animal studies have shown developmental toxicity (see **NON-CLINICAL TOXICOLOGY**). There are no data for the use of XERMELO in pregnant women.

7.1.2 Breast-feeding

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

7.1.3 Pediatrics

Pediatrics (<18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

No dosage adjustments are required in elderly patients, but greater sensitivity of some older individuals cannot be ruled out (see **ACTION AND CLINICAL PHARMACOLOGY)**.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The overall safety of XERMELO was evaluated in 239 patients, of whom 131 patients were exposed to XERMELO for at least 48 weeks (mean duration of treatment 67 weeks), and 83% of these patients were exposed to XERMELO for at least 72 weeks (mean duration of treatment 107 weeks). Most of these patients were exposed to a higher dose of XERMELO than currently recommended, i.e., telotristat ethyl 500 mg tid.

The placebo-controlled safety dataset was derived from two 12-week placebo-controlled, double-blind studies, that included Study LX-301, the pivotal registration study, and Study LX-303, a supportive clinical study. Safety was assessed using the incidence of treatment-emergent

adverse events in both studies. This dataset includes 211 patients with carcinoid syndrome, with 70 patients treated with XERMELO 250 mg tid, 70 patients with telotristat ethyl 500 mg tid, and 71 with placebo.

The most frequently reported adverse events (AEs) in the placebo-controlled dataset were gastrointestinal disorders, including nausea and abdominal pain.

In the placebo-controlled safety dataset, 16 (22.9%) patients in the XERMELO 250 mg tid group, nine (12.9%) patients from the telotristat ethyl 500 mg tid group, and 12 (16.9%) patients in the placebo group, discontinued study treatment due to AEs. The AEs leading to discontinuation were most frequently related to gastrointestinal or liver disorders for patients treated with XERMELO. Gastrointestinal disorders accounted for discontinuation in 10.0% of patients treated with XERMELO 250 mg tid over 12 weeks, 7.1% in those treated with telotristat ethyl 500 mg tid, and 7.0% with placebo, of which, 5.7%, 2.9%, and 2.8%, were due to abdominal pain, respectively. GGT elevations accounted for 2.9%, 1.4%, and 0% of patient discontinuations, respectively.

Serious adverse events (SAE) were reported in 8 (11.4%) patients treated with XERMELO 250 mg tid, 11 (15.7%) patients with telotristat ethyl 500 mg tid, and 12 (16.9%) patients with placebo.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Adverse Events in Two 12-week Controlled Studies
In two 12-week, double-blind, placebo-controlled studies, 70 patients with carcinoid syndrome received XERMELO 250 mg tid in combination with SSA therapy. Approximately 25% of patients reported receiving one or more concomitant medications to treat depression, anxiety and/or insomnia. Other frequently reported concomitant medications were antidiarrheals and analgesics. The mean age was 63 years, 57% were older than 65 years, 50% were male, and 94% white. The mean body mass index was 24.87 kg/m^2.

AEs for the 12-week placebo-controlled studies, occurring in ≥ 5% of patients in the XERMELO 250 mg tid group and at an incidence greater than in the placebo group, are shown in Table 2, by system organ class.

Table 2 Adverse Events Reported in ≥5% of XERMELO Treated Patients and at an Incidence Greater than Placebo

	XERMELO 250 mg tid N = 70 n (%)	**Placebo N = 71 n (%)**

Gastrointestinal Disorders		
Nausea	9 (12.9)	9 (12.7)
Abdominal Pain	13 (18.6)	12 (16.9)
Abdominal Pain Upper	4 (5.7)	3 (4.2)
Constipation	4 (5.7)	3 (4.2)
Abdominal Distension	5 (7.1)	3 (4.2)
Flatulence	4 (5.7)	1 (1.4)
General Disorders and Administration Site Conditions		
Fatigue	7 (10.0)	6 (8.5)
Pyrexia	6 (8.6)	2 (2.8)
Edema Peripheral	5 (7.1)	1 (1.4)
Nervous System Disorders		
Headache	5 (7.1)	3 (4.2)
Investigations		
Increased gamma-glutamyl transferase (GGT)	5 (7.1)	0
Vascular Disorders		
Flushing	6 (8.6)	4 (5.6)
Renal and Urinary Disorders		
Urinary Tract Infection	5 (7.1)	2 (2.8)

Description of Selected Adverse Events

Hepatic Enzyme Elevations: Elevations in ALT >3 × upper limit of normal (ULN) or ALP > 2 x ULN have been reported in patients receiving therapy with XERMELO, with most cases being reported at a higher dose of XERMELO than recommended for treatment, i.e., telotristat ethyl 500 mg tid (see **WARNINGS AND PRECAUTIONS**, Hepatic/Biliary/Pancreatic). These have generally not been associated with concomitant elevations in total serum bilirubin. The increases were largely reversible on dose interruption or reduction, or recovered while maintaining treatment at the same dose.

In the placebo-controlled safety dataset of patients with carcinoid syndrome, elevations of ALT were reported as an AE in 2.9% of patients treated with XERMELO 250 mg tid, 4.3% of patients treated with telotristat ethyl 500 mg tid, and 0% of patients treated with placebo. Elevations of AST were reported in 1.4%, 2.9%, and 0% of patients in the XERMELO 250 mg tid, telotristat ethyl 500 mg tid, and placebo groups, respectively. GGT elevations as an AE occurred in 7.1%, 7.1%, and 0% of patients in the same groups, respectively. Alkaline phosphatase (ALP) increases were reported only in the telotristat ethyl 500 mg tid group in 4.3% of patients, and not in the XERMELO 250 mg tid or placebo groups.

Gastrointestinal Disorders: Constipation was reported in 5.7% of patients (4/70) in the XERMELO 250 mg group, 7.1% (5/70) in the telotristat ethyl 500 mg tid group, and in 4.2% of patients (3/71) in the placebo group. Constipation as a serious adverse event (SAE) was observed in 3 patients out of 239 patients treated at a higher dose than currently recommended, i.e., with telotristat ethyl 500 mg tid, in the overall safety population (see **WARNINGS AND PRECAUTIONS**, Gastrointestinal).

Depression: In the placebo-controlled safety dataset, depression was reported as an adverse event in 2.9% of patients treated with XERMELO 250 mg tid, 11.4% treated with telotristat ethyl 500 mg tid, and in 4.2% treated with placebo (see **WARNINGS AND PRECAUTIONS**,

Psychiatric).

8.3 Less Common Clinical Trial Adverse Reactions (<2%) (not included above)

Cardiac disorders:	palpitations
Gastrointestinal disorders:	dry mouth, gingival bleeding, intestinal obstruction
General disorders and administration site conditions:	mucosal inflammation, peripheral edema
Investigations:	liver function test abnormal, increased blood cholesterol, increased hepatic enzyme
Metabolic and nutrition disorders:	decreased appetite, hyperglycemia
Nervous system disorders:	tremor
Respiratory, thoracic and mediastinal disorders:	oropharyngeal pain
Skin and subcutaneous tissue disorders:	alopecia, night sweats, maculopapular rash

8.5 Post-Market Adverse Reactions

Gastrointestinal Disorders: Intestinal obstruction has been reported with post-marketing use of XERMELO. If intestinal obstruction develops, dose reduction, interruption, or discontinuation of XERMELO should be considered.

Neurological Disorders: Dizziness has been reported with post-marketing use of XERMELO.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

In vitro Assessment of Drug Interactions
In vitro data suggest that telotristat ethyl and telotristat are not substrates for CYP enzymes.

CYP3A4 substrates and inducers: *In vitro,* telotristat ethyl inhibits CYP 3A4 suggesting a potential interaction with CYP 3A4 substrates. Telotristat ethyl and telotristat were not shown to be inducers of CYP 3A4 based on *in vitro* findings. The potential of telotristat ethyl as an inducer of CYP 3A4 was not assessed at concentrations expected in the intestines, due to its low solubility *in vitro.*

CYP 2B6 substrates: *In vitro*, telotristat ethyl treatment resulted in concentration dependent increase in CYP 2B6 mRNA levels suggesting possible CYP 2B6 induction. Concomitant use of XERMELO may decrease the efficacy of drugs that are CYP 2B6 substrates (e.g. valproic acid, bupropion, sertraline) by decreasing their systemic exposure. Monitoring for suboptimal efficacy is recommended.

P-glycoprotein (P-gp) and Multi-Resistance Protein 2 (MRP-2) transporters: Telotristat ethyl and telotristat are not substrates of the transporters, P-gp and MRP-2. *In vitro,* telotristat ethyl inhibited P-gp and BCRP, but telotristat did not, at the clinically relevant concentrations. *In vivo* drug interaction potential via inhibition of BCRP is low based on *in vitro* studies and *in vivo* findings. Based on *in vitro* studies, *in vivo* drug interaction potential via inhibition of organic

cation transporter 1 (OCT1), OCT2, organic anion transporter 1 (OAT1), OAT3, organic anion transporting polypeptide 1B1 (OATP1B1), OATP1B3, or bile salt export pump (BSEP) transporters by telotristat ethyl and telotristat is low at the recommended dosage. Telotristat ethyl inhibited MRP2-mediated transport (98% inhibition).

9.4 Drug-Drug Interactions

CYP 3A4 Substrates
Concomitant use of XERMELO may decrease the efficacy of drugs that are CYP 3A4 substrates (e.g., midazolam, everolimus, sunitinib, simvastatin, ethinyloestradiol, amlodipine, cyclosporine) by decreasing their systemic exposure. Monitor for suboptimal efficacy and consider increasing the dose of concomitant CYP 3A4 substrates, if necessary.

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 tid (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.

Short-acting Octreotide
A study examining the effect of short-acting octreotide (3 doses of 200 micrograms injected subcutaneously 8 hours apart) on the single dose pharmacokinetics of telotristat ethyl 500 mg in healthy volunteers showed an 86% and 81% decrease in geometric mean C_{max} and $AUC_{0\text{-}last}$ of telotristat ethyl. The geometric mean C_{max} and $AUC_{0\text{-}last}$ of telotristat were 79% and 68% lower, respectively. If treatment with short-acting octreotide is needed in combination with XERMELO, administer short-acting octreotide at least 30 minutes after administration of XERMELO (see **DOSAGE AND ADMINISTRATION**).

Reduced exposures to telotristat ethyl and telotristat were not observed in a 12-week double-blind, placebo-controlled, randomised, multicentre clinical studies in adult patients with carcinoid syndrome on long-acting SSA therapy given single doses of XERMELO or multiple doses of telotristat ethyl 500 mg tid.

Fexofenadine (sensitive P-gp substrate and MRP-2 substrate)
The C_{max} and AUC of fexofenadine (a P-gp and MRP-2 substrate) increased by 16% when a single dose of fexofenadine 180 mg was co-administered orally with multiple doses of telotristat ethyl 500 mg tid (twice the recommended dose) for 5 days. These changes in exposures and maximal concentrations are not considered clinically significant. Clinically meaningful interactions with P-gp and MRP-2 substrates are unlikely.

Acid Reducers
Concomitant use of telotristat etiprate with acid-reducers (omeprazole and famotidine) showed that the AUC of telotristat ethyl was increased 2-3 times, 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.

Carboxylesterase 2 (CES2)
In vitro, telotristat ethyl inhibited CES2 with an IC_{50} of approximately 0.56 µM. In phase 3 clinical trials, telotristat was routinely combined with loperamide with no evidence of safety concerns. 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.

9.5 Drug-Food Interactions

XERMELO is recommended to be administered with food (see **ACTION AND CLINICAL PHARMACOLOGY**, **Pharmacokinetics**, *Food Effect)*.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Both the prodrug (telotristat ethyl) and its active metabolite (telotristat) are inhibitors of L-tryptophan hydroxylase (TPH1 and TPH2), the rate limiting step in serotonin biosynthesis. *In* vitro inhibitory potency of telotristat towards tryptophan hydroxylase is about 29 times higher than that of telotristat ethyl. 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. Serotonin is converted to 5-hydroxyindoleacetic acid (5-HIAA) which is excreted in the urine. Through inhibition of peripheral TPH1, XERMELO reduces the production of serotonin which can be measured by u5-HIAA levels.

10.2 Pharmacodynamics

In healthy subjects, telotristat ethyl 500 mg tid (twice the recommended dose) for 14 days decreased whole blood serotonin and 24-hour u5-HIAA from baseline. A decrease in 24-hour u5-HIAA was observed as early as after 5 days of treatment.

In two clinical studies in patients with well-differentiated metastatic neuroendocrine tumours having carcinoid syndrome, 24-hour u5-HIAA was decreased from baseline following 6 and 12 weeks of treatment with XERMELO 250 mg tid.

Cardiac Electrophysiology
A thorough QT study was conducted, that was a randomized, double-blind, placebo- and positive-controlled crossover study evaluating the effects of a single dose of 1500 mg (as free base) telotristat etiprate on ECG intervals in healthy subjects (N=47). No clinically meaningful

effects on the QTcF interval, the QRS duration, the PR interval, or heart rate were observed.

10.3 Pharmacokinetics

After oral administration, telotristat etiprate is rapidly hydrolysed to telotristat ethyl and hippuric acid. Telotristat ethyl then metabolized via carboxylesterases to its active and major metabolite telotristat prior to reaching the systemic circulation.

The pharmacokinetics of telotristat ethyl and telotristat have been characterized in healthy volunteers and patients with carcinoid syndrome**.**

Absorption: After oral administration of XERMELO 250 mg tablet, single dose to healthy volunteers, telotristat ethyl was rapidly absorbed, and metabolized to its active metabolite telotristat. Peak plasma levels of telotristat ethyl were achieved in 0.50 to 2.00 hours, and those of telotristat in 1.00 to 4.00 hours and thereafter declined in a biphasic manner with a relatively fast terminal phase for telotristat ethyl (1.15 h), and longer terminal elimination for telotristat (3.90 h). After oral administration of telotristat ethyl 500 mg tid for 14 days in healthy volunteers, steady state mean plasma AUC_{0-6} and C_{max} were 3255 ng.hr/mL and 1028 ng/mL, respectively for telotristat and AUC_{0-6} and C_{max} were 15.06 ng.hr/mL and 4.89 ng/mL, respectively for telotristat ethyl (Table 3). Peak plasma concentration and AUC of telotristat ethyl and telotristat appeared to be dose proportional following administration of a single dose of telotristat ethyl in the range of 100 mg to 1000 mg under fasted conditions.

The AUC_{0-6}, C_{max} and t_{max} of telotristat ethyl after single dose administration of 250 mg telotristat ethyl (administered as telotristat etiprate) in carcinoid patients are 15.3 ng.hr/mL, 3.97 ng/mL and 1.07 hours. The AUC_{0-6}, C_{max} and t_{max} of telotristat after single dose administration of 250 mg of telotristat ethyl in carcinoid patients are 1423 ng.hr/mL, 523 ng/mL and 2 hours. In patients treated with XERMELO 250 mg tid, a slight accumulation of telotristat levels was observed with a median accumulation ratio based on AUC_{0-4h} of 1.55, with a high inter-subject variability.

The pharmacokinetics of telotristat ethyl and telotristat following administration of multiple doses of telotristat ethyl 500 mg tid (twice the recommended clinical dose) with meal in patients with carcinoid syndrome on long-acting SSA therapy is noted below in Table 3.

Table 3 Summary of Telotristat Ethyl and Telotristat Mean Pharmacokinetic Parameters in Healthy Subjects and Carcinoid Patients on Background SSA Therapy at Steady-State at a Dose of Telotristat Ethyl 500 mg TID (twice the recommended clinical dose)

	N	C_{max} (SD) (ng/mL)	$t_{1/2}$ (SD) (h)	AUC_{0-6} (SD) (ng.h/mL)	Cl/F (SD) (L/h)	t_{max} (SD) (h)
Healthy Volunteers[a]						
Telotristat ethyl	6	4.89 (1.43)	2.97 (1.39)	15.06 (4.03)	2.67(0.82)	1.50 (0.75 to 4.00)
Telotristat	6	1028 (344)	11.7 (1.74)	3255 (1030)	152 (45.7)	4.00 (2.00 to 4.00)
Carcinoid Patients[b]						
Telotristat ethyl	26	7.25 (5.41)	-	22.9 (12.5)[c]		1.04 (0.00 to 2.08)
Telotristat	26	924 (484)	-	3006 (1785)[d]		2.00 (0.717 to 4.00)

[a] From Study LX102, steady-state conditions on Day 14
[b] From Study LX301, steady-state conditions at Week 24
[c] n=13
[d] n=22

Food Effect
In a food effect study, administration of a single dose of telotristat ethyl 500 mg (twice the recommended dose) with a high-fat meal resulted in higher exposure to both telotristat ethyl (C_{max}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$ being 112%, 272%, and 264% higher, respectively compared with the fasted state and telotristat C_{max}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$, 47%, 32%, and 33% higher, respectively compared with the fasted state). XERMELO is recommended to be taken with food (see **DOSAGE AND ADMINISTRATION**).

Distribution: Both telotristat ethyl and telotristat are > 99% bound to human plasma proteins. From the population modeling, the apparent total volume of distribution for telotristat in patients with carcinoid syndrome was estimated at 348.7 L, suggesting tissue distribution.

Metabolism: After oral administration, telotristat ethyl undergoes hydrolysis via carboxylesterases to its active and major metabolite telotristat. Telotristat is further metabolized. The only metabolite of telotristat 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*.

Elimination: Following a single 500 mg oral dose of ^{14}C-telotristat ethyl, approximately 93.2% of the dose was recovered over 240 hours. The majority was eliminated in the feces (92.8%).

Telotristat ethyl and telotristat have a low renal elimination following oral administration (less than 1% of the dose recovered from 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.

Special Populations and Conditions

Pediatrics: No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

Geriatrics: Population pharmacokinetics analysis indicated that age (18 to 83 years) had no significant effect on the pharmacokinetics of telotristat. The median dose normalised (to 250 mg tid) $AUC_{0\text{-}24,ss}$ for patients >65 years were 10.56% lower, compared to patients <65 years. Evidence from clinical studies suggests that use in the geriatric population is associated with no differences in safety or effectiveness.

Hepatic Insufficiency: In a hepatic impairment study conducted at a single dose of 500 mg telotristat ethyl, exposures to telotristat ethyl and telotristat (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. Dosing adjustment of telotristat ethyl is recommended in mild and moderate hepatic impairment (respectively Child Pugh score A and B).

In a study in subjects with severe hepatic impairment, at a single dose of 250 mg, exposure to telotristat ethyl (AUC_t and C_{max}) was increased 317.0% and 529.5%, respectively, and to telotristat (AUC_t, 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 telotristat was increased (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 XERMELO is not recommended in patients with severe hepatic impairment (Child Pugh score C) (see **DOSAGE AND ADMINISTRATION**).

Renal Insufficiency: A study was conducted to investigate the impact of renal impairment on the pharmacokinetics of a single dose of telotristat ethyl 250 mg. Eight subjects with moderate to severe renal impairment not requiring dialysis [eGFR ≤ 33 mL/min at screening and ≤40 mL/min at the day prior to dosing] and eight healthy to mildly impaired subjects [eGFR ≥88 mL/min at screening and ≥83 mL/min at the day prior to dosing] were included.

In the subjects with moderate to severe renal impairment, an increase (1.3-fold) in peak exposure C_{max} of telotristat ethyl and an increase (<1.52-fold) in plasma exposure (AUC) and C_{max} of its active metabolite telotristat was observed compared to healthy to mildly impaired subjects.
Administration of a single dose of 250 mg was well tolerated in subjects with moderate to severe renal impairment.

Overall, moderate to severe renal impairment did not result in a clinically meaningful change in the PK profile or safety of telotristat ethyl and its metabolite telotristat. Therefore, dose adjustment does not appear necessary in patients with mild, moderate or severe renal impairment; who are not requiring dialysis. Given the high variability observed, it is recommended as a precautionary measure that patients with severe renal impairment will be monitored for signs of reduced tolerability.

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. (see **DOSAGE AND ADMINISTRATION**).

Sex: Population pharmacokinetic analysis indicated that sex does not affect the pharmacokinetics of telotristat to a clinically significant extent. At steady-state, following multiple dose administration of telotristat ethyl 500 mg tid, mean C_{max} and AUC_{0-6} values at week 24 were 15 % and 29 % higher in female respectively, with no apparent difference in corresponding median.

Race: Population pharmacokinetic analysis showed that there was no difference in exposure between Caucasian and African-American subjects. The median dose normalised $AUC_{0-24,ss}$ for healthy African-American subjects was 3.13% lower compared to Caucasian subjects.

Obesity: Population pharmacokinetic analysis indicated that BMI does not affect the pharmacokinetics of telotristat to a clinically significant extent. The median dose normalized $AUC_{0-24,ss}$ for patients between 40-62.5 kg was 10.16 % lower compared to patients with a body weight of 71.2-78.7 kg. The median dose normalized $AUC_{0-24,ss}$ for patients between 87-114.7 kg was 0.78% lower compared to patients with a body weight of 71.2-78.7 kg.

Genetic polymorphism: The influence of genetic polymorphism on the pharmacokinetics of telotristat ethyl and telotristat has not been evaluated.

11 STORAGE, STABILITY AND DISPOSAL

Store XERMELO at room temperature (15°C to 30°C).

Keep out of sight and reach of children.

12 SPECIAL HANDLING INSTRUCTIONS

None.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: telotristat ethyl

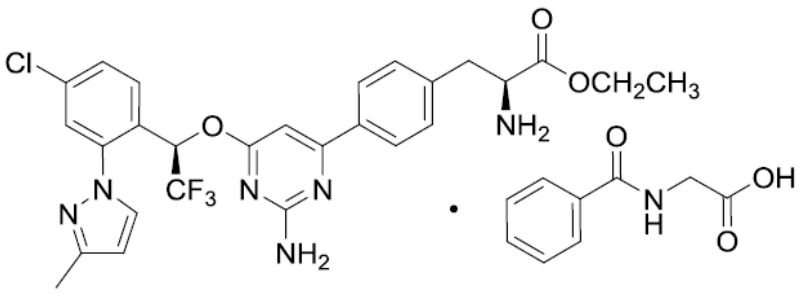
Chemical name: XERMELO tablets contain telotristat ethyl, as telotristat etiprate. Telotristat etiprate is the hippuric acid salt form of telotristat ethyl (the free base).

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).

Molecular formula and molecular mass:

telotristat etiprate:	$C_{27}H_{26}ClF_3N_6O_3 \cdot C_9H_9NO_3$	molecular mass:	754.2 g/mol
telotristat ethyl:	$C_{27}H_{26}ClF_3N_6O_3$	molecular mass:	575.0 g/mol

Structural formula:



Physicochemical properties:

Physical Description:	Telotristat etiprate is a non-hygroscopic white to off-white crystalline powder.
Solubility (25^0C):	<1.1 mg/mL in water pH 1 (0.1N HCL): solubility >71 mg/mL pH 3 phosphate buffer: solubility is 0.30 mg/mL pH 5 to 9: solubility is negligible pH 11 (0.001N NaOH): Drug substance hydrolyses
Polymorphic form:	Form 1
pKa:	pKa 1 = 3.4 (pyrimidine; measured)

pKa 2 = 6.7 (amine, measured)

Partition coefficient: log P = 5.1

Melting Point: 145.5^{0}C and 168.8^{0}C [Differential Scanning Calorimetry (DSC)] onset temperatures

14 CLINICAL TRIALS

14.1 Trial Design and Study Demographics

Two clinical studies, conducted to evaluate the effects of XERMELO in patients with carcinoid syndrome associated with metastatic neuroendocrine tumours, are summarised in Table 4, below.

Table 4 Summary of XERMELO Clinical Trials in the Treatment of Carcinoid Syndrome

Study	Trial design	Dosage, route of administration and duration	Study subjects (n)
LX-301 (TELESTAR)	A phase 3, randomized placebo-controlled parallel-group, multicentre, double-blind study in patients with CS not adequately controlled by a SSA; 12-week double blind treatment, with a 36-week open-label extension (OLE) evaluating telotristat ethyl 500 mg tid.	XERMELO (250 mg) TID, oral telotristat ethyl (500 mg) TID, oral placebo TID, oral telotristat ethyl (500 mg) TID, oral (OLE)	N=45 N=46 N=45 N=115
LX-303 (TELECAST)	A phase 3, randomized placebo-controlled parallel-group, multicentre, double-blind study in patients with CS;12-week double blind treatment, with a 36-week OLE evaluating telotristat ethyl 500 mg tid.	XERMELO (250 mg) TID, oral telotristat ethyl (500 mg) TID, oral placebo TID, oral telotristat ethyl (500 mg) TID, oral (OLE)	N=25 N=25 N=26 N=67

The efficacy and safety of XERMELO 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, randomized, multicentre phase 3 study in adult patients (TELESTAR) which included a 36-week extension during which all patients were treated with open-label telotristat ethyl at 500 mg tid.

A total of 136 patients in the TELESTAR study, with overall mean age of 63.5 years (range: 37-88 years), 52% male, and 90% Caucasian, were randomized 1:1:1 to receive treatment with XERMELO 250 mg or telotristat ethyl 500 mg or placebo three times daily. All patients had well-

differentiated metastatic neuroendocrine tumours with carcinoid syndrome. They were on SSA therapy and had ≥ 4 bowel movements (BM) per day.

The study was comprised of 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=46). During the study, patients were allowed to use rescue medication, i.e., short-acting SSA therapy, and anti-diarrheals for symptomatic relief, but were required to be on a stable dose of long-acting SSA therapy for the duration of the DBT period. XERMELO was taken not more than 15 minutes before, or 1 hour after, food.

14.2 Study Results

TELESTAR Study

The primary efficacy endpoint was the change in the mean number of BM per day from baseline, 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.

The efficacy of XERMELO was demonstrated by significantly greater reductions of BM frequency averaged over 12 weeks for both doses of telotristat ethyl studied, compared to placebo ($p<0.001$). BM frequency was noted to be comparable between XERMELO 250 mg tid and telotristat ethyl 500 mg tid groups. Statistically significant differences were also seen with XERMELO 250 mg tid in reductions in BM frequency at Week 12, in percentage of patients with durable response (Table 5), and in reductions in u5-HIAA excretion over 24 hours at Week 12, compared to placebo.

Table 5 BM response in the TELESTAR Study

	Parameter	XERMELO 250 mg tid	Placebo
BMs/day At Baseline	Number of Patients	45	45
	Baseline Mean (SD)	6.1 (2.07)	5.2 (1.35)
Primary Endpoint: Change From Baseline In BMs/day Averaged Over 12 Weeks	Number of Patients	45	45
	Change Averaged over 12 Weeks: Mean (SD)	-1.4 (1.37)	-0.6 (0.83)
	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	36	35
	Change at Week 12: Mean (SD)	-1.7 (1.71)	-0.9 (1.23)
	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)	---

	Parameter	XERMELO 250 mg tid	Placebo
Percentage Of Patients With Durable Response*	Number of Patients	45	45
	Responder, n (%)	20 (44.4)	9 (20.0)
	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.

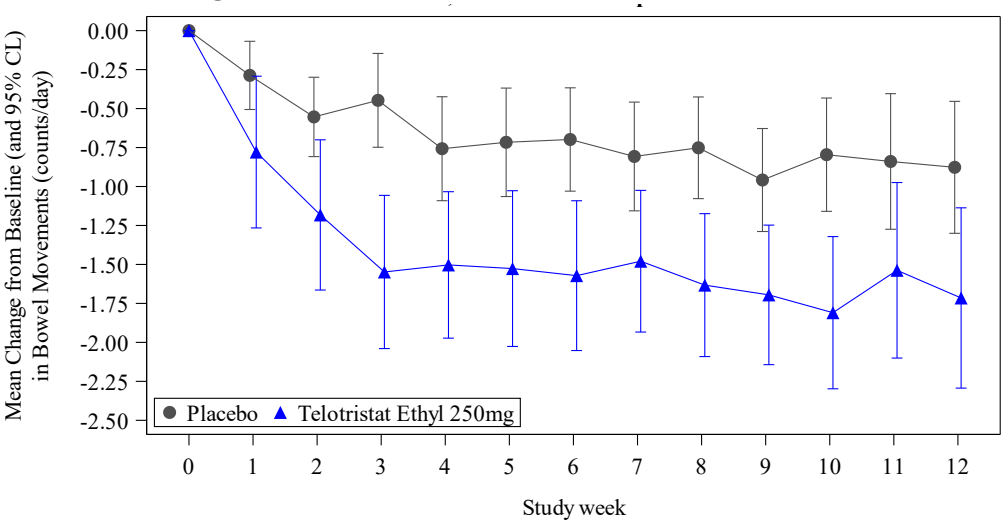
e. p=0.011

* Patients with durable response were defined as responders with ≥30% reduction in number of BM/day for ≥50% of the time during the 12-week double-blind treatment period of the study.

The reductions in urinary 5-HIAA (u5-HIAA) values from baseline were statistically significant at Week 12 for XERMELO 250 mg tid compared to placebo. The u5-HIAA excretion at baseline was 92.6 mg/24hrs for XERMELO 250 mg tid treated patients and 81.0 mg/24 hrs for placebo-treated patients. The percent change from baseline in u5-HIAA excretion at Week 12 was a reduction of 42.3% in XERMELO 250 mg tid treated patients, and an increase of 14.4% in placebo-treated patients, for a significant treatment-related reduction of 56.7% in favour of XERMELO 250 mg tid.

The weekly efficacy results in BM frequency for the 250 mg XERMELO dosage, compared to placebo, are shown in Figure 1.

Figure 1 Mean change from baseline in bowel movements by study week in TELESTAR 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 proportion of patients reporting reductions from baseline in daily BM frequency, averaged over the 12-week DBT period, were:

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

The mean values for cutaneous flushing at baseline were 2.8/day in the XERMELO 250 mg group and 1.8/day for the placebo group, respectively. There was no significant difference between treatment groups for the endpoint of flushing.

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 telotristat ethyl, i.e., 500 mg tid. Mean absolute reductions of approximately 2 BM per day from study entry, and reductions in urinary and plasma 5-HIAA levels, were maintained throughout the open-label extension period.

TELECAST Study

In this study of similar design to the TELESTAR study, a total of 76 patients were evaluated for efficacy. Overall mean age was 63 years (range: 35-84 years), 55% were male, and 97% were Caucasian. All patients had well-differentiated metastatic neuroendocrine tumours with carcinoid syndrome. Most patients (92.1%) had fewer than 4 BM/day, and all except nine (9) were treated with SSA therapy. During the study, patients were allowed to use rescue medication, i.e., short-acting SSA therapy, and anti-diarrheals for symptomatic relief.

The primary endpoint was the change in u5-HIAA at Week 12 from baseline. The mean u5-HIAA excretion at baseline was 69.1 mg/24 hours in the XERMELO 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 -33.2% in the XERMELO 250 mg group, compared to +97.7% in the placebo group and the estimated treatment difference was -54.0% (95% CL: -85.0, -25.1; $p<0.001$).

The mean number of BM/day at baseline was 2.5 and 2.2 in the XERMELO 250 mg tid (n=25) and placebo (n=25) groups, respectively. The observed change from baseline in BM/day, averaged over 12 weeks, was -0.5 and +0.1 BM/day in the XERMELO 250 mg and placebo groups, respectively. There were 10/25 patients (40%) with durable response in the XERMELO 250 mg group, compared to no patients (0%) in the placebo group ($p=0.001$). Durable response is defined in Table 5 above.

TELEPATH Study

The long-term safety and tolerability of XERMELO was evaluated in a phase 3, non-randomized, multicentre, open-label, long-term extension study. Patients having participated in any XERMELO phase 2 or phase 3 carcinoid syndrome studies were eligible to enter the study at the same dose level and regimen as identified in their original study, for at least 84 weeks of treatment. No new significant safety signals were identified.

16 NON-CLINICAL TOXICOLOGY

Repeat dose toxicity

In a 26-week repeat-dose toxicity study in rats, telotristat etiprate was administered at 50, 200 and 500 mg/kg/day once daily. At 200 and 500 mg/kg/day, degeneration/necrosis in the non-glandular and/or glandular portions of the stomach and/or increased protein droplets in the glandular portions were observed. Following a 4-week recovery period, microscopic changes in the gastrointestinal tract were no longer detectable. The relevance of the gastrointestinal findings to humans is not known. The No-Observed Adverse Effect Level (NOAEL) was considered to be 50 mg/kg/day, which is approximately 0.4 times human exposure (based on bound + unbound AUC_{0-24}) at the Maximum Recommended Human Dose (MRHD) of 750 mg/day for the active metabolite LP-778902.

In a 39-week repeat-dose toxicity study in dogs, telotristat etiprate was administered at 75, 150 and 300 mg/kg/day once daily. Clinical signs were limited to an increase in the frequency of liquid feces at all doses. This finding was not considered adverse. The NOAEL was considered to be 300 mg/kg/day, which is approximately 20 times human exposure (based on bound + unbound AUC_{0-24}) at the MRHD of 750 mg/day for the active metabolite LP-778902.

Carcinogenicity

In a 26-week study in transgenic (Tg.rasH2) mice, telotristat etiprate was administered at 30, 100 and 300 mg/kg/day once daily. An increased incidence of neoplastic lesions was not observed. The NOEL for tumourigenic effects was considered to be 300 mg/kg/day, which is approximately 10-15x human exposure (based on bound + unbound AUC0-24 total) at the MRHD of 750 mg/day for the active metabolite LP-778902.

In a 104-week study in rats, telotristat etiprate did not increase the incidence of tumours at doses corresponding to an exposure of approximately 2-4.5x the human exposure to the active metabolite at the MRHD.

Genotoxicity

Telotristat etiprate 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. The active metabolite, telotristat, was also evaluated the *in vitro* Ames test and the *in vitro* chromosomal aberration test using Chinese hamster ovary cells, and the results were negative.

Reproductive and Developmental Toxicity

In a fertility and early embryonic development study in rats, telotristat etiprate was administered at 100, 200 and 500 mg/kg/day once daily. There were no adverse effects on male and female fertility and the NOAEL was considered to be 500 mg/kg/day for parental toxicity, and embryo/fetal viability, which is approximately 2-3x human exposure (based on bound + unbound AUC_{0-24}) at the MRHD of 750 mg/day for the active metabolite LP-778902.

In an embryo-fetal development study in rats, telotristat etiprate was administered at 250, 500 and 750 mg/kg/day once daily from Gestation Day 7 through to 17. Maternal toxicity (mortality, impaired bodyweight gain, and decreased food consumption) was noted at 750 mg/kg/day. No adverse effects on embryo-fetal development, including teratogenicity, were noted. The NOAEL

was considered to be 500 mg/kg/day for maternal toxicity and ≥ 750 mg/kg/day for embryo-fetal development which is, respectively, approximately 4x and 7x human exposure (based on bound + unbound AUC_{0-24} total) at the MRHD of 750 mg/day for the active metabolite LP-778902.

In an embryo-fetal development study in rabbits, telotristat etiprate was administered at 125, 250 and 500 mg/kg/day once daily from Gestation Day 7 through to 19. Maternal toxicity (mortality, impaired body weight gain, decreased food consumption) was noted at 250 and 500 mg/kg/day. Maternal toxicity was associated with post-implantation loss at the same dose levels and decreased fetal weight at 500 mg/kg/day. Teratogenicity was not observed. The NOAEL for maternal toxicity and embryo-fetal development was considered to be 125 mg/kg/day, which is approximately 4x human exposure (based on bound + unbound AUC_{0-24} total) at the MRHD of 750 mg/day for the active metabolite LP-778902.

In a pre- and post-natal develop study in rats, telotristat etiprate was administered at 100, 200 and 500 mg/kg/day once daily from Gestation Day 6 to Lactation Day 20. Maternal toxicity was not observed. In pups born to dams dosed at 500 mg/kg/day, an increased incidence of mortality was observed from post-natal days 0-4. In surviving offspring, no other abnormalities were detected with respect to growth, development, learning and memory, or reproductive performance. The NOAEL was considered to be 500 mg/kg/day for maternal toxicity and 200 mg/kg/day for surviving offspring which is, respectively, approximately 4x and 2x human exposure (based on bound + unbound AUC_{0-24} total) at the MRHD of 750 mg/day for the active metabolite LP-778902.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

XERMELO™
telotristat ethyl tablets

Read this carefully before you start taking **XERMELO** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **XERMELO**.

What is XERMELO used for?

- This medicine is used in adults to treat diarrhea caused by a condition called 'carcinoid syndrome'.
- XERMELO is used if your diarrhea is not well controlled with injections of other medicines called 'somatostatin analogues' (lanreotide or octreotide). You should keep having injections of these other medicines when taking XERMELO.

How does XERMELO work?

Carcinoid syndrome happens when a cancerous tumour releases chemicals into your bloodstream causing symptoms, such as:

- Diarrhea and stomach (abdominal) pain
- Flushing of your skin, particularly the face
- Low blood pressure
- Rash
- Weight loss

The symptoms are not the same for everyone. XERMELO works by reducing the amount of a chemical called serotonin, made by the tumour. This can reduce the number of bowel movements you are having.

What are the ingredients in XERMELO?

Medicinal ingredients: telotristat ethyl (as telotristat etiprate)
Non-medicinal ingredients: croscarmellose sodium, hydroxypropylcellulose, lactose anhydrous, macrogol 3350, magnesium stearate, polyvinyl alcohol - partially hydrolysed, silica, colloidal anhydrous, talc, titanium dioxide

XERMELO comes in the following dosage forms:

Tablets: 250 mg Telotristat ethyl (as telotristat etiprate)

Do not use XERMELO if:

- you are allergic to telotristat or any of the other ingredients of this medicine.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take XERMELO. Talk about any health conditions or problems you may have, including if you:

- have liver problems.
- have severe kidney problems, end-stage kidney disease and/or are on dialysis.
- are intolerant to some sugars, since lactose is an ingredient in XERMELO**.**
- are pregnant, think you may be pregnant or are planning to become pregnant. XERMELO is not recommended during pregnancy.
- are breastfeeding or planning to breastfeed. You should not breastfeed while taking XERMELO. It is not known if XERMELO passes into breastmilk.
- have a gastrointestinal obstruction including constipation or narrowing of the large intestine (strictures) or any disease that affects the movement of your bowels. This is because taking XERMELO can cause intestinal obstruction. This is a blockage that stops or impairs food and liquid from passing through your intestines. These conditions may make you at a higher risk for an intestinal obstruction during your treatment.

Other warnings you should know about:
Liver Problems
Your healthcare professional will do blood tests before you start taking XERMELO and while you are taking it. This is to check that your liver is working normally.

Tell your healthcare professional immediately if you notice any of the following signs and symptoms. These can suggest a problem with your liver:
- feeling or being sick (unexplained nausea or vomiting), abnormally dark urine, yellow skin or eyes, pain in the upper right belly.

Constipation
XERMELO reduces the number of bowel movements you are having. In some cases however, it can reduce the number of bowel movements too much causing constipation. Sometimes, the constipation can be severe. If you notice you are not having very many bowel movements or you think you might be constipated talk to your healthcare professional.

Depression
Some patients taking XERMELO have had symptoms of depression, depressed mood and loss of interest.

Birth Control
Women should use effective methods of birth control while taking XERMELO. Talk to your healthcare professional about the birth control options that are right for you.

Children and Adolescents
XERMELO is not recommended in patients below 18 years old.

Driving and Using Machines
XERMELO may affect your ability to drive or use any tools or machines. If you feel tired, you should wait until you feel better before driving or using any tools or machines.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with XERMELO:

- medicines for diarrhea. XERMELO and these medicines both reduce the number of bowel movements you have and taken together, they can cause severe constipation.
- medicines used to treat epilepsy, such as valproic acid
- medicines used to treat your neuroendocrine tumour, such as sunitinib or everolimus
- medicines to treat depression, such as bupropion or sertraline
- medicines used to avoid transplant rejection, such as cyclosporine
- medicines used to lower cholesterol levels, such as simvastatin
- oral birth control that contains estrogen
- medicines used to treat high blood pressure, such as amlodipine
- midazolam, used before surgery to make you sleepy and less anxious
- medicines used to treat some types of cancers, such as irinotecan, capecitabine and flutamide
- medicines used to reduce the chance of a blood clot forming, such as prasugrel
- octreotide, which is used in the treatment of cancerous tumours called carcinoid tumours.

How to take XERMELO:

- Always take XERMELO exactly as your healthcare professional has told you. Check with your healthcare professional if you are not sure.
- Your healthcare professional will decide how long you should take XERMELO. Do not stop taking XERMELO without talking to your healthcare professional.
- Always take XERMELO with a meal or some food.
- You should keep having injections of somatostatin analogues (lanreotide or octreotide) when taking XERMELO.
- If you are being treated with short-acting octreotide subcutaneous injection, it must be given 30 minutes after XERMELO.

Usual dose:

The recommended adult dose is one tablet (250 mg) three times a day.
If you have liver problems, your healthcare professional may decide to reduce your daily dose of XERMELO.

Overdose:

If you take too much XERMELO you may feel sick, vomit, have diarrhea or a stomach ache. If this happens, talk to a healthcare professional. Take the medicine pack with you.

If you think you, or a person you are caring for, have taken too much XERMELO, contact a healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you forget to take a dose, skip that dose and take your next dose when it is due.
Do not take a double dose to make up for a forgotten dose.

What are possible side effects from using XERMELO?

These are not all the possible side effects you may feel when taking XERMELO. If you experience any side effects not listed here, contact your healthcare professional.

- Stomach (abdominal) pain
- Dizziness
- Feeling tired or weak (fatigue)
- Gas
- Fever
- Headache
- Swollen stomach
- Decreased appetite
- Nausea
- Dry skin
- Rash
- Flushing
- Urinary tract infection

XERMELO can cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
UNKNOWN **Liver Problems:** yellow skin or eyes, abnormally dark urine, pain in upper right belly, nausea, vomiting, loss of appetite		**X**	
COMMON **Constipation:** passing a small number of stools in a week or no stool at all, hard, lumpy stool, straining to have a bowel movement		**X**	
Peripheral Edema: swelling of the legs, ankles or feet	**X**		
Depression: feeling sad, depressed mood, loss of interest in daily activities		**X**	
VERY RARE **Intestinal obstruction** (blockage that stops or impairs food and liquid from passing through your intestines):			**X**

cramping pain in abdomen that may begin suddenly, bloating, loss of appetite, pain that comes and goes but will then last, nausea and vomiting, constipation or diarrhea			

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15˚C and 30˚C).

Keep out of reach and sight of children.

Do not use this medicine after the expiry date which is stated on the carton and the blister after EXP. The expiry date refers to the last day of that month.

If you want more information about XERMELO:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website at https://www.canada.ca/en/health-canada.html; the manufacturer's website at www.ipsen.ca or by calling 1-855-215-2288.

This leaflet was prepared by Ipsen Biopharmaceuticals Canada Inc.

Last Revised: January 4, 2022