Telotristat ethyl (Xermelo™)

Introduction

Carcinoid syndrome occurs in less than 10 percent of patients with carcinoid tumors and results from the tumor spreading to the liver. Most of the tumors are found in gastrointestinal tract and are rare and slow-growing. These tumors release excess amounts of serotonin and causes the most prominent symptom, diarrhea. The initial treatment for carcinoid syndrome diarrhea is somatostatin analogs; however, patients may develop recurrent symptoms. Telotristat ethyl (Xermelo) was approved on February 28, 2017, for the treatment of carcinoid syndrome diarrhea in addition to somatostatin analogs. The FDA granted the product orphan status and the application was given fast track designation and priority review.  

Indications

Telotristat ethyl is approved for use in combination with a somatostatin analog (SSA) in adults with carcinoid syndrome diarrhea not controlled by SSA therapy alone.  

Mechanism of Action

Telotristat ethyl and its metabolite, telotristat, are tryptophan hydroxylase inhibitors that decrease the production of peripheral serotonin and reduces the frequency of diarrhea.  

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**Dosage and Administration**

Telotristat ethyl is available as a 250 mg tablet and the recommended dose is one tablet three times daily with food. If used in combination with octreotide, administer octreotide at least 30 minutes after telotristat ethyl.

**Efficacy and Safety**

The safety and efficacy of telotristat ethyl were assessed in an international, multi-center, randomized, double-blind, placebo-controlled, Phase III trial in patients with carcinoid syndrome not adequately controlled with somatostatin analogue (SSA) therapy. There were a total of 135 patients (mean range of 62.4–64.9 years of age) randomized to receive 250 mg of telotristat ethyl three times daily (n=45), 500 mg of telotristat ethyl three times daily (n=45), or placebo three times daily (n=45) for 12 weeks. The use of SSA therapy was continued for all 12 weeks. There were 115 patients from this study that later enrolled in an open label extension study and received telotristat 500 mg three times daily.

The primary end point of the study was mean reduction from baseline in daily bowel movements (BM) over 12 weeks. Responders were defined as patients experiencing a ≥30% reduction in BM frequency for ≥50% of the trial period. The secondary endpoints included HIAA at week 12, the number of flushing episodes and abdominal pain severity over 12 weeks, change from baseline in the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) scores, rescue short-acting SSA use, stool consistency, and the proportion of days with urgency to defecate.

In the telotristat ethyl 250 mg and 500 mg groups, 44% and 42% of patients were classified as responders compared to 20% of patients in the placebo group. The results were consistent in terms of bowel movement reductions in the open label study. Treatment with telotristat had a statistically significant reduction in urinary 5-HIAA levels compared to placebo. The flushing and abdominal pain ratings were not statistically significant. In terms of the EORTC QLQ-C30 scores, the telotristat ethyl 250 mg and 500 mg group had a statistically significant improvement compared to the placebo group.

The treatment groups had an improvement in stool consistency, reduction in urgency to defecate and use of rescue short-acting octreotide.

The incidence of treatment-emergent adverse events was similar among all three groups. A total of five deaths were reported in the study with three deaths in the placebo group, and two in the telotristat groups.

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**HIGHLIGHTS**

Telotristat (Xermelo)

Manufacturer: Lexicon

Approval Date: February 28, 2017

Pronunciation: tel OH tri state ETH il

Telotristat ethyl received product orphan status and the application was given fast track designation and priority review.

Telotristat ethyl is available as a 250 mg tablet and the recommended dose is one tablet three times daily with food.

There are no contraindications for telotristat ethyl.
The following adverse events had an >5% incidence rate in all three groups: nausea, abdominal pain, fatigue, hypokalemia, depression-related.  

Adverse Events
The most commonly reported adverse events with an incidence rate of ≥5% were headache, nausea, increased GGT (gamma-glutamyltransferase), depression, flatulence, decreased appetite, peripheral edema, and pyrexia.  

Drug Interactions
Telotristat ethyl may decrease the levels of drugs that are CYP3A4 substrates; therefore, increasing the dose of CYP3A4 substrates may be necessary. Octreotide should be administered at least 30 minutes after telotristat due to decreased levels of telotristat.  

Contraindications
There are no contraindications for telotristat ethyl.  

Renal Impairment
The pharmacokinetics of telotristat was not affected by creatinine clearances in the range of 20 – 89 mL/min. Use in patients with end-stage renal disease who require dialysis has not been evaluated.  

Hepatic Impairment
The pharmacokinetics of telotristat is not impacted by mild hepatic impairment. There is no data available for use of telotristat in moderate or severe hepatic impairment.  

Monitoring and Counseling Points
Telotristat ethyl should be taken with food. If taken with short-acting octreotide, the octreotide should be administered at least 30 minutes following telotristat ethyl dosing. Patients should contact their healthcare provider if signs of severe or worsening abdominal pain and/or severe constipation occur.  

Ocrelizumab (Ocrevus™)
Introduction
Multiple sclerosis (MS) is among the most common causes of neurological disability in young adults with most people experiencing their first symptoms of MS between the ages of 20 and 40.  

Multiple sclerosis includes episodes of worsening function known as relapses and are followed by recovery periods or remissions. Eventually, recovery may be incomplete and lead to progressive decline in function and increased disability.  

Ocrelizumab (Ocrevus) was approved by the US Food and Drug Administration on March 28, 2017, for the treatment of patients with either relapsing form of multiple sclerosis (RMS) or primary progressive multiple sclerosis (PPMS).  

This is the first drug approved by the FDA for PPMS which affects 10 to 15% of patients with MS. The FDA granted the product breakthrough therapy designation, fast track designation, and priority review.  

Indication
Ocrelizumab is approved for the treatment of relapsing or primary progressive forms of multiple sclerosis.  

Mechanism of Action
The exact mechanism by which ocrelizumab exerts its therapeutic effects is unknown.  

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It is theorized that the product binds to CD20, a cell surface antigen present on lymphocytes, which results in cell lysis.\(^6\)

**Dosage and Administration**

Ocrelizumab is available as a 300mg/10ml (30mg/ml) injection in a single dose vial and administered as an infusion. The recommended dose is 300 mg IV infusion followed by a second dose of 300mg IV infusion two weeks later. Start infusion rate at 30 mL per hour and may increase by 30 mL per hour every 30 minutes. The maximum infusion rate is 180 mL per hour and should be administered over 2.5 hours or longer. Any subsequent doses should be given as 600 mg IV every six months. Infusion rate should be started at 40 mL per hour and may increase by 40 mL per hour every 30 minutes. Maximum infusion rate is 200 mL per hour and should be administered over 3.5 hours or longer.\(^6\)

Patients should be monitored closely during and for at least an hour after infusion. If there are signs of a life-threatening or disabling infusion reaction, immediately stop and permanently discontinue treatment with ocrelizumab. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.\(^6\)

**Efficacy and Safety**

**Oratorio- Primary Progressive Multiple Sclerosis**

The Oratorio trial was a Phase 3, double-blind, randomized, placebo-controlled superiority trial that evaluated the efficacy and safety of ocrelizumab in patients with primary progressive multiple sclerosis (PPMS). Patients aged 18-55 received either 600mg ocrelizumab (n=488) or matching placebo (n=244) with 100mg IV methylprednisolone before the infusion for 24 weeks.\(^7\)

The primary endpoint measured was the percentage of patients with disability progression at 12 weeks. If the primary endpoint was found to be statistically significant, the following secondary endpoints were evaluated: percentage of patients with 24-week confirmed disability progression, change in performance on the timed 25-foot walk from baseline to week 120, change in brain volume from baseline to week 120 and from week 24 to week 120, and change in the Physical Component Summary score of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) from baseline to week 120.\(^7\)

The percentage of patients with confirmed disability progression was significantly lower in the ocrelizumab group compared to the placebo group at Week 12 and 24. The ocrelizumab group also had a significantly lower mean change from baseline to week 120 in performance on the timed 25-foot walk than placebo (38.9% versus 55.1%, respectively). The brain volume decreased in the ocrelizumab group and increased in the placebo group from baseline to week 120 and from week 24 to week 120. There was no significant difference in both groups in regards to the SF-36 score from baseline to week 120.\(^7\)

Five deaths were reported in the study with four in the ocrelizumab group due to pulmonary embolism, pneumonia, pancreatic carcinoma, and aspiration pneumonia, and one in the placebo group died of a road-traffic accident.

The most frequently reported adverse event among ocrelizumab-treated patients was infusion-related reaction. Infusion-related reactions decreased in both rate and severity with subsequent administration; none were fatal or life-threatening.

The most common infections reported were nasopharyngitis, urinary tract infection and influenza.\(^7\)
OPERA I & II - Relapsing Multiple Sclerosis

OPERA I and II were two Phase 3, multicenter, randomized, double-blind, double-dummy, active-controlled, parallel-group trials that investigated the efficacy and safety of ocrelizumab in patients with relapsing multiple sclerosis (RMS). Patients (mean age of 37 years) received either intravenous infusion of ocrelizumab 600 mg every 24 weeks or subcutaneous interferon beta-1a at a dose of 55 mcg three times weekly for 96 weeks. A total of 1656 patients underwent randomization with 821 patients ocrelizumab (n=410); interferon beta-1a (n=411) in the OPERA I trial and 835 patients assigned to the ocrelizumab group (n=417) and interferon beta-1a (n=418) in the OPERA II trial.8

The primary endpoint was the annualized relapse rate at 96 weeks. The secondary endpoints measured in a hierarchical manner included confirmed disability progression sustained for 12 weeks and confirmed disability progression sustained for 24 weeks, confirmed disability improvement for at least 12 weeks, number of T₁ gadolinium-enhancing lesions, number of new or newly enlarged T₂ hyperintense lesions, number of new T₁ hypointense lesions, change in Multiple Sclerosis Functional Composite (MSFC) and brain volume, change in physical-component summary score of the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36), and no evidence of disease activity by week 96. Additional secondary endpoints measured were pharmacokinetics, pharmacodynamics, immunogenicity and safety of ocrelizumab.8

In the OPERA I and OPERA II trials, the ocrelizumab group had a significantly lower mean annualized relapse rates compared to the interferon beta-1a group. The rates of disability progression were significantly lower for ocrelizumab group compared to interferon beta-1a group in both trials at 12 weeks and 24 weeks. The total mean number of gadolinium-enhancing lesions per T₁-weighted MRI scan and the total mean numbers of new or newly enlarged hyperintense lesions per T₂-weighted MRI scan were statistically lower in the ocrelizumab group for both trials.

The rate of confirmed disability improvement was significant for the ocrelizumab group compared to interferon beta-1a in OPERA I trial, but non-significant in the OPERA II trial. The change in the Multiple Sclerosis Functional Composite score was not statistically significant between the treatment and comparison groups. As a result, the subsequent secondary efficacy endpoints of change in the SF-36 quality-of-life physical-component summary and measure of no evidence of disease activity were non-confirmatory.8

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There were three deaths reported in both trials with the causes due to mechanical ileus and suicide. The most common adverse events were infusion-related reaction, nasopharyngitis, upper respiratory tract infection, headache, and urinary tract infection in patients treated with ocrelizumab. There were 34.3% of patients treated with ocrelizumab that reported infusion-related reactions and neoplasms occurred in 0.5% in the ocrelizumab group.

**Adverse Events**

The most commonly reported adverse events include upper respiratory tract infections and infusion reactions for RMS and upper respiratory tract infections, infusion reactions, skin infections and lower respiratory tract infections for PPMS.

**Drug Interactions**

Coadministration of ocrelizumab with immune modulating or immunosuppressive therapies (including corticosteroids) may increase risk of immunosuppression. Additive immunosuppression may occur when switching to ocrelizumab from products that have prolonged duration of action (e.g. daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone).

**Contraindications**

Ocrelizumab is contraindicated in patients with active hepatitis B virus infection and/or a history of life threatening infusion reaction to ocrelizumab.

**Specific Populations**

**Pregnancy**

There is currently no data in pregnant women, but animal studies showed perinatal mortality, depletion of B-cell, renal, bone marrow, and testicular toxicity.

**Lactation**

There is no data on the presence of ocrelizumab in human milk, the effects on the breastfed infant, or the effects of the drug on milk production. Ocrelizumab was excreted in the milk of ocrelizumab-treated monkeys. Human IgG is excreted in human milk, and the potential for absorption of ocrelizumab to lead to B-cell depletion in the infant is unknown.

**Females and Males of Reproductive Potential**

It is recommended for women of childbearing potential should use contraception during treatment and for 6 months after receiving the dose of ocrelizumab.

**Pediatrics**

The use of ocrelizumab has not been studied in the pediatric population.

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Geriatrics
There were not enough patients aged 65 and over included in the clinical trials to determine a difference in the clinical response compared to younger patients.6

Renal/Hepatic impairment
Patients with mild renal impairment and mild hepatic impairment were included in clinical trials and there were no significant changes in the pharmacokinetics of ocrelizumab observed in those patients.6

Monitoring
Parameters/Counseling Points
Patients should be aware of the signs and symptoms of infusion reactions which may occur up to 24 hours after infusion and can include rash, hives, coughing or wheezing, trouble breathing, throat irritation or pain, feeling faint, fever, flushing, tiredness, nausea, headache, swelling of throat, dizziness, faster heartbeat. Patients should contact their healthcare provider immediately for signs or symptoms of infusion reactions.6

There is an increased risk of malignancy, including breast cancer, with ocrelizumab and patients should follow standard breast cancer screening guidelines. If a planned infusion of ocrelizumab is missed, administer ocrelizumab as soon as possible and do not wait until the next scheduled dose.

The dosing schedule should be revised to include administration of the next sequential dose 6 months after the missed dose.

Doses of ocrelizumab must be separated by at least 5 months. Patients should be administered all required vaccinations at least 6 weeks prior to starting ocrelizumab. A hepatitis B virus screening should be conducted prior to treatment. Patients may be pre-medicated with 100 mg of methylprednisolone (or another corticosteroid) administered intravenously approximately 30 minutes prior to each infusion, and with antihistamine approximately 30-60 minutes before each infusion. Antipyretics, such as acetaminophen, may be added.6

Abaloparatide
(Tymlos™)

Introduction
The National Osteoporosis Foundation estimates there are 10.2 million people in the United States that have osteoporosis. Over 2 million osteoporosis related fractures occur annually with more than 70% of these fractures occurring in women.9,10 According to the American Association of Clinical Endocrinologists (AACE) 2016 guidelines, the initial treatment for osteoporosis include bisphosphonates, zoledronic acid, and denosumab.11 Patients that cannot use oral formulations may consider teriparatide, denosumab or zoledronic acid and are preferred for those at an increased high fracture risk.7

On April 28, 2017, the FDA approved a second anabolic treatment for osteoporosis, abaloparatide (Tymlos). Abaloparatide is the first new 15 years.12

Indication
Abaloparatide is used to treat osteoporosis in postmenopausal women at high risk for fractures including a history of osteoporotic fracture, multiple risk factors for fracture, or who have failed or are intolerant to other options.13

Mechanism of Action
Abaloparatide is a parathyroid-1 receptor (PTH1R)
agonist that activates cAMP signaling pathway. Animal models have shown an increase in bone strength at vertebral and/or nonvertebral sites.\textsuperscript{13}

**Dosage and Administration**
Abaloparatide is available as a single-patient-use pen prefilled with 3120 mcg/1.56 mL and delivers a total of 30 doses. The recommended daily dose is 80 mcg injected subcutaneously into the periumbilical region of the abdomen. Injections should be administered daily at approximately the same time, and injection sites should be rotated daily.\textsuperscript{13}

**Efficacy and Safety**
A Phase 3, 18-month, international, placebo- and active-controlled randomized trial evaluated the safety and efficacy of abaloparatide in women with postmenopausal osteoporosis. A total of 2463 patients ranging from 49 to 86 years of age were randomly assigned to treatment with abaloparatide 80 mcg (n=824), placebo (n=821), or teriparatide 20 mcg (n=818). Abaloparatide and placebo were administered double-blinded; however, teriparatide was given open label due to its trademark. The primary endpoint evaluated was the percentage of patients with one or more incidents of new morphometric vertebral fracture. The secondary efficacy endpoints included nonvertebral fractures (excluded fractures in the spine, sternum, patella, toes, fingers, skull, or face) and BMD changes in femoral neck, lumbar spine and hip measured at 6, 12, and 18 months.

Additional secondary endpoints included bone turnover, pro-collagen type I N-terminal propeptide (s-PINP) and carboxy-terminal cross-linking telopeptide of type I collagen (s-CTX) at months 1, 3, 6, 12 and 18.\textsuperscript{14}

There was a significantly lower number of patients in the abaloparatide group that developed new morphometric vertebral fractures compared to placebo (0.58\% vs 4.22\%, respectively). There were 0.84\% of participants in the teriparatide group that developed new morphometric vertebral fractures compared to placebo. After 18 months, significant differences were found in BMD from baseline in the abaloparatide group compared to placebo at the femoral neck (3.60\% vs -0.43\%), lumbar spine (11.20\% vs 0.63\%) and total hip (4.18\% vs -1.01\%). Patients in the abaloparatide group had more significant increases in BMD (6.58\%) compared to the teriparatide group (5.25\%). In terms of serum markers (s-PINP, s-CTX) in select patients, both the abaloparatide and teriparatide groups had bone formation and resorption markers expressed more significantly at 3, 6, and 12 months. Over time, it was found that the abaloparatide-treated participants had decreased bone

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formation after three months compared to teriparatide. Adverse events that led to discontinuation of abaloparatide included nausea, dizziness, headache, and palpitations. There were 11 deaths reported (3 in the abaloparatide group, 5 in the placebo group and 3 in the teriparatide group) and the causes were related to bowel cancer, intestinal obstruction, MI, dissecting aneurysm of aorta, sudden, sepsis, bronchiectasis, ischemic heart disease pancreatic cancer, general health deterioration and cardiorespiratory arrest. The most commonly reported adverse events in all three treatment groups were hypercalciuria, dizziness, arthralgia, back pain, nausea, upper respiratory tract infection, headache, palpitations, pain in extremity, and constipation.

**Adverse Events**

The most commonly reported adverse events with an incidence of greater than 2% were hypercalciuria, dizziness, arthralgia, back pain, nausea, upper respiratory tract infection, headache, hypertension, nasopharyngitis, urinary tract infection, palpitations, pain in extremity, and constipation.

**Drug Interactions**

No induction or inhibition of cytochrome P450 enzymes has been shown to occur in vitro at therapeutic levels. Other drug-drug interactions with abaloparatide have not been evaluated.

**Contraindications**

Currently, there are no contraindications for abaloparatide.

**Special Populations**

**Pregnancy**

No human or animal data are available evaluating the use of abaloparatide in pregnant women. Any associated drug risks are unknown and use in females of reproductive potential is not recommended.

**Lactation**

It is unknown whether abaloparatide is excreted into breast milk. The effects of abaloparatide on the breast fed infant and milk production are unknown as well.

**Pediatric Use**

The use of abaloparatide in pediatric patients has not been established. Patients that are predisposed to osteosarcoma due to hereditary disorders or have open epiphyses should not use abaloparatide.

**Geriatric Use**

Differences in the safety and efficacy of abaloparatide were not observed in subjects aged 65 to 75 years and older; however, an increase in sensitivity to abaloparatide in the geriatric population should be considered.

**Renal Impairment**

In patients with mild, moderate or severe renal impairment, dosage adjustment of Tymlos is not required. Patients with severe renal impairment may have a greater risk of adverse reactions due to increased exposure to abaloparatide.

**Monitoring Parameters / Counseling Points**

Signs and symptoms of possible osteosarcoma such as new tissue tenderness upon palpitation and/or localized pain that persists should be reported. Use of abaloparatide for longer than two years is not recommended due to potential risk of osteosarcoma. Hypercalcemia may occur in patients taking abaloparatide. Patients should promptly report any signs or symptoms of hypercalcemia including nausea, vomiting, lethargy, muscle weakness, or constipation. After injecting abaloparatide, patients should sit or lie down if feelings of lightheadedness or dizziness occur. Patients should consult their healthcare provider promptly if these symptoms do not resolve or worsen. Used pen needles should be disposed in a sharps container. Unopened pens should be stored in the refrigerator and may be kept at room temperature after first use. Discard the pen and any unused medication after 30 days of use.
References


