ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Xermelo 250 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains telotristat etiprate equivalent to 250 mg telotristat ethyl.

Excipient with known effect

Each tablet contains 168 mg of lactose.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

White to off-white film-coated oval tablets (approximately 17 mm long by 7.5 mm wide) 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 analogue (SSA) therapy in adults inadequately controlled by SSA therapy.

4.2 Posology and method of administration

Posology

The recommended dose is 250 mg three times daily (tid).

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).

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 population

Elderly

No specific dose recommendations are available for elderly patients (see section 5.2).

Renal impairment

No change in dose is required in patients with mild, moderate or severe renal impairment; who are not requiring dialysis (see section 5.2). 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 requiring dialysis) because efficacy and safety of Xermelo in these patients have not been established.

Hepatic impairment

In patients with mild hepatic impairment (Child Pugh score A), it may be necessary to reduce the dose to 250 mg twice daily according to tolerability. In patients with moderate hepatic impairment (Child Pugh score B), it may be necessary to reduce the dose to 250 mg once daily according to tolerability. The use of telotristat is not recommended in patients with severe hepatic impairment (Child Pugh score C) (see section 5.2).

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 sections 5.1 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Hepatic enzymes elevations

Elevations in hepatic enzymes were observed in clinical studies (see section 4.8). 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 reactions 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 studies and from post- marketing in some patients treated with telotristat (see section 4.8). Patients should be advised to report any symptoms of depression, depressed mood and decreased interest to their physicians.

Excipients

Lactose
Xermelo contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products 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).
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.

Carboxylesterase 2 (CES2) inhibitors
The IC_{50} of the inhibition of loperamide on the metabolism of telotristat ethyl by CES2 was 5.2 µM (see section 5.2). In phase 3 clinical studies, telotristat was routinely combined with loperamide with no evidence of safety concerns.

Effect of Xermelo on other medicinal products

CYP2B6 substrates
Telotristat induced CYP2B6 *in vitro* (see section 5.2). 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.

CYP3A4 substrates
Concomitant use of Xermelo may decrease the efficacy of medicinal products that are CYP3A4 substrates (e.g. midazolam, everolimus, sunitinib, simvastatin, ethinyloestradiol, amlodipine, cyclosporine…) by decreasing their systemic exposure (see section 5.2). Monitoring for suboptimal efficacy is recommended.

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) (see section 5.2). If co-administration is unavoidable, monitor for suboptimal efficacy and adverse reactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

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

Pregnancy

There are no data from the use of telotristat ethyl in pregnant women. Animal studies have shown reproductive toxicity (see section 5.3). Xermelo is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

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

Fertility

No studies on the effect of telotristat on human fertility have been conducted. Telotristat had no effect on fertility in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

Xermelo has minor influence on the ability to drive and use machines. Fatigue may occur following administration of telotristat, patients with fatigue should be advised to refrain from driving or using machines until symptoms have subsided. (see section 4.8).

4.8 Undesirable effects

Summary of the 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 tid in combination with SSA therapy in placebo-controlled clinical studies 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 dose of 500 mg 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.

Gastrointestinal disorders
The most frequently reported adverse event in patients receiving telotristat ethyl 250 mg tid 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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

Symptoms

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

Management

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 gastrointestinal 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 tid) 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 (refer to Table 3 for TELESTAR and information provided for TELECAST). Statistically significant reductions in u5-HIAA were seen for telotristat ethyl 250 mg tid compared with placebo in both phase 3 studies.

Clinical efficacy and safety

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 were evaluated for efficacy. The mean age was 64 years (range 37 to 88 years), 52% were male and 90% were white. All patients had well-differentiated metastatic neuroendocrine tumours and carcinoid syndrome. They were on SSA therapy and had ≥ 4 daily BM.

The study included a 12-week double-blind treatment (DBT) period, in which patients initially received placebo (n = 45), telotristat ethyl 250 mg (n = 45) or a higher dose (telotristat ethyl 500 mg; n = 45) tid. During the study, patients were allowed to use rescue medicinal product (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.

Table 2: BM response (TELESTAR study)

	Parameter	Placebo	Telotristat ethyl 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)
ANCOVA[a]	Least square mean difference	---	-0.6
	97.5% CL for difference	---	-1.16, -0.06
	p value	---	0.01
Percentage of patients with durable response[b]	Number of patients	45	45
	Responder, n (%)	9 (20.0)	20 (44.4)[c]

Parameter	Placebo	Telotristat ethyl 250 mg tid

BM = bowel movement; CL=confidence limit; tid=three times daily; SD=standard deviation.

a. Analysis of covariance including treatment group and urinary 5-HIAA stratification at randomisation as fixed effects, and the baseline number of BM as a fixed covariate.

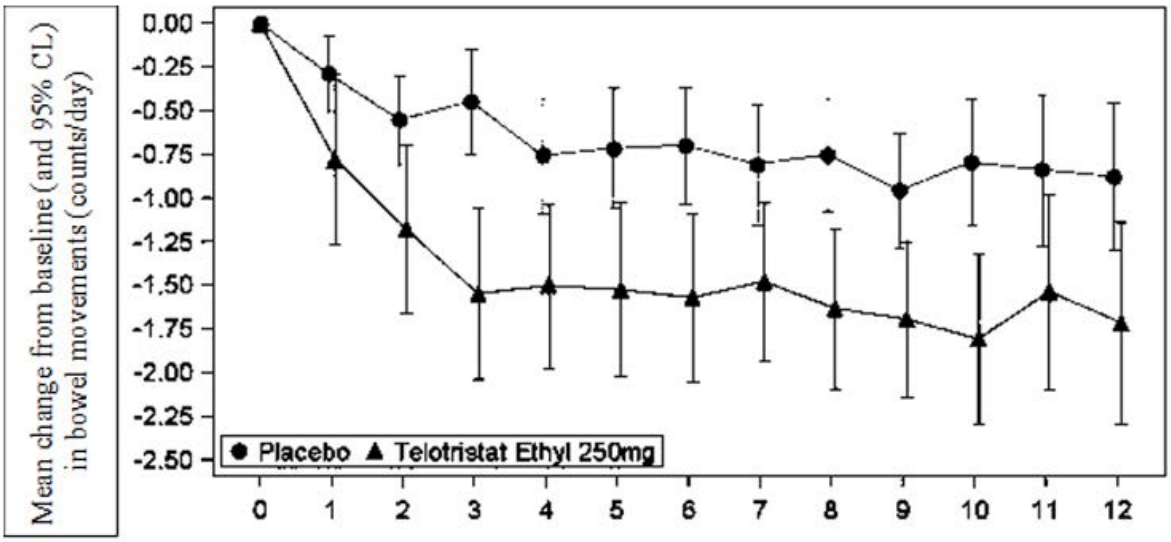
b. Defined as the proportion of responders with ≥ 30% reduction in daily number of BMs for ≥ 50% of time over the DBT period.

c. p =0.01

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 BMs by study week during the DBT 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	Telotristat ethyl 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)
	Estimate of treatment difference (95% CL)[b]	---	-53.4 [c] (-69.32, -38.79)

CL=confidence limit; tid=three times daily; SD=standard deviation; u5-HIAA = urinary 5-hydroxyindoleacetic acid.

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 randomisation. 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 telotristat. The proportions of patients who were "very satisfied" were 0/9 (0%) on placebo, 5/9 (56%) on telotristat ethyl 250 mg tid and 7/15 (47%) on a higher dose of telotristat ethyl.

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 telotristat ethyl (500 mg) tid.

In a phase 3 study of similar design (TELECAST), a total of 76 patients were evaluated for efficacy. The mean age was 63 years (range 35 to 84 years), 55% were male and 97% were 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/24 hours 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.

The mean number of daily BM at baseline was 2.2 and 2.5 respectively in the placebo (n =25) and 250 mg group (n = 25). The change from baseline in daily BM averaged over 12 weeks was + 0.1 and -0.5 in the placebo and 250 mg groups respectively. Telotristat ethyl 250 mg showed that stool consistency, as measured by Bristol Stool Form Scale, was improved compared with placebo. There were 40% patients (10/25) with durable response (as defined in Table 2) in the telotristat ethyl 250 mg group, versus 0% in the placebo group (0/26) (p = 0.001).

The long-term safety and tolerability of telotristat was evaluated in a nonpivotal (nonrandomised), phase 3, multicentre, open-label, long-term extension study. Patients having participated in any Xermelo phase 2 or phase 3 carcinoid syndrome study 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.
The secondary objective of this study was to evaluate changes in patients' quality of life (QOL) through week 84. QOL was generally stable over the course of the study.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Xermelo in all subsets of the paediatric population in the treatment of carcinoid syndrome (see section 4.2 for information on paediatric use).

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 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 2 320 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.

Biotransformation

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 (active metabolite) in the mass balance study. LP-951757 was pharmacologically inactive at TPH1 *in vitro*.

Interactions

Cytochromes
CYP2B6

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 (see section 4.5).

CYP3A4

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 engages in an allosteric interaction with CYP3A4 resulting at the same time in a reduced conversion of midazolam to 1'-OH-MDZ, and increased conversion to 4-OH-MDZ.

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 (see section 4.5). When 3 mg midazolam was coadministered orally after 5-day treatment with telotristat ethyl 500 mg tid (twice the recommended dose), the mean C_{max}, and AUC0-inf for midazolam were decreased by 25%, and 48%, respectively, compared with administration of midazolam alone. The mean C_{max}, and AUC0-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.

Carboxylesterases
The IC_{50} of the inhibition of loperamide on the metabolism of telotristat ethyl by CES2 was 5.2 µM (see section 4.5).
In vitro, telotristat ethyl inhibited CES2 with an IC50 approximately of 0.56 µM.

Transporters
P-glycoprotein (P-gp) and multi-drug resistance associated protein 2 (MRP-2)

In vitro telotristat ethyl inhibited P-gp, but its active metabolite did not at the clinically relevant concentrations.
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.

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 normal healthy volunteers showed an 86% and 81% decrease in geometric mean C_{max} and $AUC_{0\text{-}tlast}$ of telotristat ethyl (see section 4.5). Reduced exposures were not observed in a 12◦week double-blind, placebo-controlled, randomised, multicentre clinical study in adult patients with carcinoid syndrome on long-acting SSA therapy

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 × more active than telotristat ethyl, no dose adjustments are required when using Xermelo with acid reducers.

Elimination

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.

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.

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 tid, 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.

Special 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 to investigate the impact of renal impairment on the pharmacokinetics of a single dose of telotristat ethyl 250 mg. Eight subjects with severe to moderate 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 this study.
In the subjects with severe to moderate renal impairment, an increase (1.3-fold) in peak exposure Cmax of telotristat ethyl and an increase (< 1.52-fold) in plasma exposure (AUC) and Cmax of its

active metabolite telotristat was observed compared to healthy to mildly impaired subjects. Variability of the main plasma telotristat PK parameters was higher in subjects with severe to moderate renal impairment, with CV% ranging from 53.3% for Cmax to 77.3% for AUC as compared to 45.4% for Cmax and 39.7% for AUC in healthy to mildly impaired subjects, respectively.

Administration of a single dose of 250 mg was well tolerated in subjects with severe to moderate renal impairment.

Overall, severe to moderate 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.

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 compound 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 score A and B) based on tolerability (see section 4.2).

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_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 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 score C) (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeat dose toxicity, genotoxicity, carcinogenic potential.

In rats decrease in brain serotonin (5-HT) was observed at doses ≥ 1 000 mg/kg/day of telotristat etiprate per os. Brain 5-HIAA levels were unchanged at all doses of telotristat ethyl examined. This is approximately 14 times the human exposure (AUC total) at the maximum recommended human dose (MRHD) of 750 mg/day for the active metabolite LP-778902.

In a 26-week repeat-dose toxicity study in rats a No-Observed Adverse Effect Level (NOAEL) of 50 mg/kg/day was determined. This is approximately 0.4 times the human exposure (AUC total) at MRHD of 750 mg/day for the active metabolite LP-778902. At doses of 200 and 500 mg/kg/day degeneration/necrosis in the nonglandular and/or glandular portions of the stomach and/or increased protein droplets in the glandular portions were observed. The microscopic changes in the gastrointestinal tract reversed with a 4-week recovery period. Relevance of these gastrointestinal findings to humans is unknown.

In dogs decreases in brain 5-HT and 5-HIAA levels were observed at dose of 200 mg/kg/day and 30 mg/kg/day of telotristat etiprate per os, respectively. This is approximately 21 times the human exposure (AUC total) at MRHD of 750 mg/day for the active metabolite LP-778902. No decrease in brain 5-HT and 5-HIAA levels were observed after intravenous application of active metabolite. The

clinical significance of the decrease in brain 5-HIAA with or without a concomitant decrease in brain 5-HT is unknown.

In a 39-week repeat-dose toxicity study in dogs NOAEL of 300 mg/kg/day was determined. Clinical signs were limited to increase in frequency of liquid faeces at all doses. This is approximately 20 times the human exposure (AUC total) at MRHD of 750 mg/day for the active metabolite LP-778902.

The carcinogenic potential of telotristat etiprate was studied in transgenic mice (26 weeks) and rats (104 weeks). These studies confirmed that telotristat did not increase the incidence of tumours in both species and sexes, at doses corresponding to an exposure of approximately 10- to 15-fold and 2- to 4.5-fold the human exposure to the active metabolite at the MRHD in mice and rats, respectively.

In rats, there were no adverse effects on male and female fertility. Prenatal development in rats and rabbits was affected by increased prenatal lethality (increased early and late resorptions), while no adverse effects were noted on postnatal development in rats. The NOAEL for parental/maternal/prenatal and postnatal toxicity is 500 mg/kg/day in rats corresponding to 3 to 4 times the estimated human exposure (AUC_{0-24}) of the active metabolite LP-778902 at the MRHD. In rabbits the NOAEL for maternal and prenatal toxicity is 125 mg/kg/d corresponding to 1.5 to 4 times the estimated human exposure (AUC_{0-24}) of the active metabolite LP-778902 at the MRHD.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Lactose
Hydroxypropylcellulose
Croscarmellose sodium
Magnesium stearate
Colloidal anhydrous silica

Film-coating

Poly(vinyl alcohol) (E1203)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Talc (E553b)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PCTFE/PVC/Al blister
The blisters are packaged in a carton.

Pack sizes of 90 and 180 film-coated tablets. Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

SERB SAS
32 rue de Monceau
75008 Paris
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1224/001
EU/1/17/1224/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2017
Date of latest renewal: 14 June 2022

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

SERB SAS
32 rue de Monceau
75008 Paris
France

Tjoapack Netherlands B.V.
Nieuwe Donk 9
4879 AC Etten-Leur
Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.
An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Xermelo 250 mg film-coated tablets
telotristat ethyl

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains telotristat etiprate equivalent to 250 mg telotristat ethyl.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

film-coated tablet

90 film-coated tablets
180 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused medicinal product or waste should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

SERB SAS
32 rue de Monceau
75008 Paris
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1224/001
EU/1/17/1224/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

xermelo

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Xermelo 250 mg film-coated tablets
telotristat ethyl

2. NAME OF THE MARKETING AUTHORISATION HOLDER

SERB SAS

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Xermelo 250 mg film-coated tablets
telotristat ethyl

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Xermelo is and what it is used for

What Xermelo is
This medicine contains the active substance telotristat ethyl.

What Xermelo is used for
This medicine is used in adults with a condition called 'carcinoid syndrome'. This is when a tumour, called a 'neuroendocrine tumour', releases a substance called serotonin into your bloodstream.

Your doctor will prescribe this medicine if your diarrhoea 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 Xermelo works
When the tumour releases too much serotonin into your bloodstream you can get diarrhoea.
This medicine works by reducing the amount of serotonin made by the tumour. It will reduce your diarrhoea.

2. What you need to know before you take Xermelo

Do not take Xermelo
- if you are allergic to telotristat or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor or pharmacist before taking Xermelo:
- if you have liver problems. This is because this medicine is not recommended for use in patients with severe liver problems. Your doctor may decide to decrease your daily dose of Xermelo in cases where your liver problems are considered mild or moderate. Your doctor will also monitor your liver.

- if you have end-stage kidney disease or are on dialysis. This is because this medicine has not been tested in patients with end-stage kidney disease, requiring dialysis.

Look out for side effects
Tell your doctor straight away if you notice any of the following signs and symptoms that suggest that your liver may not be working properly:
- feeling or being sick (unexplained nausea or vomiting), abnormally dark urine, yellow skin or eyes, pain in the upper right belly.

Your doctor will do blood tests to check your liver and will decide whether you should keep taking this medicine.

Talk to your doctor or pharmacist:
- if you feel down, depressed, or if you feel you have no interest or take any pleasure in doing your normal activities, whilst taking this medicine, as depression, depressed mood and decreased interest have been reported in patients treated with telotristat.
- if you have signs of constipation, as telotristat reduces the number of your bowel movements.

Tests
- Your doctor may carry out blood tests before you start taking this medicine and while you are taking it. This is to check that your liver is working normally.

Children and adolescents
This medicine is not recommended in patients below 18 years old. This is because the medicine has not been studied in this age group.

Other medicines and Xermelo
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Xermelo can affect the way some other medicines work, or other medicines can affect the way Xermelo works. This could mean that your doctor needs to change the dose(s) that you take. You should tell your doctor about every medicine. This includes:
- medicines for diarrhoea. Xermelo and these medicines reduce the number of your bowel movements and taken together, they can cause severe constipation. Your doctor may need to change the dose of your medicines.
- 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 contraceptives, such as ethinyloestradiol.
- medicines used to treat high blood pressure, such as amlodipine.
- 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. If you need treatment with octreotide subcutaneous injections, you should have your injection at least 30 minutes after taking Xermelo.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you might be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
You should not take this medicine if you are pregnant or might become pregnant. It is not known how telotristat may affect the baby.
Women should use effective methods of contraception while taking this medicine.
You should not breast-feed if you are taking Xermelo, as this medicine may be passed on to your baby and may harm your baby.

Driving and using machines
Xermelo may have a small effect on 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.

Xermelo contains lactose
Xermelo contains lactose (a type of sugar). If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

Xermelo contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

3. How to take Xermelo

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

How much to take
The recommended dose is one tablet (250 mg) three times a day. The maximum dose of Xermelo is 750 mg in 24 hours.
Your doctor will decide for how long you should take Xermelo.
If you have liver problems, your doctor may decide to reduce your daily dose of Xermelo.

Taking this medicine
- Always take this medicine with a meal or some food.
- You should keep having injections of somatostatin analogues (lanreotide or octreotide) when taking Xermelo.

If you take more Xermelo than you should
You may feel sick or be sick, have diarrhoea or stomach ache. Talk to a doctor. Take the medicine pack with you.

If you forget to take Xermelo
If you forget to take a dose, take your next dose when it is due, skipping the missed dose.
Do not take a double dose to make up for a forgotten dose.

If you stop taking Xermelo
Do not stop taking Xermelo without talking with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor immediately if you notice any of the following side effects:
- feeling or being sick, abnormally dark urine, yellow skin or eyes, pain in the upper right belly. These may be signs that your liver is not working properly. This might also be shown by changes in your blood test results, such as an increase of liver enzymes: gamma-glutamyl transferase (very common, may affect more than 1 in 10 people), transaminases and blood alkaline phosphatase (common, may affect up to 1 in 10 people).

Other side effects
Tell your doctor, pharmacist or nurse if you notice any of the following side effects**:**

Very common side effects (may affect more than 1 in 10 people):
- Belly (abdominal) pain
- Feeling tired or weak (fatigue)
- Feeling sick (nausea)

Common side effects (may affect up to 1 in 10 people):
- Wind
- Fever
- Headache
- Constipation
- Swollen stomach
- Decreased appetite
- Swelling (build-up of fluid in the body)
- Depression, you may experience decreased self-esteem, lack of motivation, sadness or low mood

Uncommon side effects (may affect up to 1 in 100 people):
- Impacted stools (bowel obstruction, faecaloma), you may experience, constipation, watery diarrhoea, pale skin (anaemia), nausea, vomiting, weight loss, back pain or stomach pains particularly after eating or a reduction in passing water (urination).
  Tell your doctor immediately if you experience any of the following side effects:
- Breathing problems, rapid heartbeat, fever, incontinence (uncontrollable urination), confusion, dizziness or agitation.

Tell your doctor, pharmacist or nurse if you notice any of the side effects listed above**.**

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Xermelo

Keep this medicine out of the sight and reach 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.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

This medicine does not require any special storage conditions.

6. Contents of the pack and other information

What Xermelo contains
- The active substance is telotristat ethyl. Each film-coated tablet contains telotristat etiprate equivalent to 250 mg telotristat ethyl.
- The other ingredients are:
  Tablet core: lactose (see section 2 under ‘Xermelo contains lactose’), hydroxypropylcellulose, croscarmellose sodium, magnesium stearate and colloidal anhydrous silica.

Film-coating: poly(vinyl alcohol) (E1203), titanium dioxide (E171), macrogol 3350 (E1521) and talc (E553b).

What Xermelo looks like and contents of the pack
The tablets are white to off-white, film-coated and oval shaped. Each tablet is approximately 17 mm long by 7.5 mm wide with 'T-E' debossed on one side and '250' debossed on the other. The tablets are packaged in a PVC/PCTFE/PVC/Al blister. The blisters are packaged in a carton.

Cartons of 90 and 180 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder
SERB SAS
32 rue de Monceau
75008 Paris
France

Manufacturer
SERB SAS
32 rue de Monceau
75008 Paris
France

Tjoapack Netherlands B.V.
Nieuwe Donk 9
4879 AC Etten-Leur
Netherlands

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.