Plecanatide (Trulance) for Chronic Idiopathic Constipation and Irritable Bowel Syndrome With Constipation

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INTRODUCTION

Constipation is the difficult or infrequent passage of stool, often accompanied by straining or a sensation of incomplete evacuation. Chronic idiopathic constipation (CIC) is a functional gastrointestinal (GI) disorder with features like those of constipation that occur for at least three months, but there is usually no evident underlying physiological abnormality. Although a number of definitions of CIC have been proposed, the Rome criteria are most often used in clinical trials and, therefore, most relevant when evaluating medications to manage this condition. The Rome criteria look at the frequency of straining, lumpy or hard stools, and sensation of incomplete evacuation, among other symptoms. The prevalence of CIC in North America is approximately 14%. Traditional treatment options for chronic constipation include lifestyle modifications, such as increased fluid intake and increased exercise. Fluid works to increase stool volume by augmenting luminal fluid, and increasing exercise improves motility by decreasing GI transit time. Fiber therapy increases fluid secretion into the GI tract, and causes accelerated transit. In animal models, plecanatide has been shown to stimulate secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, plecanatide has been shown to increase fluid secretion into the GI tract, accelerate intestinal transit, and cause changes in stool consistency.

CHEMICAL PROPERTIES

Plecanatide, a GC-C agonist, is a 16-amino-acid peptide with the chemical name: L-Leucine, L-asparaginyl-L-\(\alpha\)-aspartyl-L-\(\alpha\)=glutamyl-L-cysteinyl-L-\(\alpha\)-glutamyl-L-leucyl-L-cysteinyl-L-valyl-L-asparaginyl-L-valyl-Lalananyl-L-cysteinyl-L-threonylglycyl-L-cysteinyl, cyclic (4→12),(7→15)-bis(disulfide). The molecular formula of plecanatide is \(C_{65}H_{104}N_{18}O_{26}S_4\), and the molecular weight is 1682 daltons. The amino acid sequence for plecanatide is shown in Figure 1. The solid lines linking cysteines illustrate disulfide bridges. Plecanatide is an amorphous white to off-white powder that is soluble in water. It is supplied as a 3-mg tablet for oral administration. The inactive ingredients consist of magnesium stearate and microcrystalline cellulose.

MECHANISM OF ACTION/PHARMACOLOGY

Plecanatide is structurally related to human uroguanylin, and like uroguanylin, it functions as a GC-C agonist. Both plecanatide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation of intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen, mainly through activation of the cystic fibrosis transmembrane conductance regulator ion channel, resulting in increased intestinal fluid and accelerated transit. In animal models, plecanatide has been shown to increase fluid secretion into the GI tract, accelerate intestinal transit, and cause changes in stool consistency.

PHARMACOKINETICS AND PHARMACODYNAMICS

Plecanatide is minimally absorbed with negligible systemic availability following oral administration. Concentrations of plecanatide and its active metabolite in plasma are below the limit of quantitation after an oral plecanatide dose of 3 mg. Therefore, standard pharmacokinetic parameters,

![Figure 1 Amino Acid Sequence for Plecanatide](image-url)

Figure 1: The solid lines linking cysteines illustrate disulfide bridges. Plecanatide is an amorphous white to off-white powder that is soluble in water. It is supplied as a 3-mg tablet for oral administration. The inactive ingredients consist of magnesium stearate and microcrystalline cellulose.
such as area under the curve, maximum concentration, and half-life, cannot be calculated. Given that plecanatide concentrations following clinically relevant oral doses are not measurable, plecanatide is expected to be minimally distributed in tissues. Oral plecanatide is localized to the GI tract where it exerts its effects with negligible systemic exposure. Plecanatide exhibits little to no binding to human serum albumin or human α-1-acid glycoprotein.

Plecanatide is metabolized in the GI tract to an active metabolite by loss of the terminal leucine moiety. Both plecanatide and the metabolite are proteolytically degraded within the intestinal lumen to smaller peptides and naturally occurring amino acids.

No excretion studies have been conducted in humans. Plecanatide and its active metabolite are not measurable in plasma following administration of the recommended clinical doses.

In regard to food effects, patients who received either a low-fat, low-calorie meal or a high-fat, high-calorie meal reported looser stools than fasted patients up to 24 hours after a single 9-mg dose of plecanatide (three times the recommended dose). In clinical studies, plecanatide was administered with or without food. In a crossover study of 24 healthy individuals given one 9-mg dose of plecanatide in three states—fasted, after a low-fat, low-calorie meal, and after a high-fat, high-calorie meal—plecanatide was detected in one person in the fasted state at 30 minutes and one hour after administration. Plecanatide concentrations were below the limit of quantitation for all other time points and for all other individuals. The active metabolite was not detected in any of the participants.

**CLINICAL TRIALS**

**CIC Studies**

The efficacy of plecanatide for the management of CIC symptoms was established in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients. In the intention-to-treat (ITT) population, 905 patients (Study 1) and 870 patients (Study 2) were randomized 1:1 to either placebo or plecanatide 3 mg once daily. The study medication was administered without respect to food intake. The overall mean age of the patients was 45 years (range, 18–80 years), 80% were women, 72% were Caucasian, and 24% were African-American.

The efficacy of plecanatide was assessed using a responder analysis and change from baseline in complete spontaneous bowel movement (CSBM) and SBM endpoints. Efficacy was assessed using information provided by patients on a daily basis in an electronic diary. A responder was defined as a patient who had at least three CSBMs in a given week and an increase of at least one CSBM from baseline in the same week for at least nine weeks of the 12-week treatment period and at least three of the last four weeks of the study. In both studies, improvements in the frequency of CSBMs per week were seen as early as week 1 with improvement maintained through week 12. The difference between the plecanatide group and the placebo group in the mean change of frequency of CSBMs per week from baseline to week 12 was approximately 1.1 CSBMs per week. Over the 12-week treatment period, improvements were observed in stool frequency (number of CSBMs per week and SBMs per week), stool consistency, and/or in the amount of straining with bowel movements in the plecanatide group compared with placebo.

**IBS-C Studies**

The efficacy of plecanatide for the management of symptoms of IBS-C was established in two 12-week, double-blind, placebo-controlled, randomized, multicenter clinical studies in adult patients. In the ITT population, 699 patients (Study 3) and 754 patients (Study 4) received treatment with placebo or plecanatide 3 mg once daily. In clinical studies, study medication was administered without respect to food intake. The overall mean patient age was 44 years (range, 18–83 years), 74% were women, 73% were Caucasian, and 22% were African-American.

The efficacy of plecanatide was assessed using a responder analysis based on abdominal pain intensity and a stool frequency responder (CSBM) endpoint. Efficacy was assessed using information provided by patients on a daily basis through an electronic phone diary system. A responder was defined as a patient who met both the abdominal pain intensity and stool frequency responder criteria in the same week for at least six of the 12 treatment weeks.

In both IBS-C studies, the proportion of responders who were also weekly responders for at least two of the four treatment weeks in month 3, the last month of treatment, was greater in the plecanatide groups compared with placebo. Over the 12-week treatment period, improvements were observed in both stool consistency and in the amount of straining with bowel movements in the 3-mg plecanatide group compared with placebo.

In all four of these studies, a third randomized treatment arm of plecanatide 6 mg once daily did not demonstrate additional treatment benefit over the 3-mg dose; therefore, plecanatide 6 mg once daily is not recommended.

**CONTRAINDICATIONS**

The plecanatide labeling contains a boxed warning about the risk of serious dehydration in pediatric patients. Plecanatide is contraindicated in patients younger than 6 years of age and should be avoided in patients 6 years to less than 18 years of age. The safety and effectiveness of plecanatide have not been established in this population.

The drug is also contraindicated in patients with known or suspected mechanical GI obstruction.

**ADVERSE EVENTS**

According to the safety data from clinical trials, the only adverse reaction reported in at least 2% of plecanatide-treated patients and at an incidence greater than placebo was diarrhea (5% for plecanatide versus 1% for placebo). Severe diarrhea was reported in 0.6% of plecanatide-treated patients compared with 0.3% of placebo-treated patients. The majority of reported cases of diarrhea occurred within four weeks of treatment initiation, and severe diarrhea was reported to occur within the first three days of treatment.

Discontinuations due to adverse reactions occurred in 4% of plecanatide-treated patients and in 2% of placebo-treated patients. The most common adverse reaction leading to discontinuation was diarrhea: 2% of plecanatide-treated and 0.5% of placebo-treated patients withdrew due to diarrhea.

Less common adverse reactions that were reported in less than 2% of plecana-
Table 1  Comparison of Agents for the Treatment of Constipation

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Class</th>
<th>Strength(s) Available</th>
<th>Indication(s)/ Recommended Doses*</th>
<th>AWP$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plecanatide</td>
<td>GC-C agonist</td>
<td>3-mg oral tablets</td>
<td>CIC, 3 mg once daily IBS-C, 3 mg once daily</td>
<td>$466 for 30 tablets</td>
</tr>
<tr>
<td>Trulance, Synergy Pharmaceuticals, Inc.$</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Linaclotide</td>
<td>GC-C agonist</td>
<td>72-mcg, 145-mcg, and 290-mcg oral capsules</td>
<td>CIC, 145 mcg once daily IBS-C, 290 mcg once daily</td>
<td>$464 for 30 capsules regardless of strength</td>
</tr>
<tr>
<td>Linzess, Allergan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lubiprostone</td>
<td>Chloride-channel activator</td>
<td>8-mcg and 24-mcg oral capsules</td>
<td>CIC, 24 mcg twice daily IBS-C, 8 mcg twice daily OIC, 24 mcg twice daily</td>
<td>$445 for 60 capsules regardless of strength</td>
</tr>
<tr>
<td>Amitiza, Sucampo AG³</td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

* Consult the full prescribing information for details regarding indications and dosages.

AWP = average wholesale price; CIC = chronic idiopathic constipation; GC-C = guanylate cyclase-C; IBS-C = irritable bowel syndrome with constipation; OIC = opioid-induced constipation.

drugs patients and at an incidence greater than placebo were: sinusitis, upper respiratory tract infection, abdominal distension, flatulence, abdominal tenderness, and increased levels on liver biochemical tests.$

DRUG–DRUG INTERACTIONS

Neither plecanatide nor its active metabolite inhibits the cytochrome P450 (CYP) enzymes 2C9 and 3A4, and they did not induce CYP3A4 in vitro. Plecanatide and its active metabolite are neither substrates nor inhibitors of the transporters P-glycoprotein or breast cancer resistance protein in vitro.$

SPECIAL POPULATIONS

Pregnancy and Lactation

Plecanatide and its active metabolite are negligibly absorbed systemically, and maternal use is not expected to result in fetal exposure to the drug. The available data on plecanatide use in pregnant women are not sufficient to inform any drug-associated risks for major birth defects and miscarriage. In animal developmental studies, no effects on embryo-fetal development were observed with oral administration of plecanatide in mice and rabbits at doses much higher than recommended human dosage.$

There is no information regarding the presence of plecanatide in human milk or its effects on milk production or the breastfed infant. No lactation studies have been conducted in animals. It is unknown whether the negligible systemic absorption of plecanatide by adults will result in a clinically relevant exposure to breastfed infants. Exposure to plecanatide in breastfed infants has the potential for serious adverse effects, such as dehydration, so the developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for plecanatide and any potential adverse effects on the infant.$

Geriatric and Pediatric Use

Clinical studies of plecanatide did not include sufficient numbers of patients 65 years of age and older to determine if this population responds differently than younger patients.$

Plecanatide is contraindicated in pediatric patients younger than 6 years of age and should be avoided in patients 6 years to less than 18 years of age.$

Renal and Hepatic Impairment

Due to plecanatide’s minimal absorption and negligible systemic availability following oral administration, there are no recommendations for dosing adjustments based on renal or hepatic function.$

DOSE AND ADMINISTRATION

The recommended dosage of plecanatide is 3 mg taken by mouth once daily. A plecanatide tablet can be taken with or without food and should be swallowed whole. For adults with swallowing difficulties, plecanatide tablets can be crushed and administered orally either in apple sauce or with water or administered with water via a nasogastric or gastric feeding tube, using the specific directions found in the prescribing information.$

COST

The average wholesale price (AWP) of plecanatide is $466 for a 30-day supply of 3-mg tablets. Its cost is comparable to the other available agents. The AWP of linaclotide is $464 for a 30-day supply of capsules of all available strengths. Lubiprostone has an AWP of $445 for a 30-day supply of capsules of all available strengths.$

P&T COMMITTEE CONSIDERATIONS

Although no direct comparisons have been made, there may be an advantage to using plecanatide when patients experience headache or other side effects associated with the use of the other available agents. The only adverse event seen in greater than 2% of plecanatide-treated patients and with greater incidence than placebo was diarrhea.$¹⁰ The rate of diarrhea was 5% and 1% for plecanatide and placebo, respectively, and 20% versus 3% for linaclotide and placebo, respectively.$⁶ ¹⁰ There is little cost difference among the available agents. See Table 1 for a comparison of these agents.

CONCLUSION

The approval of plecanatide provides another option for patients suffering from CIC or IBS-C. Because no single medication works for everyone, the availability of new therapies allows patients and their doctors to select the most appropriate treatment for their condition and provides alternatives when initial therapy fails or is not tolerated. A future trial comparing the available agents for efficacy could help determine specific recommendations.

REFERENCES

1. Ford AC, Moayyedi P, Lacy BE. American College of Gastroenterology monograph on the management of irritable bowel syndrome. continued on page 232
Drug Forecast

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