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# Drug Information Newsletter

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*In this issue…*



The University at Buffalo School of Pharmacy and Pharmaceutical Sciences (UB SPPS) Drug Information Newsletter is dedicated to providing timely information relevant to healthcare practitioners in New York. The newsletter supplies information on clinical practice guidelines, medication safety issues, new drug approvals/medications under development, medication shortages, and drug class reviews.

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## Drug Class Review: the GLP-1/Basal Insulin Combination Products

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*Introduction*

An estimated 415 million people are diagnosed with diabetes worldwide, corresponding to 8.8% of the adult population, and this number is expected to rise to 642 million by 2040.[1] Type 2 diabetes is characterized by impaired insulin secretion, peripheral insulin resistance, and diminished secretion and action of incretin hormones, such as glucagon-like peptide-1 (GLP-1).[2] Basal insulin regulates glucose metabolism by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production.[3,4] GLP-1 receptor agonists (RAs) stimulate glucose dependent insulin secretion, inhibit postprandial glucagon secretion, and delay gastric emptying, leading to reduced postprandial glucose absorption with a resultant reduction in postprandial glucose excursions.[5-8] Basal insulin is efficacious in reducing fasting plasma glucose but is associated with hypoglycemia and weight gain. If insufficient, additional agents such as a mealtime insulin may be necessary to cover postprandial hyperglycemia.[9] In contrast, GLP-1 RAs may improve both fasting and postprandial glucose levels without an increased risk for hypoglycemia, and they can possibly induce weight loss. However, the GLP-1 RAs are limited by gastrointestinal (GI) adverse effects.

The most recent position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) suggests that GLP-1 RAs be considered in dual and triple combination therapy, or in combination injectable therapy (i.e., in addition to metformin and a basal insulin).[10] With regard to the latter, the ADA and EASD assert that pairing basal insulin with a GLP-1 RA may be preferable to basal-bolus insulin, as most of the (then) available data have shown similar or superior efficacy, with weight loss and less hypoglycemia as added benefits. Recently, 2 fixed-ratio combinations of a basal insulin analog and a GLP-1 RA, Soliqua® 100/33 (iGlarLixi) and Xultophy® 100/3.6 (IDegLira), have been approved by the Food and Drug Administration (FDA) to treat adults with type 2 diabetes inadequately controlled on a basal insulin or a GLP-1 RA.[3,4] Both products are supplied as 3 mL prefilled pen injectors; iGlarLixi contains insulin glargine (iGlar) 100 units/mL and lixisenatide (Lixi) 33 mcg/mL, while IDegLira contains insulin degludec (IDeg) 100 units/mL and liraglutide (Lira) 3.6 mg/mL.

*Dosage and Administration*

Per the product labeling, the recommended starting dose of iGlarLixi is 15 units/day in patients inadequately controlled on <30 units of basal insulin or on Lixi, or 30 units/day in patients inadequately controlled on 30-60 units of basal insulin.[3] The maximum daily dosage is 60 units (60 units of iGlar and 20 mcg of Lixi). The recommended starting dose of IDegLira is 16 units/day, and the maximum daily dose is 50 units (50 units of IDeg and 1.8 mg of Lira).[4] The manufacturers of both products advise using alternative products if a patient persistently requires doses outside of the recommended ranges.[3,4] Individual basal insulin or GLP-1 RAs should be discontinued prior to initiation of a fixed-ratio combination agent. Both iGlarLixi and IDegLira should be administered subcutaneously. Administration of iGlarLixi should occur within the hour prior to the first meal of the day, whereas IDegLira may be given at the same time each day without regard to meals.

*Efficacy*

FDA approval of iGlarLixi was based primarily on 2 phase 3 trials: EFC12404 (LixiLan-O) and EFC12405 (LixiLan-L).[11] The efficacy of iGlarLixi was also assessed in a phase 2 proof-of concept study. IDegLira was evaluated in 5 phase 3 trials (DUAL I-V), 2 of which were considered pivotal (DUAL I and II).[12] Selected characteristics of the iGlarLixi and IDegLira trials are shown in Table 1. The basal insulin/GLP-1 RA combination products were evaluated alone and in combination with metformin, metformin with a sulfonylurea (SU), with or without meglitinides or thiazolidinediones (TZDs).[8,13-19] They were also evaluated against their component parts (iGlarLixi vs. iGlar or Lixi, and IDegLira vs. IDeg or Lira), alternative GLP-1 RAs, placebo, or alternative basal insulins. The 2 phase 3 trials of iGlarLixi were 30 weeks in duration,[11] all of the phase 3 trials of IDegLira were designed to be 26 weeks in duration – the duration of DUAL I was further extended to 52 weeks, to demonstrate long-term efficacy and safety.[12] The primary endpoint for all aforementioned trials was the change from baseline in glycosylated hemoglobin (HbA1c) at week 30 for iGlarLixi and week 26 for IDegLira.

Overall, patients in these studies had a mean baseline HbA1c of approximately 8%.[8,13-20] Whether administered in combination with metformin with or without other oral antidiabetic drugs (OADs), the combination agents consistently showed HbA1c reduction. Compared to placebo or added to metformin, TZDs, SU, or meglitinides, statistically significant differences were observed favoring iGlarLixi and IDegLira. Noninferiority was met when iGlarLixi was compared to iGlar.[13-15] iGlarLixi also met statistical superiority compared to the corresponding basal insulin at equivalent doses in both of the phase 3 trials. Statistical superiority was also shown when comparing iGlarLixi to Lixi (LixiLan-O). IDegLira met statistical noninferiority when compared to IDeg and iGlar (DUAL I and V) and was further found to meet criteria for statistical superiority when compared to IDeg (DUAL II), iGlar (DUAL V), Lira (DUAL I and III), and placebo (DUAL IV), each with background OAD therapy.[8,16-19]

In addition to HbA1c, weight was evaluated in all of the outlined studies.[8,13-19] IDegLira and iGlarLixi were associated with weight gain when compared to placebo (+1.48 kg) and GLP-1 RAs (+2.27 kg) alone. They

demonstrated a more favorable weight loss profile compared to basal insulin alone (-1.72 kg). The largest mean weight gain was observed in DUAL III when compared to a maximum dosage of a GLP-1 RA. iGlarLixi also displayed a similar, statistically significant weight loss when compared to iGlar.[13-15] However, greater weight loss was observed with Lixi compared to iGlarLixi in the Lixilan-O trial.[15]

Liakopoulou et al conducted a meta-analysis to assess the efficacy and safety of the fixed-ratio combinations of basal insulin and GLP-1 RAs in which they included all of the aforementioned trials.[20] Weighted mean differences were calculated for continuous variables using an inverse variance weighted random effects model and odds ratios were calculated for dichotomous variables using the Mantel-Haenszel fixed effects formulae. Heterogeneity was assessed using the $I^2$ statistic. Overall, they found the fixed-ratio combination products to be associated with better glycemic control compared with the individual components (mean change in HbA1c compared to basal insulin: -0.31%, 95% confidence interval [CI] -0.47 to -0.16, $I^2$=81%; compared to GLP-1 RA: -0.73%, 95% CI -0.87 to -0.58, $I^2$=74%). They also found that switching patients from basal insulin to the combination products was associated with a reduction in HbA1c of 0.72% (95% CI -1.03 to -0.41, $I^2$=93%). Switching from GLP-1 RAs to the combination products also induced a reduction in HbA1c (0.94%, 95% CI -1.11 to -0.77, $I^2$=not applicable [findings from 1 trial]). A high degree of heterogeneity was noted for these comparisons; the investigators attributed this to intraclass differences and differences between the comparators (e.g., IDeg vs. iGlar). Generally, switching from GLP-1 RAs to the fixed-ratio combination products was associated with the most weight gain: mean difference 2.89 kg, 95% CI 2.17 to 3.60, $I^2$=not applicable [findings from 1 trial]). The largest weight loss was seen when switching from a basal insulin to the combination agents: mean difference -2.35 kg, 95% CI -3.52 to -1.19, $I^2$=93%.

Table 1. Summary of selected phase 2 and 3 trials evaluating efficacy and safety of iGlarLixi and IDegLira.

| Study | Design and Duration | Interventions | Population | LS Mean Change from Baseline[a] | |
|---|---|---|---|---|---|
| | | | | HbA1c | Weight |
| iGlarLixi trials | | | | | |
| Rosenstock et al, 2016<br><br>LixiLan-Proof of Concept Phase 2 Study[13] | R, OL<br><br>24 weeks | iGlarLixi (n=161)<br>iGlar (n=162)<br><br>Titrated to FPG 80-100 mg/dL to maximum of 60 units/day | n=323 patients inadequately controlled on metformin and insulin-naïve<br><br>Baseline HbA1c (mean):<br>8.0 – 8.1% | **iGlarLixi: -1.82%**<br>iGlar: -1.64%<br>• Treatment difference: -0.17% (95% CI -0.31 to -0.04, P=0.01)<br>**Demonstrated noninferiority and statistical superiority to iGlar** | **iGlarLixi: -1.0 kg**<br>iGlar: +0.5 kg<br>• Treatment difference: -1.44 kg (95% CI -2.1 to -0.8, p<0.0001) |
| Aroda et al, 2016<br><br>LixiLan-L[14] | R, OL<br><br>30 weeks | iGlarLixi (n=367)<br>iGlar (n=369)<br><br>Titrated to FPG <100 mg/dL to maximum of 60 units/day | n=736 patients inadequately controlled on basal insulin ± metformin<br><br>Baseline HbA1c (mean): 8.1% | **iGlarLixi: -1.1%**<br>**iGlar: -0.6%**<br>• Treatment difference: -0.5% (95% CI -0.6 to -0.4, P<0.0001)<br>**Demonstrated statistical superiority to iGlar** | **iGlarLixi: -0.7 kg**<br>iGlar: +0.7 kg<br>• Treatment difference: -1.4 kg (95% CI -1.8 to -0.9, p<0.0001) |
| Rosenstock et al, 2016<br><br>LixiLan-O[15] | R, OL<br><br>30 weeks | iGlarLixi (n=469)<br>iGlar (n=467)<br>Lixi (n=234)<br><br>Titrated insulin to FPG <100 mg/dL to maximum of 60 units/day; maximum dose of Lixi: 20 mcg/day | n=1170 patients inadequately controlled on metformin ± 1 OAD<br><br>Baseline HbA1c (mean): 8.1% | **iGlarLixi: -1.6%**<br>iGlar: -1.3%<br>**Lixi: -0.9%**<br>• Treatment difference from iGlar: -0.3% (95% CI -0.4 to -0.2, p<0.0001)<br>**Met noninferiority to iGlar**<br>• Treatment difference from Lixi: -0.8% (95% CI -0.9 to -0.7, p<0.0001)<br>**Demonstrated noninferiority to iGlar and statistical superiority to Lixi** | **iGlarLixi: -0.3 kg**<br>iGlar: +1.1 kg<br>**Lixi: -2.3 kg**<br>• Treatment difference from iGlar: -1.4 kg (95% CI -1.9 to -0.9, p<0.0001)<br>• Treatment difference from Lixi: +2.0 kg (95% CI 1.4 to 2.6, no p-value) |
| IDegLira trials | | | | | |

| Study | Design and Duration | Interventions | Population | LS Mean Change from Baseline[a] | |
|---|---|---|---|---|---|
| | | | | HbA1c | Weight |
| Gough et al, 2014<br><br>DUAL I[8] | R, OL<br><br>52 weeks | IDegLira (n=833)<br>IDeg (n-413)<br>Lira (n=414)<br><br>Titrated insulin to FPG between 72 and 90 mg/dL; maximum dose of Lira: 1.8 mg/day | n=1660 patients inadequately controlled on metformin ± pioglitazone<br><br>Baseline HbA1c (mean): 8.3% | **IDegLira: -1.9%**<br>IDeg: -1.4%<br>Lira: -1.3%<br>• Treatment difference from IDeg: -0.47% (95% CI -0.58 to -0.36, p<0.0001)<br>• Treatment difference from Lira: -0.64% (95% CI -0.75 to -0.53, p<0.0001)<br>**Demonstrated noninferiority to IDeg and statistical superiority to Lira** | **IDegLira: -0.5 kg**<br>IDeg: +1.6 kg<br>**Lira: -3.0 kg**<br>• Treatment difference from IDeg: -2.22 kg (95% CI -2.64 to -1.80, p<0.0001)<br>• Treatment difference from Lira: +2.44 kg (95% CI 2.02 to 2.86, p<0.0001) |
| Buse et al, 2014<br><br>DUAL II[16] | R, DB<br><br>26 weeks | IDegLira (n=207)<br>IDeg (n=206)<br><br>Titrated to FPG between 72 and 90 mg/dL; maximum of 50 units/day | n=413 patients inadequately controlled on metformin ± SU/glinides<br><br>Baseline HbA1c (mean): 8.7 – 8.8% | **IDegLira: -1.9%**<br>IDeg: -0.9%<br>• Treatment difference: -1.1% (95% CI -1.3 to -0.8, p<0.0001)<br>**Demonstrated statistical superiority to IDeg** | **IDegLira: -2.7 kg**<br>IDeg: 0.0 kg<br>• Treatment difference: -2.5 kg (95% CI -3.2 to -1.8, p<0.0001) |
| Linjawi et al, 2016<br><br>DUAL III[17] | R, OL<br><br>26 weeks | IDegLira (n=292)<br>Lira or exenatide (n=146)<br><br>Insulin titrated to FPG between 72 and 90 mg/dL; maximum of 50 units/day | n=438 patients inadequately controlled on metformin ± pioglitazone ± SU<br><br>Baseline HbA1c (mean): 7.7 – 7.8% | **IDegLira: -1.3%**<br>GLP-1 RA: -0.3%<br>• Treatment difference: -0.94% (95% CI -1.11 to -0.78, p<0.001)<br>**Demonstrated statistical superiority to GLP-1 RA** | **IDegLira: +2.0 kg**<br>GLP-1 RA: -0.8 kg<br>• Treatment difference: +2.89 kg (95% CI 2.17 to 3.62, p<0.001) |

| Study | Design and Duration | Interventions | Population | LS Mean Change from Baseline[a] | |
|---|---|---|---|---|---|
| | | | | HbA1c | Weight |
| Rodbard et al, 2016<br><br>DUAL IV[18] | R, DB<br><br>26 weeks | IDegLira (n=289)<br>Placebo (n=146)<br><br>Titrated to FPG between 72 and 108 mg/dL; maximum of 50 units/day | n=435 patients inadequately controlled on SU ± metformin<br><br>Baseline HbA1c (mean): 7.9% | **IDegLira: -1.45%**<br>Placebo: -0.46%<br>• Treatment difference: -1.02% (95% CI -1.18 to -0.87, p<0.001)<br>**Demonstrated statistical superiority to placebo** | IDegLira: +0.5 kg<br>**Placebo: -1.0 kg**<br>• Treatment difference: -1.48 kg (95% CI 0.90 to 2.06, p<0.001) |
| Lingvay et al, 2016<br><br>DUAL V[19] | R, OL<br><br>26 weeks | IDegLira max: 50 dose steps (n=278)<br>IGlar: no maximum dose (n=279)<br><br>Titrated to FPG between 72 and 90 mg/dL | n=557 patients inadequately controlled on iGlar and metformin<br><br>Baseline HbA1c (mean): 8.2 – 8.4% | **IDegLira: -1.81%**<br>IGlar: -1.13%<br>• Treatment difference: -0.59% (95% CI -0.74 to -0.45, p<0.001)<br>**Demonstrated noninferiority and superiority** | **IDegLira: -1.4 kg**<br>IGlar: +1.8 kg<br>• Treatment difference: -3.20 kg (95% CI -3.77 to -2.64, p<0.001) |

CI=confidence interval; DB=double-blind; FPG=fasting plasma glucose; HbA1c=glycosylated hemoglobin; IDeg=insulin degludec; IDegLira=insulin degludec; iGlar=insulin glargine; iGlarLixi=insulin glargine and lixisenatide; Lira=liraglutide; Lixi=lixisenatide; LS=least-squares; OADs=oral antidiabetic drugs; OL=open-label; PO=by mouth; R=randomized; SC=subcutaneously; SU=sulfonylurea; TID=3 times daily; TZD=thiazolidinedione

[a]Change from baseline at 30 weeks for iGlarLixi trials; change from baseline at 26 weeks for IDegLira trials

*Safety Concerns*

*Boxed Warnings*

The Lira component of IDegLira carries a boxed warning for dose-dependent and treatment duration-dependent thyroid C-cell tumors at clinically relevant exposure in rats and mice.[4,12] It is unknown whether IDegLira will cause thyroid C-cell tumors in humans. Lixi does not carry this boxed warning, though the manufacturer states that thyroid C-cell adenomas were observed in rats with exposure tantamount to ≥15 times the human exposure achieved at the usual daily dosage of 20 mcg.[3]

The FDA and the European Medicines Agency (EMA) have evaluated the available data pertaining to pancreatic safety associated with incretin-based drugs.[21] Although both recognize pancreatitis as an associated risk, the agencies agree that the current data are insufficient to substantiate a causal link between incretin-based drugs and pancreatitis.

*Hypoglycemia*

In phase 3 trials assessing IDegLira, confirmed hypoglycemia was defined as episodes requiring medical attention or in episodes where plasma glucose levels were less than 56 mg/dL regardless of symptoms, whereas iGlarLixi phase 3 trials classified hypoglycemia as plasma glucose levels less than 70 mg/dL including typical hypoglycemia symptoms.[20] In a meta-analysis of these trials, Liakopoulou and colleagues estimated the comparative risk for hypoglycemia and found that the risk was increased with the basal insulin/GLP-1 RA combinations compared to placebo and GLP-1 RAs-alone, but the risk was decreased when compared to insulin. These findings are shown in Table 2.

*GI Effects*

In phase 3 trials, more patients treated with combination basal insulin and GLP-1 RAs experienced nausea compared with basal insulin.[20] There was also an increase in incidence of nausea observed among patients who switched from basal insulin to a fixed-ratio combination. Lower incidence of nausea or vomiting was noted when fixed-ratio combinations were compared to a GLP-1 RA administered alone.

Table 2. Findings for selected secondary outcomes regarding fixed-ratio combinations of basal insulin/GLP-1 RAs.[20] Adapted from a meta-analysis by Liakopoulou et al.

| Comparison | Number of Studies | Odds Ratio (95% CI); $I^2$ | | |
|---|---|---|---|---|
| | | Hypoglycemia | Nausea | Vomiting |
| Fixed-ratio combo vs. placebo [18] | 1 | 3.46 (2.12 to 5.64); N/A | 1.33 (0.47 to 3.81); N/A | 0.88 (0.25 to 3.07); N/A |
| Fixed-ratio combo vs. basal insulin [6,8,13,15] | 3 | 0.89 (0.74 to 1.06); 53% | 3.01 (2.03 to 4.47); 25% | 2.57 (1.40 to 4.71); 0% |
| Fixed-ratio combo vs. GLP-1 RA [6,8,15] | 2 | 5.89 (4.23 to 8.21); 0% | 0.37 (0.28 to 0.49); 0% | 0.45 (0.30 to 0.68); 0% |
| Switch from basal insulin to fixed-ratio combo [14,16,19] | 3 | 0.70 (0.57 to 0.86); 85% | 6.89 (3.73 to 12.74); 79% | 6.70 (1.50 to 29.92); N/A |
| Switch from GLP-1 RA to fixed-ratio combo [17] | 1 | 16.56 (5.95 to 46.09); N/A | 0.74 (0.26 to 2.12); N/A | NR |

CI=confidence interval; combo=combination; HbA1c=glycosylated hemoglobin A1c; GLP-1 RA=glucagon-like peptide-1 receptor agonist; N/A= not applicable; NR=not reported

*Place in Therapy*

Based on the recommendations of the American Diabetes Association (ADA) and American Association of Clinical Endocrinologists (AACE), GLP-1 RAs may be appropriate as additional agents in dual or triple combination.[9,10] The manufacturer of IDegLira further recommends that IDegLira, should not be used as first-line pharmacologic therapy.[4] There is no recommendation regarding place in therapy in the iGlarLixi product label.[3]

The DUAL V trial evaluating IDegLira against a basal insulin intensification group demonstrated superiority of the combination to basal insulin alone while also displaying less weight gain.[19] The safety profiles of iGlarLixi and IDegLira reflect the established safety profiles of their components with complementary but not additive effects with respect to efficacy and tolerability.[20] They counterbalance hypoglycemia risk, weight gain, and GI adverse events while providing similar or more effective glycemic control as compared to other available antidiabetic agents.

*Cost*

Hunt and colleagues evaluated the short-term cost-effectiveness of IDegLira compared to maximally titrated iGlar using data from the DUAL V trial.[5,7] Costs per patient achieving different targets (i.e., costs of control) were calculated and compared, and the analysis was conducted over a 1-year timeline. Annual treatment costs were found to be higher for patients using IDegLira than for patients using iGlar; the difference was attributed to higher acquisition costs of IDegLira. However, differences in cost of control values were greatest when treatment targets, including hypoglycemia and/or weight gain, were considered. IDegLira was associated with a lower cost of control in patients with higher HbA1c values at baseline, especially HbA1c greater than 9%. To bring 1 patient to a goal HbA1c of ≤6.5% or ≤7% without confirmed hypoglycemia and weight gain would require spending $2.77 or $2.08 on iGlar respectively, for every $1 spent on IDegLira. The authors hypothesized that the treatment characteristics of IDegLira, compared to those of its individual components, result in the preserved efficacy of glycemic control while minimizing risk of hypoglycemia and weight gain, and this improved efficacy offsets increased treatment costs to result in lower cost of control.

In a separate publication, Hunt et al evaluated the long-term cost-effectiveness of IDegLira compared to maximally titrated iGlar using data from the DUAL V trial.[7] Long-term projections of clinical outcomes and direct costs were made using the IMS CORE Diabetes Model relative to a healthcare payer perspective. IDegLira was associated with an improved discounted life expectancy and quality-adjusted life expectancy (relative to maximally titrated iGlar, by 0.18 years and 0.27 quality-adjusted life years (QALYs), respectively). These improvements were thought to result from reduced incidence and increased time to onset of complications. Despite an increase in direct costs of $16,970, IDegLira was associated with an incremental cost-effectiveness ratio (ICER) of $63,678 per QALY vs. iGlar in patients uncontrolled on basal insulin. Per Hunt et al, this ICER is within the range described as high care value (<$100,000 per QALY gained) by the Institute for Clinical and Economic Review. Thus, they concluded that IDegLira is a cost-effective treatment option.

Notably, cost-effectiveness studies of iGlarLixi were not identified at the time of this writing.

*Conclusions*

IDegLira and iGlarLixi are fixed-ratio combination products approved for the treatment of adults with type 2 diabetes; they have shown several clinical advantages when compared to the individual components (basal insulin and GLP-1 RAs). [11,12] Though limited, available pharmacoeconomic analyses have demonstrated cost-effectiveness of IDegLira compared to maximally titrated basal insulin, particularly in patients with HbA1c >9% and/or patients concerned about weight gain or hypoglycemia. At this time, there are no published studies directly comparing fixed-ratio combination products, nor are there studies comparing the combination

products to dual therapy with separately titrated GLP-1 RAs and basal insulins. Selection of an agent should be individualized and based on a thorough evaluation of the patient and disease characteristics, as well as patient preference and treatment goals.

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## Navigating a Novel Drug Therapy: Pimavanserin (Nuplazid®) for Parkinson's Disease Psychosis

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### Introduction

Up to 50% of patients with Parkinson's disease (PD) will develop persistent psychotic symptoms over the course of their condition.[1,2] Parkinson's disease psychosis (PDP) typically involves hallucinations, delusions, and sensory disturbances.[1,3,4] Use of dopamine receptor agonists is 1 of the main risk factors for development of PDP.[3] Although American guidelines (American Academy of Neurology) for PD have not been updated since 2006, Canadian guidelines were published in 2012.[4] The Canadian Neurological Sciences Federation recommends that when dosage reduction and/or discontinuation of PD medications do not improve psychosis, addition of antipsychotic therapy may be warranted in order to control hallucinations and delusions.

Pimavanserin (Nuplazid®) was the first atypical antipsychotic medication approved by the Food and Drug Administration (FDA) in April 2016 for the treatment of hallucinations and delusions associated with PDP.[5,6] Unlike atypical antipsychotics, pimavanserin has no activity at dopamine receptors.[6] Its mechanism of action for treating hallucinations and delusions associated with PDP remains unknown. However, it is hypothesized that it acts as an inverse agonist and antagonist at serotonin 5-$HT_{2A}$ receptors, with lesser effects at serotonin 5-$HT_{2C}$ receptors. Pimavanserin has no effects on serotonin 5-$HT_{2B,}$ dopaminergic, adrenergic, histaminergic or muscarinic receptors or calcium channels.[6,7] In general, inverse agonists bind to receptors to elicit the opposite effects of a normal agonist in which they inactivate receptors resulting in negative efficacy.[8]

### Efficacy

Pimavanserin was granted breakthrough therapy designation and priority review by the FDA based on preliminary clinical evidence from a randomized, multicenter, double-blinded, placebo-controlled trial.[5,9,10] This study was conducted over 28 days and included patients with L-dopa or dopamine-agonist-induced PDP. The objective was to determine the efficacy and safety of pimavanserin compared to placebo. Briefly, the study included 60 patients and the primary measure of efficacy, the Scale for the Assessment of Positive Symptoms (SAPS), did not show a significant difference in the total score (p=0.09). However, compared to placebo,

patients treated with pimavanserin had significant improvement in several psychosis measures such as the SAPS global measures of hallucinations and delusions (p=0.02), persecutory delusions (p=0.009), and the Unified Parkinson's Disease Rating Scale (UPDRS) delusions/hallucinations measure (p=0.05). In terms of safety, the most commonly reported adverse events in the pimavanserin group (≥10%) included somnolence, edema, and elevations of blood urea nitrogen; however, the incidence of these events did not differ significantly compared to the placebo group.

The efficacy of pimavanserin was further evaluated in 1 phase 3 clinical trial.[7] This multicenter, outpatient study was a 6-week, randomized, double-blinded, placebo-controlled trial. Eligible patients were ≥40 years of age and had a diagnosis of PD for at least 1 year, with psychotic symptoms developing after the PD diagnosis. These symptoms had to occur at least weekly within the month prior to screening and were severe enough to require antipsychotic therapy. Patients were also required to have a Mini-Mental State Examination (MMSE) score ≥21, have the ability to self-report symptoms, and be stable on PD medications for at least 1 month prior to and throughout the study period.

Patients were excluded if their psychosis was secondary to metabolic disorders or if dementia was diagnosed before PD.[7] Other exclusion criteria included stroke, myocardial infarction within 6 months of baseline, congestive heart failure, or history of long QT syndrome. Antipsychotic drugs, centrally-acting anticholinergic agents, and drugs that may prolong the QT interval were prohibited.

At the screening visit, patients needed to have a combined score of at least 6 or an individual score of at least 4 on the neuropsychiatric inventory (NPI) items A and/or B.[7] Participants then entered a 2-week lead-in phase in which the non-pharmacologic brief psychosocial therapy for PD (BPST-PD) was administered in order to determine whether there was a placebo response before baseline. At baseline, patients were required to have a score of at least 3 on both the SAPS for positive symptoms (hallucinations/delusions) and the non-global items of the SAPS-PD. The SAPS-PD is a 9-item scale adapted for PD from the hallucinations and delusions domains of the original SAPS. Each item in the scale is scored from 0-5 with 0 being none and 5 representing severe/frequent symptoms. The overall range is 0-45, with higher numbers indicating increased severity. Assessments were completed at baseline and on days 15, 29, and 43. The primary outcome was the change in the total SAPS-PD score between baseline and day 43. Selected secondary outcomes included the change in clinical global impression-severity (CGI-S) and CGI-improvement (CGI-I) scale scores by day 43. In terms of safety, adverse events and lab results were monitored throughout the study.

A total of 199 patients were randomized in a 1:1 ratio to pimavanserin 40 mg (two 20 mg tablets) and matching placebo once daily.[7] Demographics and clinical features did not differ between the groups at baseline. The mean age was 72.4 years in both groups, and the mean MMSE score was 26.6 in the pimavanserin group and 26 in the placebo group. For the primary outcome. pimavanserin was statistically superior to placebo in decreasing severity and/or frequency of hallucinations and delusions, as measured by SAPS-PD at 6 weeks, in patients with PDP.[6,7] (See Table 1).

Table 1. Primary efficacy results based on SAPS-PD.[6,7]

| Endpoint | Treatment Group | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
|---|---|---|---|---|
| **SAPS-PD (total)** | Pimavanserin | 15.9 (6.12) | -5.79 (0.66) | -3.06 (-4.91, -1.20) |
| | Placebo | 14.7 (5.55) | -2.73 (0.67) | -- |
| SAPS-PD hallucinations[b] | Pimavanserin | 11.1 (4.58) | -3.81 (0.46) | -2.01 (-3.29, -0.72) |
| | Placebo | 10.0 (3.80) | -1.80 (0.46) | -- |
| SAPS-PD delusions[b] | Pimavanserin | 4.8 (3.59) | -1.95 (0.32) | -0.94 (-1.83, -0.04) |
| | Placebo | 4.8 (3.82) | -1.01 (0.32) | -- |

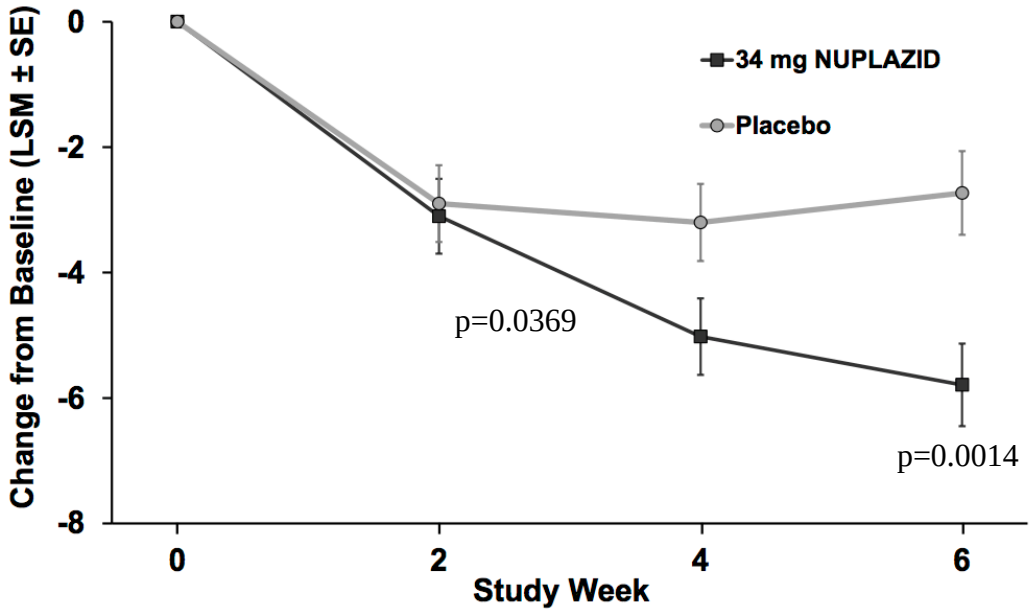
CI=confidence interval; LS Mean=least-squares mean; SAPS-PD=Parkinson's disease-adapted scale for the assessment of positive symptoms; SD=standard deviation; SE=standard error

[a]Difference (drug minus placebo) in least-squares mean change from baseline; findings were statistically significant

[b]Supportive analysis

Pimavanserin improved SAPS-PD scores throughout the 6-week trial as seen in Figure 1.[6]

Figure 1. SAPS-PD change from baseline through 6 weeks.[6,7]




For selected secondary outcomes, compared to placebo patients, patients treated with pimavanserin had significantly greater improvement in the CGI-S and CGI-I scores, indicating antipsychotic benefit.[6] For CGI-S, the least squares means were -0.44 and -1.02 for placebo and pimavanserin, respectively (95% confidence interval [CI]: -0.92 to -0.25; p=0.0007). For CGI-I, the least squares means were 3.45 and 2.78 for placebo and pimavanserin, respectively (95% CI: -1.06 to -0.27; p=0.0011).

**Dosage and Administration**

Pimavanserin is supplied as a 17 mg tablet.[6] For the treatment of hallucinations and delusions associated with PDP, the manufacturer recommends a dose of 34 mg taken orally as two 17 mg tablets once daily, without titration, with or without food.

**Safety**

*Contraindications:* Besides hypersensitivity, no contraindications have been documented.[6]

*Boxed warnings:* Although pimavanserin is not approved for use in elderly patients with dementia-related psychosis unrelated to PDP, an increase in the all-cause risk of death has been reported with all antipsychotics in this population, with most deaths appearing to be of cardiovascular or infectious etiology.[6]

*Warnings/precautions:* Pimavanserin has been shown to prolong the QT interval.[6] Concomitant use of pimavanserin with drugs that may prolong the QT interval is not recommended. Pimavanserin should also be avoided in patients with known QT prolongation or in patients with a history of cardiac arrhythmias and other conditions that may increase the risk of torsade de pointes, such as symptomatic bradycardia or congenital QT prolongation.

*Adverse reactions:* In a 6-week, placebo-controlled study, adverse reactions occurring in ≥5% of patients and at least twice the rate of placebo were peripheral edema (7% vs. 2%, respectively) and confusional state (6% vs. 3%, respectively).[6,7] Adverse reactions that were reported at an incidence of ≥2% and greater than the placebo

rate included nausea (7% vs. 4%, respectively), constipation (4% vs. 3%, respectively), gait disturbances (2% vs. <1%, respectively) and hallucinations (5% vs. 3%, respectively). Hallucinations included auditory, visual, tactile and somatic hallucinations. A total of 8% of patients treated with pimavanserin discontinued treatment due to adverse effects, while 4% of placebo-treated patients discontinued treatment. There were no differences in adverse effects when comparisons were made based on age (≤75 vs. >75 years).

*Drug interactions:* Pimavanserin is primarily metabolized by cytochrome P450 (CYP) 3A4; therefore, strong enzyme inhibitors and inducers can affect the concentration of pimavanserin.[6] The manufacturer recommends reducing the pimavanserin dose to 17 mg daily if used with a strong CYP 3A4 inhibitor, as strong CYP 3A4 inhibitors increase plasma concentrations and exposure of pimavanserin. On the other hand, strong CYP 3A4 inducers may reduce pimavanserin concentrations, which could result in decreased efficacy. The manufacturer recommends monitoring for reduced efficacy when pimavanserin is used concomitantly with strong CYP 3A4 inducers. In terms of dosage adjustment, it is recommended to reduce the dose of pimavanserin by one-half for CYP 3A4 inhibitors and to possibly increase the dose for CYP 3A4 inducers.

There is a potential for increased risk of cardiac arrhythmias with pimavanserin, and therefore, it is recommended to avoid its use in combination with drugs known to prolong the QT interval.[6]

*Special populations:* Safety and efficacy of pimavanserin have not been studied in patients with hepatic impairment, and therefore, its use is not recommended in this population.[6] For patients with mild to moderate renal impairment (creatinine clearance [CrCl] ≥30 mL/min), no dosage adjustment is required. However, pimavanserin is not recommended in patients with severe renal impairment (CrCl <30 mL/min), as safety and efficacy have not been established. No dosage adjustments are required for elderly patients.

There are currently no data available on pimavanserin use in pregnant women.[6] Administration of pimavanserin to pregnant rats and rabbits during organogenesis showed no adverse effects. There is no information on the presence of pimavanserin in human breast milk. At this time, the manufacturer recommends to weigh the risk versus benefit for lactating patients.

## Place in Therapy

Psychosis in PD is associated with poor outcomes including increased mortality and nursing home placement.[3,4] Prior to the availability of atypical antipsychotics, 100% of patients with PDP died within 2 years of nursing home placement.[11] Clozapine (Clozaril®) and olanzapine (Zyprexa®) have demonstrated efficacy in reducing symptoms of PDP.[3,4] The efficacy of pimavanserin for the treatment of PDP was established in 1 phase 3 clinical trial.[7] Unfortunately, the lack of head-to-head trials comparing pimavanserin to other atypical antipsychotics precludes conclusion about its comparative efficacy. Although clozapine and olanzapine carry the same boxed warning as pimavanserin, both clozapine and olanzapine have notable adverse effects.[11,12] In addition, clozapine requires monitoring, while olanzapine may worsen motor function.[4] Quetiapine (Seroquel®) is also commonly used for treatment of PDP but lacks efficacy based on the results of 2 randomized controlled trials.[3] In patients suffering from PDP in which dosage reduction of anti-PD medications is not sufficient to control symptoms of psychosis, pimavanserin therapy is recommended prior to use of alternative antipsychotics, such as clozapine, given its efficacy and more tolerable side effects.[3,7]

## Conclusions

Pimavanserin is a newly approved atypical antipsychotic for the treatment of hallucinations and delusions associated with PDP.[6] One phase 3 clinical trial demonstrated its efficacy in treating hallucinations and delusions in patients suffering from PDP.[7] Pimavanserin is unique in that none of the predecessor atypical antipsychotic medications are FDA-approved for PDP. Based on the results of 1 phase 3 clinical trial, pimavanserin appears to be generally well-tolerated compared to other antipsychotics such as clozapine and olanzapine, although it has not been directly compared to these agents. In summary, pimavanserin is the first

FDA-approved agent to treat PDP and may offer a better safety profile relative to other atypical antipsychotics.[6] However, given its lack of long-term efficacy and safety, use of pimavanserin should only be considered when psychotic symptoms persist despite dosage reduction or discontinuation of medications used to treat PD.[3,4]

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## Effect of Evolocumab on Risk of Cardiovascular Events: Review of the FOURIER Trial

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Repatha® (evolocumab) is a proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitor indicated for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who are on maximally tolerated statin therapy but require further lowering of low density lipoprotein cholesterol (LDL-C).[1] Evolocumab is also indicated for use with other LDL-lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH), who require further lowering of LDL-C. PCSK9 inhibitors are human monoclonal antibodies that bind to PCSK9 and prevent it from binding to the LDL receptor (LDLR). As a result, PCSK9-mediated LDLR degradation is averted, which leads to an increase in available LDLRs. These LDLRs are then able to clear more LDL from the blood, thus reducing LDL-C levels.

In clinical trials (Open Label Study of Long Term Evaluation Against LDL-C [OSLER]-1 and OSLER-2), administration of evolocumab at doses approved by the Food and Drug Administration (FDA), in conjunction with standard lipid-lowering therapy, was associated with a reduction of 61% in LDL-C levels.[2,3] In a

prespecified but exploratory analysis of data from the OSLER trials, investigators also observed a significant reduction in the incidence of major adverse cardiovascular events with use of evolocumab.[3] The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) study was designed to provide a more definitive assessment of the cardiovascular benefit of evolocumab.[4]

The FOURIER trial was a randomized, double-blind, multinational, placebo-controlled superiority study.[4] Investigators assessed the clinical efficacy and safety of evolocumab when added to high-intensity or moderate-intensity statin therapy in patients between 40 and 85 years of age with clinically evident ASCVD. ASCVD was defined as a history of myocardial infarction (MI), nonhemorrhagic stroke, or symptomatic peripheral artery disease. Patients were also required to be at a higher cardiovascular risk, with at least 1 major risk factor (e.g., diabetes, recent history of non-hemorrhagic stroke or MI) or 2 minor risk factors (e.g., metabolic syndrome, history of non-MI related coronary revascularization).[4,5] Patients also had to have a fasting LDL-C level of at least 70 mg/dl or a non-high density lipoprotein (non-HDL) cholesterol level of at least 100 mg/dl while they were taking an optimized regimen of lipid-lowering therapy (defined as atorvastatin 20 mg daily or equivalent, with or without ezetimibe).

Patients were randomized in a 1:1 ratio to receive evolocumab (140 mg every 2 weeks or 420 mg every month) subcutaneously or placebo.[4] Dosing frequency was based on patient preference. Randomization was stratified according to the screening LDL-C level and region. Laboratory assessments were performed at weeks 4, 12, and 24, and then every 6 months. The primary efficacy endpoint was time to cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization, whichever occurred first.[4,6] The key secondary endpoint was the composite of cardiovascular death, MI, or stroke. Safety analyses were performed using data on adverse events and laboratory testing.

All efficacy analyses were conducted on an intention-to-treat basis and safety analyses included patients who received at least 1 dose of a study agent.[4] As an event-driven study, it was determined that 1,630 cardiovascular events (cardiovascular death, MI, or stroke) were required for 90% power to detect a 15% relative risk reduction with evolocumab compared to placebo. The investigators used a Cox proportional-hazards model to calculate hazard ratios (HR) and 95% confidence intervals (CI). Log-rank tests were used to calculate p values for the time-to-event analyses. Per study protocol, if the rate of the primary endpoint was significantly lower in the evolocumab group ($p<0.05$), then, the key secondary endpoint and cardiovascular death were to be tested at a significance level of 0.05, in a hierarchical fashion.

A total of 27,564 patients underwent randomization.[4] Of these, 13,784 patients were placed in the evolocumab group and 13,780 patients were placed in the placebo group. Baseline characteristics of the patients were similar between the 2 groups, with the exception of weight (mean 85.0 kg treatment vs. 85.5 kg placebo, $p=0.01$) and the use of aspirin, a $P2Y_{12}$ inhibitor, or both (92.7% treatment vs. 92.0% placebo, $p=0.01$). However, the clinical significance of these differences is questionable. A total of 27,525 patients (99.9%) received at least 1 dose of the study agent. Approximately 12.5% of patients prematurely discontinued the study regimen, 0.7% withdrew consent, and 0.1% were lost to follow-up, with similar discontinuation rates between the 2 groups. The median duration of the follow-up was 2.2 years, which resulted in 59,585 patient-years of follow-up.

In terms of LDL-C, evolocumab was found to lower levels by 59% from baseline compared to placebo.[4] With regard to the primary endpoint, there was a statistically significant reduction in the risk of major cardiovascular events with evolocumab vs. placebo. These events occurred in 1,344 patients (9.8%) in the evolocumab group compared to 1,563 patients (11.3%) in the placebo group, demonstrating a 15% risk reduction (HR 0.85; 95% CI, 0.79 to 0.92; $p<0.001$). There was a statistically significant reduction in the risk of the secondary composite endpoint as well, occurring in 816 patients (5.9%) taking evolocumab and 1,013 patients (7.4%) in the placebo group. This demonstrated a 20% risk reduction (HR 0.80; 95% CI, 0.73 to 0.88; $p<0.001$). For both the primary and secondary endpoint, the magnitude of the risk reduction tended to increase over time. The risk reduction increased from 12% in the first year to 19% beyond the first year for the

primary endpoint. Similarly, the risk reduction for the secondary endpoint increased from 16% in the first year to 25% beyond the first year. For individual outcomes, there were reductions of 21-27% in the risk of MI (HR 0.73; 95% CI, 0.65 to 0.82; p<0.001), stroke (HR 0.79; 95% CI, 0.66-0.95; p=0.01), and coronary revascularization (HR 0.78; 95% CI, 0.71 to 0.86; p<0.001) for patients taking evolocumab. However, there were no statistically significant differences between groups in the rates of hospitalization for unstable angina, hospitalization for worsening heart failure, cardiovascular death, or death from any cause. In fact, the rates of cardiovascular death and all-cause death were slightly higher in the evolocumab group compared to placebo (HR 1.05; 95% CI, 0.88 to 1.25; p=0.62, and HR 1.04; 95% CI, 0.91 to 1.19; p=0.54, respectively).

With regard to safety, there were no significant differences observed between groups in the overall rates of adverse events or serious adverse events.[4] The rate of any adverse event was 10,664 (77.4%) in the evolocumab group and 10,644 (77.4%) in the placebo group. Serious adverse events occurred in 3,410 patients (24.8%) in the evolocumab group compared to 3,404 patients (24.7%) in the placebo group. The rates of individual adverse events such as muscle-related events, cataract, neurocognitive events, and hemorrhagic stroke did not differ significantly between the groups. Although rare, injection-site reactions were more prevalent in the evolocumab group than in the placebo group (2.1% vs. 1.6%; p<0.001). The majority of these reactions were classified as mild.

Based on the results of the trial, the authors concluded that when added to statin therapy, evolocumab significantly reduced the risk of cardiovascular events in patients with ASCVD compared to statin therapy, with or without ezetimibe, alone.[4] The authors also stated that because there is a well-documented delay between the onset of LDL-C lowering and the emergence of the full clinical benefit of the intervention in regards to clinical risk reduction, they believe patients taking evolocumab will see even more benefits when taking the drug for a longer period of time. However, this claim would require further investigation.

One major limitation was acknowledged by the authors of the trial. They stated that this trial had a relatively short duration of follow-up, a median of 2.2 years, compared to the average follow-up period of 5 years for several other lipid-lowering trials.[4] Notably, an open-label extension study designed to assess long term safety of evolocumab is currently recruiting participants from the FOURIER trial.[7] Additionally, the FOURIER trial required participants to have clinically evident ASCVD;[4] thus, the study findings may not be extrapolated to patients at high risk for ASCVD without clinical evidence of the disease, though they may qualify for treatment with evolocumab.

Findings from the FOURIER trial suggest that decreasing LDL-C levels with PCSK9 inhibition results in a clinically meaningful cardiovascular benefit.[4] However, the absolute risk reduction from taking evolocumab in addition to an optimized statin regimen is minimal at only 1.5%. This figure may be underwhelming to some, especially in consideration of the average wholesale price (AWP) of evolocumab, which is about $16,000 per patient per year.[8] With a median follow-up period of only 2 years, authors of the trial note that the magnitude of risk reduction may grow over time.[4] Similar to findings in trials with other LDL-C lowering therapies, there may be a delay between the onset of LDL-C lowering and the emergence of full clinical benefit from the drug. This may be elucidated with the completion of the extension study.

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## FDA Safety Update: Eluxadoline and Pancreatitis

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Eluxadoline, marketed in the United States as Viberzi®, was approved in May 2015 for treatment of diarrhea-predominant irritable bowel syndrome (IBS-D).[1] It is a mixed opioid receptor agonist with action at the mu, delta, and kappa receptors, although its strongest affinity is for the mu receptor. This mechanism is thought to produce its effect of reducing abdominal pain and diarrhea when given at the recommended dose of 100 mg by mouth twice daily. The package insert for eluxadoline currently indicates that a lower dose of 75 mg twice daily should be utilized in certain populations including patients without a gallbladder, patients taking an OATP1B1 inhibitor (such as cyclosporine, gemfibrozil, and anti-retrovirals), and patients with mild or moderate hepatic impairment.[2]

Eluxadoline was studied in 2 randomized controlled trials, IBS-3001 and IBS-3002, the results of which were pooled and published by Lembo et al in January 2016.[3] A total of 2425 adult patients with IBS-D were included in these 26-week, randomized, placebo-controlled, parallel-group, multicenter studies. Patients were randomized to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. A key difference between the 2 studies was that in IBS-3001 patients continued for an additional 26 weeks of double-blinded safety assessment, while in IBS-3002, the first 26-week period was followed by a 4-week, single-blinded placebo withdrawal period. The primary efficacy endpoint in both studies was the proportion of patients who achieved a composite response of greater than 50% of days with at least 30% reduction in abdominal pain and a stool consistency score of <5 on the same days at 12 weeks (Food and Drug Administration [FDA] end-point response), or at 26 weeks (European Medicines Agency [EMA] end-point response). At 26 weeks, the proportion of patients reporting the composite outcome was 31.0% in the eluxadoline 100 mg group, 26.7% in the eluxadoline 75 mg group, and 19.5% in the placebo group ($p<0.001$ for both dosing groups). The most common side effects among the pooled patient groups were constipation (8.0%), nausea (7.7%), and abdominal pain (6.5%).

Five patients in these studies were determined by the adjudication committee to have developed pancreatitis.[3] Three of these patients received eluxadoline at doses of 100 mg twice daily in the study, and 2 patients received 75 mg twice daily. A total of 8 patients had abdominal pain along with abrupt increases in hepatic enzyme levels. All 8 of these cases, plus 1 of the cases of pancreatitis, were determined to be consistent with a spasm of the sphincter of Oddi; none of the patients had a gallbladder. The authors stated that all pancreatitis cases happened in patients who either had biliary disorders (spasm of the sphincter of Oddi and biliary sludge) or alcohol use, and all cases resolved within the first week after onset. On March 15, 2017, the FDA released a safety announcement warning of an increased risk of pancreatitis in patients without a gallbladder who were being treated with eluxadoline.[4] This announcement included that this increased risk may be associated with the spasm of the sphincter of Oddi. The press release states that from drug approval through February 2017

there have been 120 reports of serious cases of pancreatitis or death reported through the FDA Adverse Event Reporting System (FAERS). Only 68 (56.7%) of these reports indicated the patient's gallbladder removal status, however 56 of these 68 events (82.4%) occurred in patients known to have no gallbladder despite most using the recommended lower dose. There have been 2 deaths associated with eluxadoline that have been reported: 1 was in a patient with pancreatitis and 1 in a patient with a sphincter of Oddi spasm.

This announcement warns patients of this potential adverse event and advises patients taking eluxadoline to get emergency care with symptoms of pancreatitis, including new or worsening abdominal pain, or pain in the upper right side of your abdomen that may move to your back or shoulder, with or without nausea and vomiting. Health care providers are recommended not to prescribe eluxadoline to patients who do not have gallbladders, or those with other listed risk factors (see Table 1 for full list). Recommended alternatives include over-the-counter medications for symptom relief such as bismuth subsalicylate or loperamide, as well as approved prescription medications, such as alosetron or rifaximin, if clinically appropriate.

Table 1. FDA recommendation of patients who should NOT receive eluxadoline.[4]

| **Patients who:** |
|---|
| Do not have a gallbladder |
| Have or may have had a blockage of the gallbladder or a sphincter of Oddi problem |
| Have had pancreatitis or other pancreas problems, including a blockage of the pancreas |
| Have a history of serious liver problems |
| Have a history of chronic or severe constipation |
| Have or may have had intestinal obstruction |
| Have a history of alcohol abuse, alcohol addiction, or drink more than three alcoholic beverages a day |

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## Updates in the Treatment of Helicobacter pylori

*Michael Burns, PharmD, MPH*

*Background*

*Helicobacter pylori* (*H. pylori*) infection is the most common chronic bacterial infection in humans (conservatively estimated to affect 50% of the global population), and is a major cause of gastritis, peptic ulcer disease, and gastric cancer.[1] In North America, the infection is seen most commonly in immigrants and descendants of immigrants from Africa, Asia, and Central/South America, as well as in those with lower socioeconomic status.[2] Acquisition of the infection generally occurs in childhood and persists chronically. If eradicated by successful antibiotic treatment, reinfection is uncommon (1-2%).[1]

*Historical Treatment of H. pylori*

The 2007 *American College of Gastroenterology (ACG) Guideline on the Management of Helicobacter pylori Infection* recommended use of either clarithromycin-based triple therapy for 14 days or bismuth quadruple therapy for 10-14 days as primary treatments for *H. pylori*.[3] Clarithromycin-based triple therapy consisted of a standard-dose proton pump inhibitor (PPI), clarithromycin 500 mg twice daily, and amoxicillin 1 g twice daily or metronidazole 500 mg twice daily. Bismuth quadruple therapy consisted of a standard-dose PPI or $H_2$ receptor antagonist ($H_2$RA) (ranitidine 150 mg twice daily), bismuth subsalicylate 525 mg four times daily, metronidazole 250 mg four times daily, and tetracycline 500 mg four times daily. Standard-doses of PPIs are defined as twice daily lansoprazole 30 mg, omeprazole 20 mg, pantoprazole 40 mg or rabeprazole 20 mg, or once daily esomeprazole 40 mg. Clarithromycin-based triple therapy is advisable only if patients have not previously been treated with a macrolide, with metronidazole in place of amoxicillin in penicillin-allergic patients.

When the 2007 guideline was published, sequential therapy was considered investigational in North America, but was being considered as an option due to waning efficacy with first-line therapies, particularly the clarithromycin component.[3] Sequential therapy utilized a standard-dose PPI plus amoxicillin 1 g twice daily for 5 days, followed by a PPI plus clarithromycin and tinidazole 500 mg each twice daily for 5 days. Salvage therapy for persistent infection with *H. pylori* included bismuth quadruple therapy (if not already used), or levofloxacin-based triple therapy with standard-dose PPI plus levofloxacin 500 mg daily and amoxicillin 1 g twice daily for 10 days (also considered investigational in North America but superior to bismuth quadruple therapies in studies from other regions). The use of tinidazole in place of amoxicillin and rabeprazole as the PPI with levofloxacin was alluded to in the guideline but were not explicitly recommended. Small studies of rifabutin were noted in the guideline but therapy with this medication was also not explicitly advised as a viable treatment option. A strong emphasis was placed on avoidance of previously used antibiotics for salvage therapy.

*2017 ACG Guideline for H. pylori Treatment*

The most recent ACG Guideline came out in January 2017, 10 years after its predecessor.[2] Since 2007, there have been major developments in the medicinal treatment of *H. pylori*, as shown in Table 1. With resistance and subsequent treatment failure continuing to rise for clarithromycin, treatment with **clarithromycin-based triple therapy** is now recommended only in areas of North America where resistance is documented as ≤15%. As regional documentation is poor and much of North America is believed to have >15% resistance, the utility of this therapy has been significantly compromised. **Bismuth quadruple therapy** for 10-14 days is now advised to be "strongly considered" if clarithromycin resistance exceeds 15% or the patient has received macrolide treatment for any reason.

Table 1. Current recommended first-line therapies for *H. pylori* infection.[2,3]

| Regimen | Drugs (Doses) | Dosing Frequency | Duration (Days) | Place in 2007 Guideline |
|---|---|---|---|---|
| Clarithromycin Triple | • PPI (standard or double dose)<br>• Clarithromycin (500 mg)<br>• Amoxicillin (1 g) or metronidazole (500 mg) | BID<br>BID<br>(metronidazole TID) | 14 | First-line |
| Bismuth Quadruple | • PPI (standard dose)<br>• Bismuth subcitrate (120-300 mg) or subsalicylate (300 mg)<br>• Tetracycline (500 mg)<br>• Metronidazole (250-500 mg) | BID<br>QID<br><br>QID<br>QID (250 mg), TID-QID (500 mg) | 10-14 | First-line |

| Regimen | Drugs (Doses) | Dosing Frequency | Duration (Days) | Place in 2007 Guideline |
|---|---|---|---|---|
| Concomitant | • PPI (standard dose)<br>• Clarithromycin (500 mg)<br>• Amoxicillin (1 g)<br>• Metronidazole or tinidazole (500 mg) | BID<br>BID<br>BID<br>BID | 10-14 | Not listed |
| Sequential | • PPI (standard dose) + amoxicillin (1 g)<br>followed by<br>• PPI (standard dose) + clarithromycin (500 mg) + metronidazole or tinidazole (500 mg) | BID<br><br>BID | 7<br>+<br>7 | Not listed |
| Hybrid | • PPI (standard dose) + amoxicillin (1 g)<br>followed by<br>• PPI (standard dose) + amoxicillin (1 g) + clarithromycin (500 mg) + metronidazole or tinidazole (500 mg) | BID<br><br>BID | 7<br>+<br>7 | Not listed |
| Levofloxacin Triple | • PPI (standard dose)<br>• Levofloxacin (500 mg)<br>• Amoxicillin (1 g) | BID<br>QD<br>BID | 10-14 | Second-line |
| Levofloxacin Sequential | • PPI (standard dose) + amoxicillin (1 g)<br>followed by<br>• PPI (standard dose) + amoxicillin (1 g) + levofloxacin (500 mg) + metronidazole or tinidazole (500 mg) | BID<br><br>BID<br>(levofloxacin QD) | 5-7<br>+<br>5-7 | Not listed |
| LOAD | • PPI (double dose)<br>• Levofloxacin (250 mg)<br>• Nitazoxanide (500 mg)<br>• Doxycycline (100 mg) | QD<br>QD<br>BID<br>QD | 7-10 | Not listed |

BID=twice daily; PPI=proton pump inhibitor; QD=once daily; QID=4 times daily; TID=3 times daily

The limited data that are available regarding antibiotic resistance for *H. pylori* in the United States can be found in Table 2.[2] It is important to note that clarithromycin resistance reduces the rate of treatment success with clarithromycin-based triple therapy by 50%, whereas metronidazole resistance only reduces it 25%. The efficacy of levofloxacin-based therapy is reduced by 20-40% with levofloxacin resistance.

Table 2. Antibiotic resistance rates of *H. pylori* strains in the United States, 2009-2011.[2]

| Antibiotic | Resistance Rate (%) |
|---|---|
| Metronidazole | 20 |
| Clarithromycin | 16 |
| Levofloxacin | 31 |
| Tetracycline | <2 |
| Amoxicillin | <2 |
| Rifabutin | <2 |

Since 2007, **sequential therapy** has been studied further and is now considered a viable first-line alternative to clarithromycin-based triple therapy, though it showed similar eradication rates when administered for a 10-day course.[2] A 14-day course has shown some promise outside of North America and may be considered, but success with sequential therapy is regional and comparable studies are needed to confirm improved outcomes within North America. Metronidazole 500 mg may now be used in place of tinidazole 500 mg if needed.

**Concomitant therapy** is a newly recommended first-line therapy that utilizes the same medications and doses as sequential therapy but all 4 drugs are given concurrently for 3-14 days as opposed to a split dosing regimen.[2] This combination has not yet been studied in North America but has shown eradication rates between 82 and 90% in meta-analyses from other regions, with superiority over clarithromycin-based triple therapy and comparable eradication rates to sequential therapy. Longer courses were associated with better outcomes, so 10-14 day courses are advised despite data only being available from randomized-controlled trials for up to 10 days. A cross between concomitant and sequential therapies, deemed **hybrid therapy**, involves a standard-dose PPI plus amoxicillin 1 g twice daily for 7 days followed by 7 days of all 4 medications (PPI, amoxicillin, clarithromycin, and tinidazole or metronidazole), and showed comparable eradication rates in regions outside of North America. This is also considered a first-line option in the guideline.

Despite a suspected high resistance to levofloxacin in the United States (see Table 2), compelling data from other regions has led to **levofloxacin-based triple therapy** and additional levofloxacin-based treatment options to be considered first-line options in the 2017 ACG Guideline.[2] The duration of levofloxacin-based triple therapy has been extended to 10-14 from 10 days based on international data suggesting superiority over 7 days of clarithromycin-based triple therapy. A modified sequential therapy with levofloxacin 500 mg daily plus continuation of amoxicillin in the second 5-7 days of therapy in place of clarithromycin (with the same initial 5-7 day treatment) showed superiority over a pooled 7-14 days of clarithromycin-based triple therapy or 7-14 days of standard sequential therapy (88% versus 71% eradication rates). Another novel therapy with 7-10 days of levofloxacin 250 mg daily, omeprazole 40 mg daily, nitazoxanide (Alinia®) 500 mg daily, and doxycycline 100 mg daily, deemed **LOAD**, achieved 89-90% eradication rates versus 73% with a regimen of lansoprazole, clarithromycin, and amoxicillin for 10 days;[4] however, the high cost and lack of data in North America for this regimen are noted to limit its utility.[2] A treatment algorithm for when to use these and other first-line therapies may be found in Figure 1.

The use of **adjuvant probiotics** with *H. pylori* treatment is discussed in the 2017 ACG guideline as an emerging trend.[2] *Lactobacillus* and *Bifidobacterium* species have demonstrated a potential inhibitory effect on *H. pylori* and have improved the tolerability and eradication rates of antibiotic regimens used to treat *H. pylori*. This may also improve adherence to these complex regimens. However, the available studies were from outside the United States and were not blinded, and there are no data available on how or when to dose the probiotics.

**Testing for confirmation of *H. pylori* eradication** is now advised for all patients as opposed to only those with pronounced symptoms.[2] Bismuth quadruple therapy and levofloxacin-based triple therapy remain as viable **salvage therapies** for persistent *H. pylori* infection. Rifabutin triple therapy is now suggested as a possible salvage therapy, with cost, myelotoxicity risk, and the potential for causing resistance for *Mycobacterium tuberculosis* limiting its utility. High dose **dual therapy** with standard or double-dose PPI 3 to 4 times daily plus amoxicillin 750 mg four times daily or 1 g three times daily has emerged as an option on the premises of maximizing gastric amoxicillin concentrations and low resistance to amoxicillin. Sequential therapy, hybrid therapy, and furazolidone (not available in the United States) are not recommended as salvage therapies due to poor/incomplete data. Avoidance of previously used antibiotics in selecting a salvage therapy remains critical. A treatment algorithm for *H. pylori* salvage therapies may be found in Figure 2.

Figure 1. *H. pylori* first-line treatment algorithm.[2]

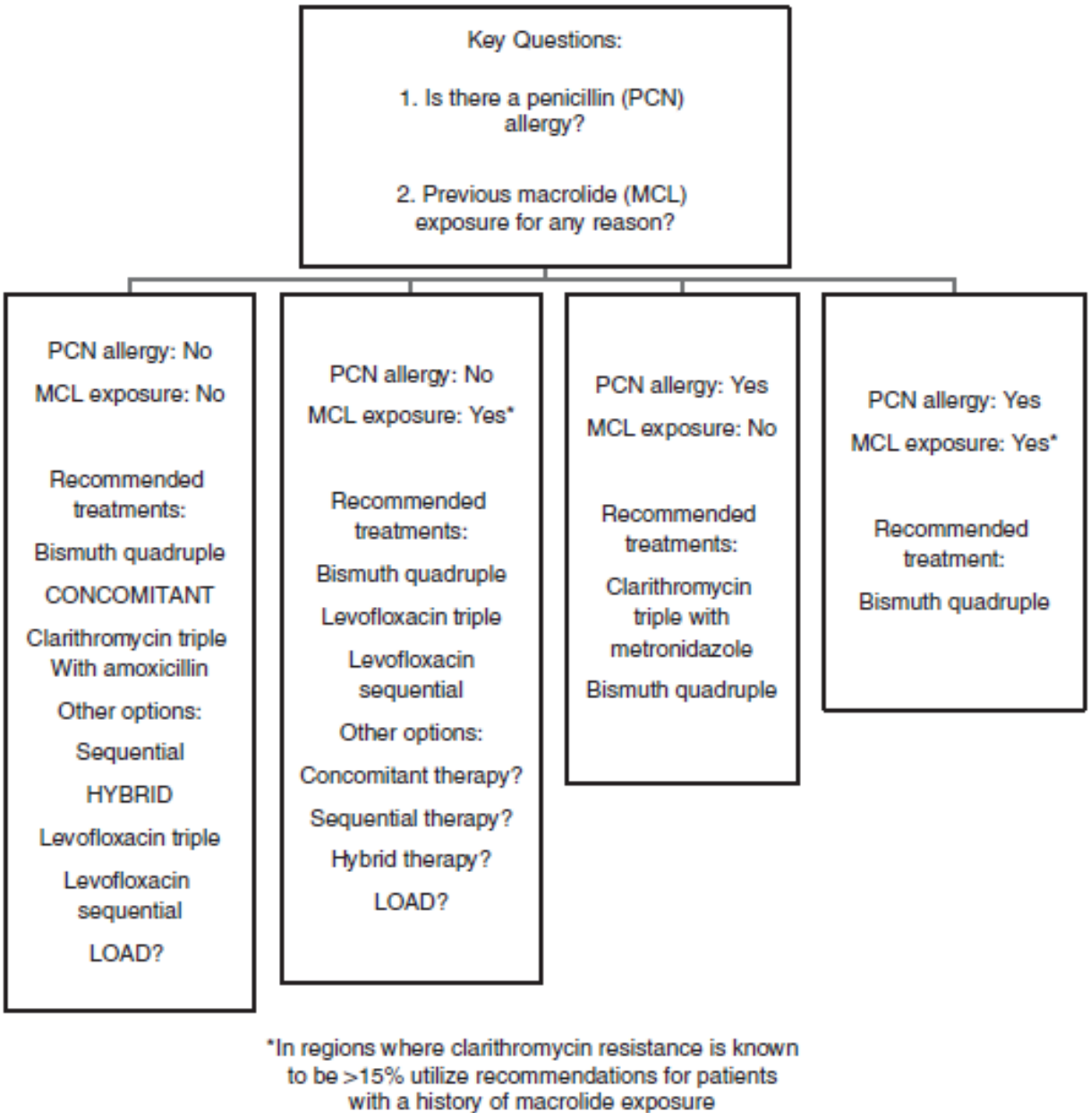
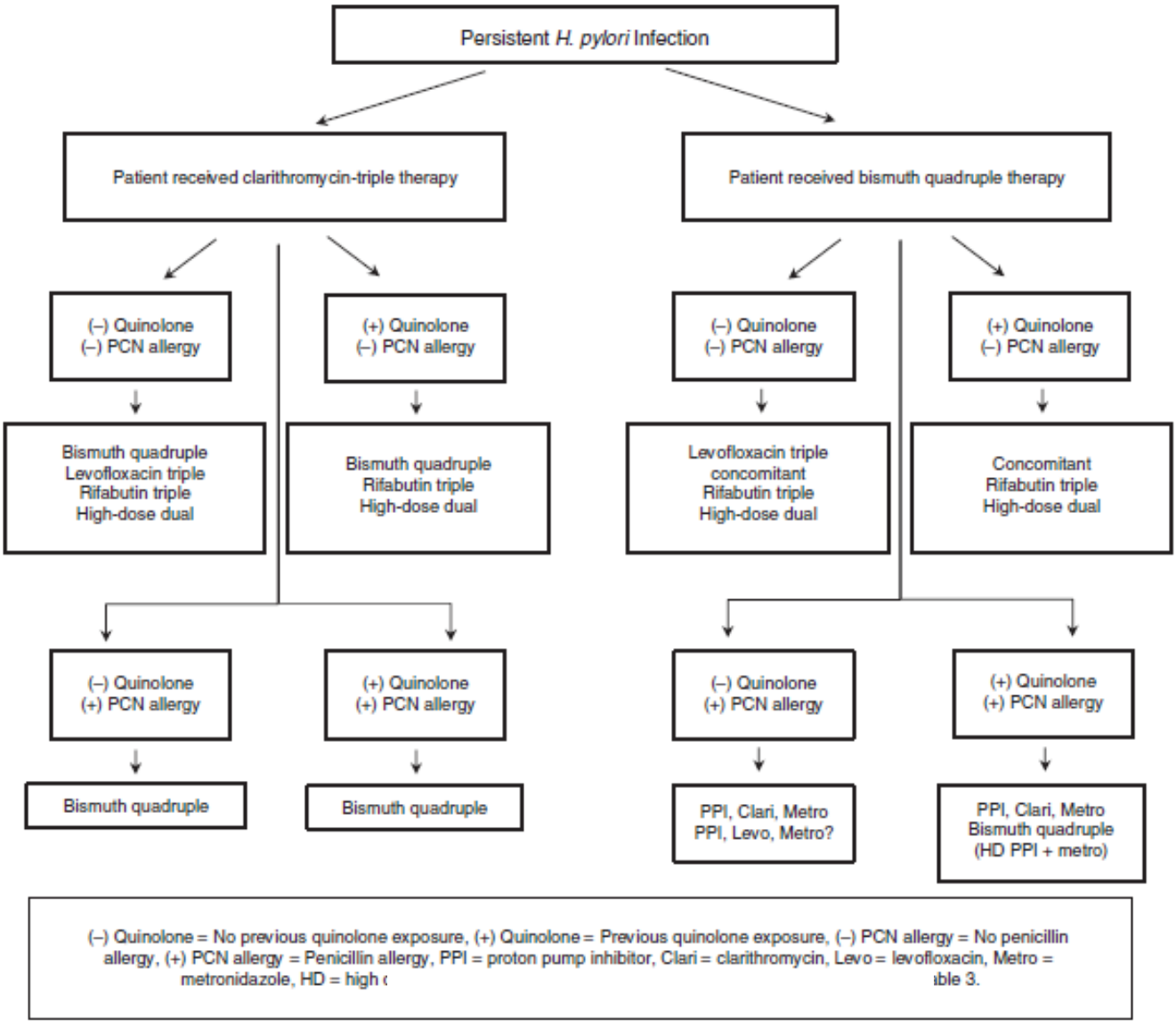


Figure 2. *H. pylori* salvage therapy algorithm.[2]




*Emerging Therapies*

Vonoprazan is a novel acid suppressant that works as a potassium-competitive acid blocker that became available exclusively in Japan in 2015 for the treatment of gastroesophageal reflux disease, peptic ulcers, and *H. pylori*.[5] Using a retrospective national *H. pylori* database, Shichijo and colleagues compared the tolerability and efficacy of either vonoprazan 20 mg (422 patients) or a conventional PPI (2,293 patients), both combined with amoxicillin 750 mg and clarithromycin 200-400 mg twice daily for 7 days. Eradication rates were 87% for vonoprazan-based triple therapy versus 72% for conventional PPI-based triple therapy, with comparable rates of adverse events (diarrhea, nausea/vomiting, and rash), none of which were classified as severe.

A prospective, single-center Chinese study evaluated the use of minocycline as an alternative to tetracycline in bismuth quadruple therapy as both an initial and a salvage therapy.[6] The regimen, referred to as EMMB, utilized esomeprazole 20 mg twice daily, minocycline 100 mg twice daily, metronidazole 400 mg four times daily, and bismuth potassium citrate 110 mg four times daily for 14 days. There were no control groups in this study. Eradication rates of 86% (intention-to-treat [ITT] analysis) to 93% (per-protocol [PP] analysis) were

reported for initial therapy and 83% (ITT analysis) to 90% (PP analysis) as salvage therapy. As international shortages of tetracycline have been resolved,[2] the present need for minocycline use is diminished; however, it may be a viable alternative if the need arises again. A double-blind clinical trial directly comparing quadruple therapies with tetracycline to those with minocycline is needed.

A randomized, parallel-controlled, open-label, prospective multicenter study of 303 patients in China assessed the addition of polaprezinc (an internationally available mucosal protective agent used to coat ulcers) to clarithromycin-based triple therapy.[7] Patients were randomized to receive polaprezinc 75 mg twice daily (Arm A; 113 patients), 150 mg twice daily (Arm B; 108 patients), or no polaprezinc (Arm C; 111 patients) for 14 days. All patients also received omeprazole 20 mg, amoxicillin 1 g, and clarithromycin 500 mg twice daily for 14 days. Eradication rates were significantly improved with polaprezinc therapy on ITT analysis at 77.0% (Arm A) and 75.9% (Arm B) for triple therapy plus polaprezinc versus 58.6% for triple therapy alone, a difference of 18.4% (95% confidence interval 6.4-30.4%, $p<0.01$) and 17.4% (95% confidence interval 5.2-29.6%, $p<0.01$), respectively. Higher dose polaprezinc did not improve outcomes, and polaprezinc did not significantly improve symptoms. Polaprezinc use was considered safe and well-tolerated.

*Conclusions*

Treatment recommendations for *H. pylori* have changed significantly between the 2007 and 2017 ACG guidelines.[2,3] Selection of a first-line therapy has become significantly more complex as new treatments have emerged and antibiotic resistance has continued to rise. Data specific to North America are presently very sparse and additional data are necessary to continue to determine best practices in the United States.

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