**Xermelo 250 mg**
(telotristat)
Film-coated tablets

**Elements for a Public Summary -**
*Summary of the Safety Risk Management Plan (RMP)*

Reference RMP EU RMP version 3.0
Products concerned (brand names): Xermelo 250 mg
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1 INTRODUCTION
The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary for “Xermelo” is a concise document and does not claim to be exhaustive. Please note that the reference document that is valid and relevant for the effective and safe use of “Xermelo” in Switzerland is the “Arzneimittelinformation/Information sur le medicament” (see www.swissmedic.ch) approved and authorised by Swissmedic. Future Health Pharma GmbH is fully responsible for the accuracy and correctness of the content of the published RMP summary for “Xermelo”.

As the RMP is an international document, the summary might differ from the “Arzneimittelinformation / Information sur le medicament” approved and published in Switzerland, eg, by mentioning risks occurring in populations or indications not included in the Swiss marketing authorisation.

2 OVERVIEW OF DISEASE EPIDEMIOLOGY
Well-differentiated neuroendocrine tumour (called NET but previously known as carcinoid tumour) is a rare type of tumour of the neuroendocrine system – the body system that produces hormones. Around 12,000 new cases occur per year in the European Union (EU). The average age of patients diagnosed with these tumours is around 61 years and they are slightly more common in women than in men.

Carcinoid syndrome (CS) is the name for the symptoms some people get when a NET releases hormones into the bloodstream. CS develops in between 7% and 35% of patients with NETs, and in the EU, around 35,000 patients are estimated to have CS, which most commonly affects people with tumours of the small intestine that have spread to the liver. Symptoms include diarrhoea, stomach pain, loss of appetite, flushing of the skin (particularly the face), fast heart rate, breathlessness and wheezing. Roughly 70% of patients with CS experience diarrhoea.

3 SUMMARY OF TREATMENT BENEFITS
Carcinoid syndrome (CS) is caused by a NET that secretes serotonin or other chemicals into the bloodstream. Currently, there are few treatment options for CS. If detected early, a NET can be removed through surgery. However, once the tumour has spread, treatment may include drugs called SSAs, chemotherapy and other therapies to help to stop the tumour progressing and help manage the symptoms. Telotristat reduces serotonin production.

Clinical studies have tested telotristat in patients who had carcinoid syndrome and whose tumour had spread (metastatic). In these studies, patients who received telotristat (70 patients had the 250 mg dose and 70 patients had the 500 mg dose) had a reduction in the number of bowel movements per day compared to patients who took the placebo (dummy treatment given to 71 patients) over 12 weeks. After these 12 weeks, patients could continue to take telotristat and in these patients the reduction in bowel movements per day was maintained.

4 UNKNOWNS RELATING TO TREATMENT BENEFITS
In the telotristat clinical trial development programme, the effectiveness of the drug was investigated using correctly chosen and clinically relevant assessments. The data gained from the clinical studies can generally be applied to all patients with carcinoid syndrome.
The clinical studies included 75 patients between 65 and 75 years of age and 30 patients over 75 years old. No adjustment in the dose of telotristat is required for elderly patients and the safety profile in the elderly is similar to that observed in adults under 65 years old.

Nearly all patients included in the clinical studies investigating the effectiveness of telotristat were White. However a significant number of Black patients were included in the initial investigations of telotristat and no difference in the effectiveness, safety and tolerability of telotristat in non-White patients is anticipated.

5 SUMMARY OF SAFETY CONCERNS

5.1 Important Identified Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
<th>Preventability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Patients may experience constipation, which is among the most common side-effects of telotristat treatment. Constipation is usually mild or moderate, and does not usually result in treatment being stopped. However, constipation should be monitored and treated if necessary to avoid the development of severe constipation.</td>
<td>Symptoms should be monitored and ongoing treatment should be assessed if constipation develops.</td>
</tr>
<tr>
<td>Abnormal liver (hepatic) tests</td>
<td>Abnormal liver tests occurred in some patients who were treated with telotristat in clinical studies. These changes are not usually serious and some patients improved by stopping or reducing their dose of telotristat.</td>
<td>Monitoring of the levels of specific liver tests prior to and during telotristat therapy is recommended. Liver tests should be carried out if patients develop new and unexplained symptoms such as nausea, yellowing of the eyes or skin (jaundice), abnormally dark urine or pain in the upper right belly.</td>
</tr>
</tbody>
</table>

5.2 Important Potential Risks

<table>
<thead>
<tr>
<th>Risk</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression and other depression-related events</td>
<td>Depression, depressed mood and loss of interest in daily activities have occurred in patients who are treated with telotristat and in patients on placebo (dummy treatment). Many patients had alternative explanations and a causal role of telotristat has not been established. Patients with carcinoid syndrome are at higher risk of depression.</td>
</tr>
<tr>
<td>Faecaloma (build-up of thickened, stone-like faeces) and intestinal obstruction</td>
<td>In patients who are treated with telotristat, there have been reports of the build-up of thickened, stone-like faeces (called faecaloma). However, very few patients have experienced this. There were only two reports of serious faecaloma and these were seen in patients taking a dose of 500 mg three times daily, which is double the recommended dose of 250 mg three times daily. In some patients treated with telotristat, there have been reports of intestinal obstruction, which is a blockage leading to a lack of bowel movements. Intestinal obstruction can be caused by the underlying carcinoid tumor or by other medications, such as opiates prescribed for pain relief. However, we are not certain whether or not telotristat itself can cause intestinal obstruction.</td>
</tr>
</tbody>
</table>

5.3 Missing Information

<table>
<thead>
<tr>
<th>Missing information</th>
<th>What is known</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use in pregnancy</td>
<td>Pregnant women were excluded from telotristat clinical trials. Women who could become pregnant should use contraception during treatment with telotristat.</td>
</tr>
<tr>
<td>Use in breast-feeding (lactation)</td>
<td>Breast-feeding women were excluded from telotristat clinical trials. Patients should not breast-feed during treatment with telotristat.</td>
</tr>
</tbody>
</table>
6 SUMMARY OF RISK MINIMISATION MEASURES BY SAFETY CONCERN

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, and the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the patient information leaflet for patients. The measures in these documents are known as routine risk minimisation measures.

No additional risk minimisation measures are proposed.

7 PLANNED POSTAUTHORISATION DEVELOPMENT PLAN

7.1 List of Studies in Postauthorisation Development Plan

<table>
<thead>
<tr>
<th>Study/activity, category</th>
<th>Objectives</th>
<th>Safety concern addressed</th>
<th>Status</th>
<th>Date for submission of interim or final reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 301: A Phase III, Randomised, Placebo-controlled, Parallel-group, Multicentre, Double-blind Study to Evaluate the Efficacy and Safety of Telotristat Etiprate (LX1606) in Patients with Carcinoid Syndrome Not Adequately Controlled by Somatostatin Analog (SSA) Therapy Category 3</td>
<td>Primary objective: to confirm that at least one or more dose groups of telotristat compared to placebo is effective in reducing the number of daily bowel movements from Baseline averaged over the 12-week double-blind portion of the trial in patients not adequately controlled by current SSA therapy. Includes a 36-week open-label Extension Period in which all patients received telotristat 500 mg tid.</td>
<td>Long term safety</td>
<td>Database lock 13 September 2016; CSR under preparation</td>
<td>Final CSR: Post approval Q4 2017</td>
</tr>
<tr>
<td>Study 302: A Multicentre, Long Term Extension Study to Further Evaluate the Safety and Tolerability of Telotristat Etiprate (LX1606) Category 3</td>
<td>To evaluate the long term safety and tolerability of orally administered telotristat.</td>
<td>Long term safety</td>
<td>Ongoing</td>
<td>Final CSR: Q4 2018 (estimated)</td>
</tr>
</tbody>
</table>
7.2 Studies which are a Condition of the Marketing Authorisation

Not Applicable

8 SUMMARY OF CHANGES TO THE RISK MANAGEMENT PLAN OVER TIME

In response to feedback from the EMA, the important identified and potential risks have been revised since Version 1.0 of the RMP. Specifically, the important identified risk of GI effects has been more precisely defined as constipation due to decreased GI motility. Faecaloma and intestinal obstruction has been added as an important potential risk. Data for the risk of hepatic enzyme increased were updated to include the 42 patients in Studies 202, 203, 301, 302 and 303 identified as having hepatic impairment based on their medical history and data from the recently completed study in patients with hepatic impairment (Study D-FR-01017-001) has been added to the RMP.

In addition, data throughout the RMP have been updated to reflect updated data from Studies 301 and 303, which were ongoing when the previous RMP was submitted.

Regarding missing information, use in pregnancy and lactation has been split into two distinct units and use in non-White patients has been added as missing information due to limited data available at this time.

In addition, text throughout the RMP has been revised in line with updates to the proposed SmPC.