Trulance™ (plecanatide)

Introduction
Approximately 42 million people in the US are affected by constipation according to the National Institutes of Health. Chronic idiopathic constipation is defined as persistent constipation with no structural or biochemical explanation. According to the American College of Gastroenterology (ACG), patients with chronic constipation may have hard or lumpy bowel movements, incomplete bowel emptying, and less than 3 bowel movements in two weeks. Trulance (plecanatide) was approved on January 19, 2017, for chronic idiopathic constipation. Plecanatide is the first product to mimic the function of human uroguanylin which stimulates fluid secretion and support more regular bowel function.

Indication
Plecanatide is approved for use in adults with chronic idiopathic constipation (CIC).

Mechanism of Action
Plecanatide acts as an agonist on guanylate cyclase-C (GC-C) on the luminal surface of the intestinal epithelium similar to human uroguanylin. Activation of GC-C leads to an increase of cyclic guanosine monophosphate (cGMP) which stimulates chloride and bicarbonate secretions. This results in an elevation of intestinal fluid in the GI tract and intestinal transit. (continued on page 2)
Plecanatide is available as 3 mg tablets in a unit dose blister pack of 30. The recommended dose is 3 mg taken by mouth once daily. If there are any issues with swallowing, the tablets can be crushed and mixed with applesauce. The tablets can also be crushed and mixed with water for administration via nasogastric or gastric feeding tube. Mixing crushed plecanatide tablets with other foods or liquids has not been studied.4

Efficacy and Safety

The efficacy and safety of plecanatide were established in two 12-week, randomized, double-blind, placebo-controlled, multicenter clinical studies in adult patients with CIC. A total of 2791 patients, between 18 and 80 years of age, were randomized to placebo (n=458), plecanatide 3 mg (n=474), or plecanatide 6 mg (n=452) once daily in Study 1 and placebo (n=466), plecanatide 3mg (n=467) and plecanatide 6mg (n=466) in Study 2.5

The primary endpoint was the proportion of patients who achieved overall complete small bowel movement (CSBM) in the 12-week treatment period. The secondary endpoints of the study were changes in frequency, stool consistency, and straining during bowel movements.

There were 21% of patients in the treatment group that met the criteria of a complete responder compared to 13% of responders in the placebo group. As for the secondary endpoints, there were improvements in stool frequency, stool consistency and the amount of straining with bowel movements in the plecanatide group compared to placebo.4

The most common adverse event that lead to discontinuation of plecanatide was diarrhea. Severe diarrhea was reported within the first 3 days of treatment. The most common adverse event reported was diarrhea with a higher incidence in the treatment group compared to placebo.4

Adverse Events

The most commonly reported adverse event was diarrhea. Plecanatide has a boxed warning for risk of serious dehydration in pediatric patients.4

Drug Interactions

Plecanatide and its metabolites do not inhibit cytochrome P450 (CYP) enzymes (2C9, 3A4) or induce CYP3A4 in vitro. The product does not inhibit P-glycoprotein (P-gp) or breast cancer resistance protein (BCRP) in vitro.4

Contraindications

Plecanatide is contraindicated in patients less than 6 years of age due to the risk of serious dehydration. It is also contraindicated in patients with known or suspected mechanical gastrointestinal obstruction.4

(continued on page 3)
Specific Populations

Pregnancy
Fetal exposure to plecanatide is not expected. Currently, there is not enough information to determine whether plecanatide carries a risk for birth defects or miscarriage. In animal studies, there were no effects on the development of the embryo and fetus after administration of plecanatide at higher doses than the recommended human dose.4

Lactation
There is no information on whether plecanatide is excreted in human milk. It is unknown if the systemic absorption in pregnant women can result in a clinically relevant exposure to breastfed infants. Serious side effects are possible if breastfed infants are exposed to the product.4

Pediatric
Plecanatide is contraindicated in patients less than 6 years of age. It should also be avoided in patients younger than 18 years old because safety and effectiveness have not been established in this population.4

Geriatric
There were not enough patients aged 65 and over in the clinical trials to determine a difference in response compared to younger patients. Selection of the dose for elderly patients should include possible decreased liver, kidney function and concomitant diseases.4

Monitoring parameters/counseling points
Patients should be aware that improvement in signs or symptoms of constipation is indicative of efficacy.4 If a dose of plecanatide is missed, skip the dose and take the next dose as scheduled. Do not take two doses at the same time. Advise patients to stop plecanatide and contact their health care provider if severe diarrhea occurs.4

Xadago® (safinamide)

Introduction
The National Institutes of Health estimates 50,000 Americans are diagnosed with Parkinson’s disease annually and one million people have the disease.7 The first line treatment for Parkinson’s disease is levodopa with carbidopa which works by delaying the conversion of levodopa to dopamine until it reaches the brain.8 The effectiveness of levodopa/carbidopa treatment may decline and lead to on-off phenomenon defined as symptoms being well controlled early after a dose and worsens as the dose wears off.9 On March 21, 2017, the FDA approved Xadago (safinamide) as an adjunctive therapy for patients with Parkinson’s disease experiencing “off” episodes.7

Indication
Safinamide is indicated as an add-on therapy to levodopa/carbidopa in adults with Parkinson’s disease experiencing “off” episodes. Safinamide is not approved to be used as monotherapy.10

Mechanism of Action
The exact mechanism of the effects of safinamide is unknown. Safinamide is a monoamine oxidase B (MAO-B) inhibitor which blocks the breakdown of dopamine and increases dopamine levels in the brain.10 (continued on page 4)
Dosage and Administration
Safinamide is available as a 50 mg and 100 mg oral tablet. The recommended dose is 50 mg daily and patients may be titrated up to 100 mg after two weeks as tolerated. Doses above 100 mg may not provide additional benefit and puts the patient at risk for adverse events.  

Efficacy and Safety
Two Phase 3, double-blind, placebo-controlled trials evaluated the efficacy of safinamide as add-on therapy in patients with Parkinson’s disease (PD) experiencing “off” episodes on levodopa/carbidopa and/or other PD medications. The primary efficacy endpoint in both studies was change from baseline to Week 24 in total daily “ON” time without troublesome dyskinesia over 18 hours. The secondary endpoints measured were “OFF” time and a decrease in the Uniform Parkinson’s Disease Rating Scale (UPDRS) Part III.  

In Study 1, a total of 645 patients were randomized to safinamide 50 mg (n=217), safinamide 100 mg (n=216) or placebo (n=212). There was a significant difference in “ON” time between the placebo group and the safinamide 50 mg and 100 mg groups. The safinamide 100 mg group had a slightly higher “ON” time than the 50 mg group (0.53 and 0.5, respectively). The “OFF” time and the UPDRS III scores in the safinamide groups were significantly decreased compared to placebo.  

In Study 2, a dose range of safinamide 50 mg to 100 mg was compared to placebo as add-on therapy with levodopa in PD patients with motor fluctuations. A total of 549 patients were randomized to receive safinamide (n=274) or placebo (n=275). Patients were initiated on 50 mg safinamide daily then increased to 100 mg daily if tolerated. The safinamide group had a significant increase in the “ON” time than the placebo group. The increase in “ON” time of drug effects led to similar changes in “OFF” time of Parkinson’s symptoms. The “OFF” time and the UPDRS III scores in the safinamide group were significantly decreased compared to placebo.  

The most frequently reported adverse event that led to discontinuation of safinamide was dyskinesia. The most common adverse event reported were dyskinesia, fall, nausea, and insomnia.  

Adverse Effects
The most common adverse events reported were dyskinesia, fall, nausea, and insomnia.  

According to the National Institutes of Health, 50,000 Americans are diagnosed with Parkinson’s disease yearly and one million people have the disease.  

Drug Interactions
MAO Inhibitors
Administration of other MAO-inhibitors or drugs that are potent inhibitors of monoamine oxidase with safinamide may increase the risk for hypertensive crisis. Isoniazid also has some activity inhibiting monoamine oxidase. Patients should be monitored for hypertension and dietary tyramine reactions when treated with both isoniazid and safinamide. A minimum of a 14-day washout period is recommended between stopping safinamide and starting other MAOIs.  

Opioids
Safinamide and opioids such as meperidine and its derivatives, methadone, or tramadol, and MAO-inhibitors should not be used together due to fatal reactions. A minimum of a 14-day washout period is recommended between stopping safinamide and starting opioids.  

Serotonergic Drugs
Safinamide should not be used with SSRIs as this may increase the risk of serotonin syndrome. Patients taking both safinamide and sympathomimetic medications should be monitored for hypertension. A minimum of a 14-day washout period is recommended between stopping safinamide and starting opioids.  

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**Dextromethorphan**  
Concomitant use of dextromethorphan and safinamide is contraindicated due to reports of psychosis or bizarre behavior.

**Sympathomimetics**  
Patients should be monitored for hypertension if safinamide is taken with nonprescription nasal, oral, or opthalmic decongestants and cold remedies. Since severe hypertensive reactions and hypertensive crisis have been reported following use of nonselective MAO-inhibitors and sympathomimetics, safinamide should not be used with methylphenidate, amphetamine, and their derivatives.

**Tyramine**  
Patients should avoid foods containing a high amount of tyramine while taking safinamide can lead to a tyramine reaction.

**Breast Cancer Resistance Protein Substrates**  
Safinamide may potentially inhibit intestinal breast cancer resistance protein (BCRP) and increase the plasma concentration of BCRP substrates. Patients taking both BCRP substrates and safinamide should be monitored for an increase in pharmacologic or adverse effects of the BCRP substrates.

**Dopamine Antagonists**  
Concurrent use of safinamide and dopamine antagonists, such as metoclopramide or antipsychotics, may decrease the effectiveness of safinamide.

**Contraindications**  
Use of safinamide is contraindicated with other MAO inhibitors and potent monoamine oxidase inhibitors, such as linezolid, due to hypertension and hypertensive crisis. Serotonin syndrome may occur if safinamide is taken concurrently with opioids, selective norepinephrine reuptake inhibitors, antidepressants (tricyclic, tetracyclic or triazolopyridine), cyclobenzaprine, methylphenidate, amphetamine and their derivatives, and St. John’s Wort. Due to an increased risk of psychosis or abnormal behavior, concomitant use of safinamide and dextromethorphan is contraindicated.

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**TABLE 1. DRUG INTERACTIONS WITH SAFINAMIDE**

<table>
<thead>
<tr>
<th>Category</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAO INHIBITORS</td>
<td>May increase the risk for hypertensive crisis.</td>
</tr>
<tr>
<td>OPIOIDS</td>
<td>A minimum of a 14-day washout period is recommended between stopping safinamide and starting opioids.</td>
</tr>
<tr>
<td>SEROTONERGIC DRUGS</td>
<td>May increase risk of serotonin syndrome and hypertension.</td>
</tr>
<tr>
<td>DEXTROMETHORPHAN</td>
<td>Reports of psychosis or bizarre behavior.</td>
</tr>
<tr>
<td>SYMPATHOMIMETICS</td>
<td>Risk for severe hypertensive crisis. Monitoring is needed with use of nonprescription products (nasal, oral or opthalmic decongestants and cold medicines).</td>
</tr>
<tr>
<td>TYRAMINE</td>
<td>Avoid foods with high amount of tyramine due to tyramine reaction.</td>
</tr>
<tr>
<td>BCRP SUBSTRATES</td>
<td>Inhibits BCRP and may increase plasma concentration of BCRP.</td>
</tr>
<tr>
<td>DOPAMINE AGONISTS</td>
<td>Decreases the effectiveness of safinamide.</td>
</tr>
</tbody>
</table>

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(continued on page 6)
Other contraindications include hypersensitivity to safinamide and severe hepatic impairment (Child-Pugh C: 10 to 15).  

**Specific Populations**  

**Pregnancy**  
Currently, there are no adequate and well-controlled studies on use of safinamide in pregnant women. Animal studies have shown developmental toxicity, fetal abnormalities, fetal visceral and skeletal malformations at varying doses of safinamide and levodopa/carbidopa. An increase in death or cardiac and skeletal malformations were observed in rabbits when safinamide was administered with levodopa/carbidopa.  

**Lactation**  
It is unknown whether safinamide is excreted into breast milk. Skin discoloration occurred in rats after exposure of safinamide through the milk.  

**Pediatric**  
The safety and efficacy of safinamide have not been studied in this population.  

**Geriatric**  
Patients over the age of 65 years did not have any notable differences in safety or efficacy compared to the younger patients in the clinical studies.  

**Hepatic impairment**  
The maximum dose is 50 mg daily for patients with moderate hepatic impairment. Safinamide is not recommended for use in patients with severe hepatic impairment. Patients that progress to severe hepatic impairment should discontinue safinamide.  

**Renal impairment**  
Based on an open-label study, moderate and severe renal impairment did not have an effect on the pharmacokinetics of safinamide.  

**Monitoring Parameters/Counseling Points**  
Monitor patients for serotonin syndrome, dyskinesia and/or hypertension during therapy. Patients should avoid foods high in tyramine such as aged, fermented, cured, smoked, and pickled foods due to a potential increase in blood pressure. Patients may develop somnolence and fall asleep during daily activities and should not drive, operate machinery, or engage in potentially dangerous activities until the patient can determine their response to the product. Additional sedative effects are possible if safinamide is taken with other sedating medications, CNS depressants or alcohol. Hallucinations, psychotic behavior and compulsive behavior (sexual, gambling or other uncontrollable urges) may occur during treatment with safinamide.  

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**Kisqali was approved on March 13, 2017, for the treatment of HR-positive, HER2-negative advanced breast cancer**  

**Kisqali® (Ribociclib)**  

**Introduction**  
Breast cancer is the most common cancer in women among all races and ethnicities in the United States. The standard of care for postmenopausal women with hormone receptor positive (HR-positive), human epidermal growth factor receptor 2 negative (HER2-negative) advanced breast cancer is endocrine therapy which includes aromatase inhibitors. Resistance to the currently marketed aromatase inhibitors have emerged in these patients; therefore, additional therapy in this disease state is needed. On March 13, 2017, the FDA approved Kisqali (ribociclib) as an adjunct to an aromatase inhibitor as the first line endocrine based treatment. The FDA granted ribociclib priority review with breakthrough therapy designation.  

**Indication**  
Ribociclib is approved as adjunct therapy to aromatase inhibitor for first line endocrine-based treatment in postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.  

**Mechanism of Action**  
Ribociclib inhibits cyclin-dependent kinase (CDK) 4 and 6 which has a role in signaling pathways of cell cycle (continued on page 7)
progression and cellular proliferation through the phosphorylation of retinoblastoma protein (pRb). In vitro, ribociclib decreased pRb phosphorylation and reduced cell proliferation in breast cancer cell lines.\textsuperscript{15}

**Dosage and Administration**

Ribociclib is available as a 200 mg film-coated tablet in blister packs. The recommended dose of ribociclib is 600 mg taken orally with or without food once daily for 21 consecutive days, then 7 days without treatment, in a full 28-day cycle. Letrozole 2.5 mg should be taken once daily continuously in the same 28-day cycle. Both products should be taken at approximately the same time each day. For any missed doses (including doses not consumed due to vomiting), no additional dose should be taken that day and the next dose should be taken as scheduled.\textsuperscript{15}

**Efficacy and Safety**

**MONALEESA-2** was a Phase 3, randomized, double blind, placebo-controlled, multicenter trial that evaluated the efficacy and safety of ribociclib in women with HR-positive, HER2-negative locally advanced or metastatic breast cancer. The patients (age range of 23 to 91) were randomized to receive either ribociclib 600 mg for 21 days out of a 28-day treatment cycle plus letrozole 2.5 mg daily (n=334) or placebo plus letrozole (n=334) for 18 months. The primary endpoint measured was locally assessed progression-free survival and the secondary endpoints included the overall survival, the overall response rate, the clinical benefit rate, safety assessments and quality of life assessments.\textsuperscript{16}

The ribociclib group had a significantly higher rate of locally assessed progression-free survival than in the placebo group. After 12 and 18 months, the progression-free survival rate was higher in the ribociclib group compared to the placebo group (72.8\% and 63\% in the ribociclib group and 60.9\% and 42.2\% in the placebo group, respectively). The overall response and clinical benefit rates were higher in the ribociclib group than the placebo group. Quality of life assessments were not reported in this journal article.\textsuperscript{16}

There were 5 deaths reported in the study and the causes were disease progression, sudden death (deemed to be related to ribociclib), and unknown cause.\textsuperscript{6} The most common serious adverse events reported in the ribociclib group were abdominal pain, vomiting, increased ALT level, anemia, constipation, dyspnea, febrile neutropenia, and nausea and pleural effusion was the most common serious adverse event reported in the placebo group.\textsuperscript{17} Adverse events that occurred in at least 35\% of the patients in either group included neutropenia, nausea, infections, fatigue and diarrhea. The most common infections reported were urinary tract infections and upper respiratory tract infections in the treatment and placebo groups.\textsuperscript{16} (continued on page 8)
**Adverse Events**

The most commonly reported adverse reactions (with an incidence ≥ 20%) were neutropenia, nausea, fatigue, diarrhea, alopecia, vomiting, constipation, headache, and back pain.\(^{15}\)

**Drug Interactions**

Concomitant use of ribociclib with strong CYP3A4 inhibitors (including but not limited to boceprevir, clarithromycin, grapefruit juice, itraconazole and conivaptan) should be avoided, as they can increase the plasma concentration of ribociclib. If concomitant use of ribociclib and a CYP3A4 inhibitor is warranted, the dose of ribociclib should be reduced to 400 mg.\(^{15}\)

Avoid using ribociclib with strong CYP3A4 inducers due to the potential for decreased plasma concentration of ribociclib. Concomitant use with other products known to potentially prolong the QT interval (amiodarone, disopyramide, procainamide, quinidine, sotalol, chloroquine, halofantrine, clarithromycin, haloperidol, methadone, moxifloxacin, bepridil, pimozide and ondansetron) should be used with caution.\(^{15}\)

**Contraindications**

Ribociclib does not have any contraindications.\(^{15}\)

**Specific Populations**

**Pregnancy**

Data from animal studies showed that ribociclib can cause fetal harm. It is recommended women of reproductive potential use contraception during treatment with ribociclib and for at least 3 weeks after the final dose.\(^{15}\)

**Breastfeeding**

It is recommended for women to avoid breastfeeding while taking ribociclib and for at least three weeks after the last dose. The effects of ribociclib on the breastfed infant or milk production and its presence in human milk are not known.\(^{15}\)

**Females and Males of Reproductive Potential**

Females of reproductive potential should take a pregnancy test prior to initiating treatment with ribociclib. In addition, it is recommended for women of reproductive potential to use contraception during treatment with ribociclib and for at least 3 weeks after the final dose. In males, ribociclib has been shown to impair fertility.\(^{15}\)

**Pediatric**

Use of ribociclib in pediatric patients has not been established.\(^{15}\)

**Geriatric**

There were no observed differences in safety and efficacy in the clinical studies between younger patients and those ≥ 65 years of age.\(^{15}\)

**Hepatic impairment**

Patients with mild hepatic impairment (Child-Pugh A) do not require any dose adjustment. The starting dose should be reduced to 400 mg for patients with moderate to severe hepatic impairment (Child-Pugh B to C).\(^{15}\) (Continued on page 9)
Monitoring Parameters/Counseling Points

Ribociclib has a risk of QT interval prolongation, hepatobiliary toxicity, and neutropenia. Patients should inform their health care provider of signs and symptoms of the aforementioned risks. Prior to beginning treatment with ribociclib, females of reproductive potential should take a pregnancy test. Women should notify their healthcare provider if there is any suspicion of pregnancy or if they become pregnant during treatment with ribociclib. Women should avoid breastfeeding during treatment with ribociclib and for 3 weeks after the final dose. Patients should avoid pomegranate, pomegranate juice, grapefruit, and grapefruit juice while taking ribociclib.15

References


