

## Criteria for Use of High-dose Oral Proton Pump Inhibitors

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

*These criteria were based on the best clinical evidence currently available. The recommendations in this document are dynamic, and will be revised as new clinical information becomes available. This guidance is intended to assist practitioners in providing consistent, high-quality, cost-effective drug therapy. These criteria are not intended to interfere with clinical judgment; the clinician must ultimately decide the course of therapy based on individual patient situations.*

Criteria	Yes	No
<i>The answer to at least one item below must be YES in order to meet criteria.</i>		
A. Gastric ulcers <i>May use <b>double-dose omeprazole as initial therapy for 4–8 weeks</b>, FDA-approved; use standard doses for other PPIs.</i>	<input type="checkbox"/>	<input type="checkbox"/>
B. <i>Helicobacter pylori</i> eradication to reduce recurrence of duodenal ulcers, as part of dual or triple antibiotic-based therapy <i>Should use <b>double-dose PPI therapy</b>, typically for 1–2 weeks; FDA-approved</i>	<input type="checkbox"/>	<input type="checkbox"/>
C. Endoscopic evidence of severe erosive esophagitis (e.g., presence of ulceration, stricture, perforation, or bleeding, or 2 most severe categories on a 4-point grading scale or 3 most severe categories on a 5-point grading scale) <i><b>Double-dose PPI</b> may be used as initial and maintenance therapy.</i>	<input type="checkbox"/>	<input type="checkbox"/>
D. Insufficient improvement in or recurrence of symptoms of GERD or other acid-related disorders (such as high-risk NSAID-related gastric ulcers) after an adequate trial ( $\geq 4$ to 8 weeks) of standard-dose PPI <i><b>Double-dose PPI</b> (for <math>\geq 4</math> weeks) may be started empirically without further diagnostic testing</i>	<input type="checkbox"/>	<input type="checkbox"/>
E. Insufficient improvement in or recurrence of symptoms of GERD or other acid-related disorders (such as high-risk NSAID-related gastric ulcers) after an adequate trial ( $\geq 4$ to 8 weeks) of double-dose PPI therapy <i><b>Higher than double-dose PPI therapy</b> may be started while awaiting further consultation and testing, and continued as maintenance therapy; titrate according to test results and symptom control. If test results suggest possible relative “resistance” to that particular PPI, then consider <b>switching to another PPI at double the standard dose</b>.</i>	<input type="checkbox"/>	<input type="checkbox"/>
F. GERD-related chronic nonspecific cough (dry and non-productive cough of $\geq 3$ weeks’ duration without any other respiratory symptom, sign, or systemic illness) OR signs and symptoms of laryngopharyngeal reflux (LPR) OR as a diagnostic trial (PPI test) for uncomplicated GERD <i><b>An 8-week therapeutic or empiric trial of double-dose PPI may be considered</b>; response should be documented; treatment plan should be re-evaluated if there is no response after 8 weeks.</i>	<input type="checkbox"/>	<input type="checkbox"/>
G. Prevention of acute rebleeding of peptic ulcers after endoscopic hemostasis <i><b>Quadruple-dose oral PPI</b> may be given in 2 or 4 divided doses for <b>5 days only</b>; <b>standard doses</b> should be used thereafter.</i>	<input type="checkbox"/>	<input type="checkbox"/>
H. Reduction of risk of upper gastrointestinal bleeding in critically ill patients who have documented intolerance, contraindication, or insufficient response to intravenous H <sub>2</sub> RA therapy <i><b>Double-dose PPI</b> for up to 2 weeks; FDA-approved for omeprazole immediate-release powder for oral suspension.</i>	<input type="checkbox"/>	<input type="checkbox"/>
I. Pathologic hypersecretory conditions (e.g., Zollinger-Ellison syndrome) <i>May start with <b>double- or triple-dose PPI therapy and titrate to response</b><sup>a</sup>; FDA-approved.</i>	<input type="checkbox"/>	<input type="checkbox"/>
Exclusions	Yes	No
<i>If the request for high-dose PPI is for the indication below (i.e., answer is YES), then high doses of oral PPIs cannot be supported based on current evidence.</i>		
Treatment of asthma in patients with or without diagnosis of GERD	<input type="checkbox"/>	<input type="checkbox"/>

NOTE: Patients should be given an adequate trial ( $\geq 4$  to 8 weeks, with PPIs taken before meals) of formulary PPI agents before considering nonformulary PPIs.<sup>b</sup>

<sup>a</sup> Double doses for pantoprazole; triple doses for lansoprazole, omeprazole, or rabeprazole; doses must be titrated to response.

<sup>b</sup> Check updated VA National Formulary at: <http://vawww.pbm.med.va.gov/natform.htm> or <http://www.vapbm.org/PBM/natform.htm>.

## Summary of Literature Review: Criteria for Use of High-dose Oral Proton Pump Inhibitors

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### Background

Although proton pump inhibitors (PPIs) are highly effective agents for the treatment of acid-related gastrointestinal disorders, some patients may not achieve an adequate response to *standard doses* (defined in this guidance, for relative quantification of higher doses, as 20 mg of omeprazole or rabeprazole; 20 or 40 mg of esomeprazole; 30 mg of lansoprazole; or 40 mg of pantoprazole<sup>c</sup>). For instance, of patients with symptom-based diagnoses of GERD who have not responded to previous histamine<sub>2</sub> receptor antagonist (H<sub>2</sub>RA) therapy (ranitidine 150 mg twice daily for 6 weeks), 30% have been reported to experience moderate to severe heartburn after 8 weeks of standard-dose PPI therapy.<sup>1</sup> Of patients with erosive esophagitis, 3% to 23% may not heal<sup>2-12</sup> and 5% to 60% may not sustain symptom resolution<sup>3,7,13</sup> by 8 weeks of PPI therapy. After an initial response to acute PPI therapy, 10% to 45% of patients with erosive esophagitis experience endoscopic relapse during 52 weeks of standard-dose PPI maintenance therapy.<sup>3,6-9,11,12,14-21</sup>

This updated guidance outlines the indications for which higher than the standard oral doses of PPIs (as defined in these criteria) are considered appropriate and briefly reviews the existing literature on PPI refractoriness. The major changes from the previous version of this guidance are (1) the addition of an H<sub>2</sub>RA at bedtime to standard-dose PPI is no longer recommended; (2) the addition of a prokinetic agent is no longer recommended unless it is used to treat concomitant gastroparesis; and (3) the 60-day PPI supply limit and 8-week re-evaluation (after the initial evaluation that determines requirement for high-dose PPI therapy) is not required.

### Reasons for Lack of Response to PPIs

There are numerous proposed explanations for a lack of clinical response to PPI therapy, and the reasons may involve failure to achieve a desired clinical response to PPIs despite acid suppression or, rarely, drug failure (i.e., decreased acid inhibitory effects of the PPI). **Patient, disease, and pharmacologic factors, or a combination of these may be responsible for lack of response to PPIs.** In patients with gastroesophageal reflux disease (GERD), the reasons include nocturnal acid breakthrough (NAB, defined as pH < 4 in the fundus for more than 1 hour during the night in patients receiving PPI therapy),<sup>22,23</sup> persistent or PPI-induced pathologic duodenogastroesophageal bile<sup>24,25</sup> or postprandial nonacid reflux,<sup>24</sup> abnormal esophageal motility or insufficiency of the lower esophageal sphincter,<sup>26</sup> intermittent but undetected esophageal acid reflux,<sup>27</sup> an unexplained dose-dependent phenomenon,<sup>28</sup> and incorrect diagnosis. Patients with Barrett's esophagus<sup>29</sup> or laryngopharyngeal reflux<sup>30</sup> not uncommonly show inadequate clinical response to standard-dose PPI therapy. In patients with peptic ulcer disease, continued ingestion of nonsteroidal antiinflammatory drugs has been associated with inadequate clinical response to PPIs.<sup>31</sup> Patients may not achieve good symptom control for other patient-related reasons, such as nonadherence to medication regimens, improper timing of doses in relationship to meals, CYP2C19 genotype,<sup>32,33</sup> and an unexplained relative resistance to certain PPIs and not to others.<sup>34</sup> The mechanism for failure of an acid-related condition to respond to PPIs in medication-adherent patients with accurate diagnoses remains unclear and it is possible that multiple etiologies play a role. Factors that might predict failure to standard-dose PPI therapy have been evaluated in a number of studies<sup>3,17,19,35</sup> but the findings generally lack a consistent pattern, and other studies have found no predictive factors.<sup>6,14</sup> Based on our current knowledge, patients with conditions that will not respond to PPI therapy cannot be prospectively identified.

### Management of Patients Not Responding to Standard or Higher Doses of PPIs

#### Is there a treatment difference between increasing the PPI dose and add-on H<sub>2</sub>RA?

**Key findings:** No randomized controlled trials; no trials in PPI nonresponders; no direct evidence. Poor-quality, indirect evidence suggests that, compared with add-on H<sub>2</sub>RAs, increasing the PPI dose may be associated with similar or greater control of NAB or intragastric pH, and similar intraesophageal pH, reflux episodes, and symptom control.

A literature search found two trials involving healthy volunteers<sup>36,37</sup> and two other trials involving patients with GERD<sup>38,39</sup> that compared an increased dose of PPI with an H<sub>2</sub>RA added on to PPI therapy. The literature search found

<sup>c</sup> Based on FDA-approved doses for healing of erosive or ulcerative esophagitis

no well-designed trials that directly addressed the key question of whether there is a treatment difference between increasing the dose of PPI and addition of an H<sub>2</sub>RA to PPI therapy in terms of clinical outcomes in patients with an acid-related disorder who have not adequately responded to PPIs. Therefore, there is a lack of direct evidence to guide optimal management of these patients.

The two studies in patients with GERD were poor-quality, prospective studies that indirectly pertained to the key question; i.e., they compared increasing the dose of PPI with add-on H<sub>2</sub>RA in patients with GERD that was not refractory to PPIs.<sup>38,39</sup> The first study, using a single-blind, placebo-controlled, nonrandomized crossover design, compared placebo, low-dose ranitidine (75 mg at bedtime), and omeprazole (20 mg at bedtime), each added on to omeprazole (20 mg) in the morning, in 16 patients with heartburn.<sup>38</sup> This study did not show a difference among the add-on placebo (i.e., standard-dose PPI), low-dose H<sub>2</sub>RA (i.e., add-on H<sub>2</sub>RA), and omeprazole (i.e., double-dose PPI) groups in terms of percentage time with NAB (57% versus 38% versus 24%), percentage time with intraesophageal pH < 4 (0.8% versus 0.8% versus 0.7%), and number of intraesophageal reflux episodes (34 versus 30 versus 32).<sup>38</sup> NAB occurred numerically but not statistically less often with double-dose PPI than add-on H<sub>2</sub>RA (and standard-dose PPI); however, the study may have lacked sufficient power to detect a significant treatment difference. The study results are tentative because of the lack of randomization, small sample size, and lack of power. The results require confirmation by well-designed trials.

The other study was an observational study that evaluated 13 patients with GERD and 9 healthy volunteers.<sup>39</sup> It compared four sequentially administered regimens on the basis of intragastric and intraesophageal pH recordings taken before and after treatment, as well as symptom control. The four treatments were (1) omeprazole 20 mg twice daily before meals for 2 weeks; (2) omeprazole twice daily plus ranitidine 300 mg at bedtime for 4 weeks followed by a mean washout period of 7 months; (3) omeprazole 20 mg in the morning and at bedtime for 2 weeks; and (4) omeprazole 20 mg every 8 hours for 2 weeks. In the overall study population, the triple-dose omeprazole regimen was associated with greater improvements in intragastric acid suppression and median percentage time intragastric pH < 4 than the other treatments; however, there was considerable overlap among the regimens. Double-dose omeprazole plus add-on ranitidine was associated with greater improvements in the same end points as compared with the regimen in which omeprazole was administered in the morning and at bedtime (however, this result does not pertain to the key question). Only results for intraesophageal pH recordings and symptom control were reported for the subgroup of patients with GERD. In this subgroup, the authors reported no statistically significant difference between any of the treatment regimens for percentage time intraesophageal pH < 4 and all patients were asymptomatic on each treatment. These results should be considered inconclusive because of the small sample size (n = 13), and the observational design prohibits inferences about causality. The results for the mixed study population overall may not be applicable to a population of patients with GERD.

The quality of evidence for each study is poor because of small sample sizes and lack of either randomization<sup>38</sup> or randomization and blinding.<sup>39</sup> Only the second study used clinical outcome measures (e.g., frequency or severity of heartburn or other reflux symptoms).<sup>39</sup> No studies were found in patients with acid-related disorders other than GERD. Better-designed trials in relevant patient populations are required.

### Do add-on H<sub>2</sub>RAs provide incremental benefit over PPI therapy?

**Key findings:** One Cochrane systematic review; 4 GERD studies; 1 fair-quality randomized trial; poor-quality evidence overall. The results suggest that add-on H<sub>2</sub>RAs do not provide incremental improvement over PPI therapy in intraesophageal pH and clinical outcomes, and even though H<sub>2</sub>RAs may add benefit in controlling intragastric pH or NAB, there was no evidence that NAB induced intraesophageal reflux.

The two trials involving healthy volunteers<sup>36,37</sup> mentioned in the section above were the only trials to meet inclusion criteria of a Cochrane systematic review evaluating the efficacy of adding H<sub>2</sub>RAs to PPI therapy to control NAB.<sup>40</sup> The systematic review concluded no implications for clinical practice because the two trials found inconsistent results, and the review suggested that the addition of H<sub>2</sub>RAs to PPI therapy should only be used in randomized trials until further evidence became available.

Six studies addressed the question of whether H<sub>2</sub>RAs add further benefit over PPI therapy. One observational study involved healthy volunteers.<sup>41</sup> Five prospective studies compared the addition of a bedtime dose of H<sub>2</sub>RA with PPI monotherapy in the treatment of patients with GERD. Four of these were small studies involving 16 to 34 subjects with apparently uncomplicated GERD. Two of the four were mentioned above as poor-quality studies involving only patients with GERD<sup>38</sup> or a mixed population (with results reported separately for the GERD subgroup).<sup>39</sup> One was a fair-quality, randomized, double-blind, placebo-controlled trial involving patients with GERD,<sup>42</sup> and the another was a poor-quality,

observational study in a mixed population of patients with GERD and healthy volunteers; however, this study is not summarized here because the results for the subgroup with GERD were not reported separately.<sup>43</sup> The fifth study was a fair-quality, comparative cohort study in 85 patients with laryngopharyngeal reflux.<sup>44</sup>

The fair-quality randomized trial compared single-dose ranitidine (150 mg at bedtime with a provocative meal) against placebo in combination with omeprazole (20 mg twice daily with meals for 1 week) in 19 *Helicobacter pylori*-negative patients with frequent heartburn (at least 4 days per week and 1 night per week for at least 6 months).<sup>42</sup> In this study, combination therapy with double-dose omeprazole plus ranitidine was better than double-dose omeprazole plus placebo in reducing the percentage time with NAB. In spite of the difference in control of intragastric pH, the study did not show a statistically significant difference between the add-on ranitidine and placebo treatment groups in terms of the percentage time that intraesophageal pH was less than 4 (estimated, 10% versus 15%, respectively), heartburn severity (mean, 1.1 versus 1.5; rating scale not reported), frequency of awakenings due to heartburn (mean, 2.7 versus 3.3), sleep quality rating (mean, 2.6 versus 2.2; visual analogue scale; dimensions not reported), and polysomnographic measures (6 items). In addition, there was no significant difference in the number of reflux events (defined as intraesophageal pH < 4 for at least 5 seconds) during periods with NAB as compared with periods without NAB (control) (each period had 4 reflux events), and no significant correlation between intragastric pH and intraesophageal pH ( $r = 0.30$ , ranitidine versus  $r = 0.23$ , placebo). Therefore, in this study, there was no evidence that NAB induces intraesophageal reflux. Since the trial was small, it may have lacked sufficient power to detect significant differences if true differences exist between treatments. In addition, the beneficial effect of one dose of H<sub>2</sub>RA added to PPI may not reflect long-term responses due to development of tolerance (see below). Therefore, the results should be considered tentative. Additional trials are required to confirm the results.

A similar pattern of results (in which a significant difference between combination therapy with PPI plus H<sub>2</sub>RA and PPI monotherapy was shown in terms of NAB but not for intraesophageal reflux) was seen in one<sup>43</sup> of the three poor-quality studies. In another poor-quality study, combination therapy was associated with better improvements in nocturnal gastric acidity than PPI monotherapy, but no significant treatment difference was shown in NAB and intraesophageal reflux.<sup>38</sup> The results of these three studies were consistent in showing that, compared with PPI monotherapy, combination PPI-plus-H<sub>2</sub>RA therapy was associated with improved gastric pH control but not esophageal acid exposure.

The cohort study involving patients with LPR found no statistically significant differences between double-dose PPI (lansoprazole) and double-dose PPI plus H<sub>2</sub>RA (omeprazole plus ranitidine) therapy in terms of responder rates (proportion of patients achieving at least 50% improvement in symptoms over baseline).<sup>44</sup> Comparisons with a third treatment group that received standard-dose PPI therapy are discussed below. Since the study used an observational study design and compared different PPIs, it is difficult to make firm conclusions about the relative efficacies of the two therapies.

Of the four studies in patients with uncomplicated GERD, two used clinical outcome measures.<sup>39,42</sup> All four assessed both intragastric and intraesophageal pH.<sup>38,39,42,43</sup> Only the results of the randomized trial allow inferences about causality between treatments and outcomes.<sup>42</sup> Other trials have also shown a lack of direct correlation between NAB and esophageal acid reflux events<sup>45</sup>; however, one trial found that the duration of NAB correlated with the number of nocturnal supine esophageal acid reflux events lasting longer than 5 minutes.<sup>45</sup> It has been suggested that NAB may not be clinically important in healthy individuals or patients with uncomplicated GERD; however, suppression of NAB may be necessary for optimal management of patients with esophageal dysmotility or Barrett's esophagus.<sup>46</sup>

### Is there a treatment difference between increasing the dose of PPI and switching to another PPI?

**Key findings:** No randomized controlled trials directly comparing treatment approaches; 2 observational studies provide best (albeit poor-quality) evidence of treating PPI nonresponders. There is better evidence supporting PPI dosage increases than for switching to another PPI. Progressively increasing the dose of PPI in subgroups of patients who did not respond to lower doses of PPIs resulted in incremental improvement in responder rates. Certain individuals may respond better to one PPI than another, but there is little documentation of this phenomenon.

Two observational studies have shown that a subgroup of patients who do not respond to at least a standard dose of PPI eventually respond to increasing doses of PPIs.<sup>28,47</sup> In the first study, 6 (85.7%) of 7 patients in a subgroup of patients with GERD refractory to omeprazole 40 mg daily showed improvement after increasing the dose to 80 mg daily in the median percentage time with intragastric pH < 4.<sup>28</sup> In the second study, a cohort of patients with GERD, who had not responded to H<sub>2</sub>RA therapy but who eventually responded to double-dose omeprazole, were followed for a mean of

48 months during standard-dose (n = 86) or double-dose (n = 5) maintenance omeprazole therapy.<sup>47</sup> Of the 86 patients receiving standard-dose omeprazole as maintenance therapy, 40 (47%; 95% CI: 36% to 58%) relapsed. All (100%) of the patients who relapsed achieved re-healing within 3 months of increasing the dose of omeprazole to 40 mg daily. Seven patients (18%; 95% CI: 7% to 33%) who experienced a second relapse after a mean of 24 months re-healed on omeprazole 60 mg daily for a mean of 36 months.

In a cohort study that compared double-dose PPI and standard-dose PPI (as well as double-dose PPI plus H<sub>2</sub>RA) in patients with LPR, the higher dose was associated with higher responder rates than the lower dose (15/30, 50% versus 7/25, 28%) after 2 months of treatment.<sup>44</sup> After treating 13 nonresponders with an additional 2 months of double-dose therapy, 7 (54%) achieved at least 50% improvement in symptoms over baseline. Among patients taking double-dose PPIs, an additional 22% of patients achieved a response at 4 months relative to 2 months of therapy, suggesting that longer therapy also improves responder rates. However, these results need confirmation in randomized controlled trials.

When double-dose omeprazole was compared with double-dose lansoprazole in 20 healthy volunteers in an open-label randomized controlled trial with two-way crossover, a remarkable degree of intersubject variability in intragastric pH control was observed with both PPIs.<sup>34</sup> Better acid control was achieved in 14 subjects on omeprazole (20 mg twice daily) and 5 subjects on lansoprazole (30 mg twice daily), where each drug was given 15 minutes before breakfast and dinner for 7 days. One individual (5%) was an outlier who obtained less gastric acid suppression on omeprazole and an average degree of acid suppression on lansoprazole. This report documented that some individuals may experience better acid suppression on a certain PPI as compared with another. The authors gave several possible explanations for a possible difference in responses to lansoprazole and omeprazole. The drugs may differ because lansoprazole has a more pronounced meal interaction than omeprazole, omeprazole may be more susceptible to acid degradation (which would favor administration with food to increase bioavailability), or there may be a differential effect based on *Helicobacter pylori* status (in these preliminary observations, lansoprazole appeared to achieve a better response in *H. pylori* serology-positive patients). The reason for the wide intersubject variability in response to PPIs is unclear. While this study was a randomized trial, its results should be considered tentative because of the small sample size. In addition, because the study was conducted in healthy volunteers, the results may not be applicable to patients with acid-related disorders who do not respond to PPIs.

A literature search found no randomized controlled trials comparing the option of increasing the dose of PPI with the alternative option of switching to another PPI in patients who have an inadequate response to at least a standard dose of PPI. There is better documentation that, in patients who are refractory to PPIs, increases in PPI dose will result in a high response rate (up to 100%). For this reason, this guidance prefers increasing the PPI dose over adding an H<sub>2</sub>RA in patients who do not respond to PPIs.

### Is there a treatment difference between once daily and divided daily doses of PPIs?

**Key findings:** No studies in patients refractory to PPI therapy; poor-quality evidence overall. A fair-quality trial in patients with GERD found that once daily and divided daily dosing of rabeprazole were equivalent. Divided daily dosing of PPIs has been shown to be better than or not different from once daily dosing in studies involving healthy volunteers, and results may depend on time of administration and CYP2C19 genotype (with better intragastric control occurring with divided daily dosing in extensive metabolizers).

One fair-quality multicenter, double-blind, randomized controlled equivalence trial evaluated the efficacy of rabeprazole 10 mg twice daily and 20 mg once daily with omeprazole 20 mg once daily (given for 4 to 8 weeks) in 310 patients with erosive esophagitis.<sup>48</sup> In terms of achieving esophageal healing and symptom control, each dosage regimen of rabeprazole was found to be equivalent to omeprazole, and all three treatments were considered to be equivalent.

Seven other studies comparing other PPI regimens involved healthy volunteers. One was a double-blind randomized crossover trial that showed differences in nocturnal gastric acid control according to CYP2C19 genotype, which was associated with differences in plasma drug concentrations. Statistically significant better results were shown with rabeprazole 20 mg twice daily than 40 mg at bedtime in percentage time that nocturnal gastric pH was less than 4.0 and in median gastric pH control in heterozygous extensive metabolizers (EMs), but no significant differences were seen in homozygous EMs.<sup>32</sup> Significant differences favoring divided dosing were also noted between 10 mg four times daily and the 40-mg once daily regimen in both types of EMs. Poor metabolizers met the defined level of pH control (nocturnal gastric pH < 4.0 for less than 16.7% of the time) on once daily regimens of rabeprazole (20 or 40 mg). Another double-blind randomized controlled crossover trial found no significant difference between lansoprazole (30 mg) dosed once daily or twice daily in divided doses in gastric acid suppression.<sup>49</sup> In an open-label randomized controlled trial with three-way crossover in 19 healthy male volunteers, twice daily omeprazole and evening-dosed

omeprazole were both superior to morning-dosed omeprazole (each totalling 40 mg daily) in reducing NAB; there was no difference between twice daily dosing and evening dosing of omeprazole.<sup>50</sup> No esophageal reflux was noted in any treatment group. The remaining four studies also found a twice-daily regimen of PPI (esomeprazole 40 mg, omeprazole 40 mg, or rabeprazole 20 mg, total daily dose) to be better than once daily dosing in terms of NAB,<sup>51,52</sup> gastric acid suppression<sup>51-54</sup> or esophageal acid exposure.<sup>53</sup> All of these studies were short-term (5 to 7 days) and their results may not be applicable to long-term management of patients with acid-related disorders refractory to PPIs.

There is only one well-designed trial comparing once daily and divided daily dosing of PPIs in patients with acid-related disorders. Studies involving patients who are refractory to PPIs are lacking. The overall quality of evidence is poor. The best designed study suggested that once-daily dosing and twice daily administration of divided doses of a PPI are equivalent in patients with GERD, whereas studies in healthy volunteers have found a divided daily dosage to be either better or not different from once-daily administration, and the results may depend on the time of administration of the once daily dose as well as CYP2C19 genotype.

### What is the clinical relevance of H<sub>2</sub>RA tolerance?

**Key findings:** The clinical relevance of H<sub>2</sub>RA tolerance is unclear. Although tolerance has been shown to develop within the first week of H<sub>2</sub>RA therapy, study results have been inconsistent and contradict the well-documented long-term efficacy of H<sub>2</sub>RAs in acid-related disorders. Tolerance has been shown in healthy volunteers but not in patients with acid-related disorders.

Tolerance has been reported to occur with oral H<sub>2</sub>RA monotherapy in a number of randomized controlled trials in healthy volunteers,<sup>55-60</sup> but was not observed in patients with duodenal ulcers.<sup>61</sup> One study showed that tolerance to H<sub>2</sub>RA monotherapy occurred only at night with evening H<sub>2</sub>RA doses,<sup>62</sup> whereas another study found that the reduction in gastric acid suppressive effects occurred primarily during the day than at night.<sup>59</sup>

Nwokolo suggested that H<sub>2</sub>RA tolerance was probably of little clinical relevance.<sup>60</sup> This possibility is supported by the well-documented, sustained efficacy of H<sub>2</sub>RAs after 3 to 12 months of maintenance therapy in patients with GERD,<sup>63-65</sup> peptic ulcer disease,<sup>66-68</sup> and nonsteroidal antiinflammatory drug-related peptic ulcers.<sup>69</sup>

Tolerance to H<sub>2</sub>RAs has also been observed with add-on H<sub>2</sub>RA therapy. Two studies, one an observational study involving a mixed population of patients with GERD and healthy volunteers<sup>43</sup> and the other a randomized, double-blind, omeprazole-controlled trial in healthy volunteers,<sup>59</sup> showed that gastric acid suppressive effects of H<sub>2</sub>RA may wane after the first day of administration.

However, there is some inconsistency in demonstrating tolerance to H<sub>2</sub>RAs, as a partially randomized study (in which sequence was randomized for all treatments except the PPI),<sup>36</sup> a nonrandomized study,<sup>38</sup> and a retrospective study<sup>70</sup> have reported a benefit in reducing the percentage of NAB time after add-on H<sub>2</sub>RA therapy lasting 4 to 21 days, 6 days, or more than 28 days, respectively.

All of the reports describing tolerance to add-on H<sub>2</sub>RA therapy assessed NAB; esophageal reflux and clinical outcomes were not evaluated. H<sub>2</sub>RA tolerance has been demonstrated primarily in healthy volunteers, whereas tolerance has not been demonstrated in patients with acid-related disorders. As discussed earlier, there seems to be a disparity between NAB and intraesophageal reflux events in patients with GERD.<sup>42</sup> Since the overall evidence is poor, it is unclear whether tolerance to H<sub>2</sub>RAs added on to PPIs is clinically important during long-term management of patients who have not responded to previous PPI therapy.

### Is there a benefit to adding other agents to PPI therapy if a patient does not respond to PPI monotherapy?

**Key findings:** No prospective trials evaluating prokinetics in PPI nonresponders. Metoclopramide and cisapride are associated with adverse events that are not desirable for long-term therapy; access to cisapride is limited; and tegaserod has been shown to be ineffective for GERD. In patients with gastroparesis, a short trial of add-on metoclopramide is reasonable. Add-on baclofen showed promising results for PPI-refractory GERD, but they need to be confirmed in randomized trials.

**Promotility agents.** There is a lack of evidence that promotility agents add further benefit to PPI therapy in the treatment of GERD or other acid-related disorders.

- Metoclopramide is also associated with a 1% to 9% risk of extrapyramidal symptoms including acute dystonic reactions, Parkinson-like symptoms, and tardive dyskinesia, making it undesirable for long-term therapy. An

apparent benefit of add-on metoclopramide (following inadequate response to double-dose omeprazole or standard-dose lansoprazole or rabeprazole) has only been reported in a retrospective study describing a diagnostic protocol for GERD-related chronic cough.<sup>71</sup> In trials evaluating acid aspiration prophylaxis regimens in women undergoing Caesarean section, add-on metoclopramide showed no statistically significant benefit over double-dose PPI alone in terms of pH control and gastric volume.<sup>72,73</sup> *A short course (up to 12 weeks) of metoclopramide may be considered in addition to PPI therapy in patients with diabetic gastroparesis or other type of delayed gastric emptying disorder which may be contributing to GERD symptoms.* However, this recommendation is based on its FDA-approved indication in diabetic gastroparesis and poor-quality evidence of efficacy in delayed gastric emptying,<sup>74</sup> since its efficacy in GERD is equivocal (monotherapy)<sup>75-77</sup> or undocumented (add-on therapy). *A short trial (up to 12-weeks) of add-on metoclopramide may be considered on a case-by-case basis for patients who have GERD without documented gastroesophageal dysmotility and who have not responded to standard or double doses of PPI.* The decision to continue add-on metoclopramide should take into consideration the potential risks versus unknown benefits of long-term therapy.

- Cisapride is only available through an investigational limited access program because of an increased risk of serious cardiac arrhythmias. There are also three randomized trials (one fair<sup>78</sup> and two poor in quality<sup>16,79</sup>) that showed lack of incremental benefit from adding cisapride to a PPI (pantoprazole or omeprazole) in patients with GERD.
- Tegaserod is a selective 5-HT<sub>4</sub> receptor partial agonist that was evaluated in a fair-quality pilot study involving 23 patients with mild to moderate GERD to determine its dose-response effects on acid exposure and lower esophageal sphincter pressure.<sup>80</sup> In this multicenter, double-blind, randomized controlled trial with crossover, tegaserod (1, 4, 12, and 24 mg per day in two divided doses) was not significantly different from placebo in all except one of the primary efficacy end points (3-hour postprandial lower esophageal sphincter pressure, esophageal acid exposure time, and number of reflux episodes) and secondary efficacy end points (GERD activity index, number of transient lower esophageal sphincter relaxations, lower esophageal sphincter pressure, and distal peristaltic amplitude). Only the lowest dosage of tegaserod (1 mg per day) was significantly different from placebo in the percentage time of esophageal acid exposure 3 hours postprandially (5% vs. 13%, respectively;  $p = 0.05$ , unadjusted for multiple comparisons). Since the trial was small, it may have lacked sufficient power to detect a statistically significant treatment difference if a true difference exists. A literature search found no clinical studies comparing PPIs with add-on tegaserod or tegaserod monotherapy. *Given the lack of evidence that tegaserod is efficacious in GERD, this guidance does not recommend tegaserod for the treatment of patients who have GERD or do not respond to PPIs for other acid-related disorders.* (Also see the addendum to the national Pharmacy Benefits Management drug monograph on tegaserod at [www.vapbm.org](http://www.vapbm.org) or [vaww.pbm.med.va.gov](http://vaww.pbm.med.va.gov).)

**GABA-B receptor agonists.** In a poor-quality, small ( $N = 16$ ) prospective observational study of patients who had persistent non-acid duodenal reflux and were refractory to PPI therapy, the addition of baclofen to PPI therapy was associated with improvements in duodenal reflux and reflux symptoms as compared with baseline results on PPI alone.<sup>81</sup> The efficacy of baclofen in PPI-refractory patients remains to be verified in randomized controlled trials.

### Selected indications for high-dose PPIs

1. **Maintenance doses for severe reflux esophagitis.** When used for maintenance therapy in erosive esophagitis of any severity, healing doses (standard doses as defined in this guidance except for esomeprazole 20 mg/d rather than 40 mg/d) have been shown to have a lower relapse rate than half the healing doses in a good-quality Cochrane meta-analysis.<sup>82</sup> Relapse rates were 17.5% and 29.1% for healing doses and half-healing doses, respectively; and the relative risk for relapse was 0.63 (95% CI: 0.55 to 0.73; NNT 9.1; 95% CI: 6.7 to 14.3). Data on higher than standard healing doses and on nonerosive reflux disease or nonselected patient populations are lacking. *After healing or symptom resolution of severe esophagitis on higher than standard doses of PPI, this guidance recommends continuation of the same dose for maintenance therapy.*
2. **GERD-related chronic cough.** A Cochrane systematic review of treatments for GERD-related chronic ( $\geq 3$  weeks) non-specific cough included five trials using double (3 trials) or quadruple doses (2 trials) of PPIs.<sup>83</sup> These trials may have entered patients with laryngopharyngeal reflux (LPR) if cough was evaluated as an outcome. In pooled analyses, there was a small, statistically nonsignificant benefit in resolving cough with PPIs. A small benefit with omeprazole in improving cough was only seen in subgroup analyses; however, responders are difficult to predict. Analysis of efficacy by different doses was not done; therefore, there is a lack of evidence



regarding optimal dose. There may be substantial placebo and period effects (i.e., chronic cough may improve with time). Since chronic cough may be associated with substantial morbidity, and PPI therapy is relatively safe, *an 8-week trial of double-dose PPIs may be considered for GERD-related chronic nonspecific cough.* The potential benefit of PPI therapy should be weighed against a small increased risk of community acquired pneumonia (adjusted relative risk, 1.89; 95% CI, 1.36 to 2.62).<sup>84</sup>

3. *Empiric diagnosis and treatment of LPR.* In a poor-quality open-label cohort study, a trial of double-dose was better than standard-dose PPI, and 4 weeks was better than 2 weeks, as an empiric diagnostic test for LPR.<sup>85</sup> Results of studies evaluating PPIs for treatment of LPR are conflicting. Two open-label cohort studies (one fair<sup>44</sup> and the other poor<sup>85</sup> in quality) have shown that double-dose PPI therapy is associated with better symptomatic improvement than standard-dose PPI, and two fair-quality, double-blind randomized controlled trials have shown that quadruple-dose PPI for 8 weeks<sup>86</sup> or double-dose PPI for 12 weeks<sup>87</sup> is superior to placebo in improving laryngeal symptoms or responder rates. Other trials, however, have shown no statistically significant decrease in laryngeal signs or symptoms with 8- to 12-week double-dose PPI therapy over placebo.<sup>88,89</sup> Considering that (1) only high doses have been evaluated against placebo; (2) benefits have been inconsistent; and (3) the optimal dosing regimen of PPIs is unclear, this guidance recommends that *double-dose PPI for at least 8 weeks may be considered as an initial therapeutic trial for LPR.*
4. *Diagnostic PPI Test for Uncomplicated GERD and Noncardiac Chest Pain.* For diagnosis of GERD, there is a lack of definitive evidence that higher doses are better than standard doses of PPIs.<sup>90,91</sup> Although higher doses (or weaker definitions of response) were associated with higher sensitivities in patients with uncomplicated GERD, the PPI test still had only moderate diagnostic discriminability.<sup>90</sup> For diagnosis of noncardiac chest pain, meta-analysis showed that the PPI test had sufficient discriminant power. Dosage regimens used in the six included trials were standard doses for 3 weeks (1 trial), double to triple doses for 1 or 2 weeks (4 trials), and quadruple-dose PPI for unknown duration in 1 trial. *Current evidence suggests that high-dose PPI is not helpful for diagnosis of uncomplicated GERD. However, since many patients will respond to an empiric trial, an 8-week course of double-dose PPI may be considered in patients without alarm symptoms or other reflux-related complications. Ultimately, the dosage and duration of empiric PPI therapy (ranging from standard to quadruple doses typically for 1 to 4 weeks) should be individualized. For noncardiac chest pain, double-dose PPI for 2 weeks may be a useful diagnostic test.* The potentially deficient accuracy of the PPI test in diagnosing uncomplicated GERD<sup>90</sup> as well as the paucity of well-designed trials evaluating the diagnostic accuracy of PPI tests in LPR<sup>85</sup> should be taken into consideration.
5. *Prevention of rebleeding of peptic ulcers.* Refer to *Summary of Literature Review: Criteria for Non-formulary Use of Intravenous Pantoprazole for Upper Gastrointestinal Bleeding* available at <http://www.pbm.va.gov/criteria/IV%20PAN%20CFU%20Lit.pdf>.

## Unsupported indications

1. *Treatment of asthma.* The use of PPIs for treatment of asthma in patients with or without a co-existing diagnosis of GERD cannot be recommended because of inconsistent benefits in improving lung function, airway responsiveness, or asthma symptoms at doses ranging from standard to eight-times standard doses.<sup>92</sup>

## Summary

There is a lack of trials investigating different approaches to managing patients with acid-related disorders recalcitrant to PPI therapy. Based on poor-quality, tentative evidence that only indirectly address this issue, there is a lack of evidence that suggests an advantage with either increasing the PPI dose or adding a bedtime dose of H<sub>2</sub>RA to PPI therapy in reducing intraesophageal acid reflux or improving symptoms of GERD. There is poor-quality evidence overall that H<sub>2</sub>RAs added on to PPI therapy, in comparison with PPI alone, do not further improve intraesophageal reflux or symptoms of GERD, even though add-on H<sub>2</sub>RAs may improve intragastric NAB. In subgroups of patients who did not initially respond to PPIs, progressively increasing the dose of PPI has been observed to improve intragastric pH control or esophageal healing rates. The benefits of switching to another PPI are less well documented. Recommendations to use twice-daily dosing over once-daily dosing of PPIs are based on poor-quality evidence in healthy volunteers. At this time, there is a lack of compelling evidence that divided daily dosing of PPIs produces better clinical outcomes than a once-daily regimen. The clinical impact of H<sub>2</sub>RA tolerance is unclear when H<sub>2</sub>RAs are added to PPIs in PPI-refractory patients. There is currently insufficient evidence to support adding promotility or GABA-B receptor agonist agents to PPIs if the response to PPI therapy is inadequate, and their risks must be weighed against their

potential benefits. Other indications that may be considered for high-dose PPIs include maintenance therapy of severe reflux esophagitis, GERD-related chronic nonspecific cough, treatment of LPR, empiric trial for uncomplicated GERD, and diagnostic test for noncardiac chest pain. Based on current evidence, the use of high-dose PPI for asthma therapy cannot be recommended.

Strength of Recommendation and Evidence Rating	Reference	Quality of Evidence	Overall Quality
Grade A (always indicated and acceptable):			
Double-dose PPI therapy for gastric ulcers and <i>Helicobacter pylori</i> eradication to reduce recurrence of duodenal ulcers as part of triple antibiotic-based therapy	Product information		
Double-dose PPI (omeprazole immediate-release powder for oral suspension) for reduction of risk of upper GI bleeding in critically ill patients	Product information		
Double- or triple-dose PPI therapy for pathologic hypersecretory conditions	Product information		
Grade B (may be useful/ effective):			
Double-dose PPI for endoscopically-documented severe erosive esophagitis (* = Evidence not or equivocally supportive of recommendation)	Richter (2000) <sup>93</sup> Dent (1994) <sup>19</sup> Hetzel (1988) <sup>94*</sup> Sontag (1992) <sup>95*</sup>	Fair Fair Fair* Fair*	Fair
Quadruple-dose, orally administered PPI (omeprazole 20 mg every 6 h or 40 mg every 12 h) for prevention of re-bleeding of high-risk peptic ulcer bleeding after endoscopic hemostasis	Leontiadis (2005), meta-analysis <sup>96</sup> Kaviani (2003) <sup>97</sup> Javid (2001) <sup>98</sup> Coraggio (1998) <sup>99</sup> Khuroo (1997) <sup>100</sup>	Good Fair Fair Poor Fair	Fair
Continuation of healing dose of PPI for maintenance therapy in GERD	Donnellan (2005) <sup>82</sup>	Good	Fair
Double-dose PPI for 2 weeks as a diagnostic test for noncardiac chest pain	Wang (2005) <sup>91</sup>	Good	Fair
Grade C (may be considered):			
Use of double-dose PPI as an empiric trial in suspected uncomplicated GERD (although there will be diagnostic uncertainty)	Numans (2004), meta-analysis <sup>90</sup>	Fair	Fair
Use of higher than standard PPI doses for empiric diagnosis of LPR	Siupsinskiene (2003) <sup>85</sup>	Poor	Poor
Double-dose PPI for treatment of LPR (* = Evidence not supportive of recommendation)	Park (2005) <sup>44</sup> Siupsinskiene (2003) <sup>85</sup> Noordzij (2001) <sup>86</sup> El-Serag (2001) <sup>87</sup> Steward (2004) <sup>88*</sup> Eherer (2003) <sup>89*</sup>	Fair Poor Fair Fair Fair Fair	Fair
Increase the dose of PPI in patients who do not initially respond to PPI therapy	Robinson (2002) <sup>38</sup> Ours (2003) <sup>39</sup> Leite (1996). <sup>28</sup> Klinkenberg-Knol (1994) <sup>47</sup>	Poor Poor Poor Poor	Poor
Trial of high-dose PPIs for treatment of GERD-related chronic nonspecific cough	Chang (2005), systematic review <sup>83</sup>	Good	Fair
Administer PPIs either once daily or twice daily in divided doses in patients with acid-related disorders	Delchier (2002) <sup>48</sup>	Fair	Poor
Grade D (may not be useful/ effective; possibly harmful):			
High-dose PPIs for treatment of asthma with or without coexistent GERD	Gibson (2005), systematic review <sup>92</sup>	Good	Fair
H <sub>2</sub> RAs added on to PPI therapy in patients with GERD	Robinson (2002) <sup>38</sup> Ours (2003) <sup>39</sup> Orr (2003) <sup>42</sup> Fackler (2002) <sup>43</sup>	Poor Poor Fair Poor	Poor
Cisapride added on to PPI therapy in patients with GERD	Van Rensburg (2001) <sup>78</sup> Vigneri (1995) <sup>16</sup> Kimmig (1995) <sup>79</sup>	Fair Poor Poor	Poor
Tegaserod in patients with GERD	Kahrilas (2000) <sup>80</sup>	Fair	Poor
Grade I (insufficient evidence to recommend for or against):			
Switch to another PPI at double the standard dose if increases to higher than double doses of a PPI suggest possible relative "resistance" to that PPI in patients with acid-related disorders	No clinical trials		
Metoclopramide, tegaserod, or baclofen added on to PPI for acid-related disorders	No clinical trials		

Evidence rating scheme based on the methods used by the third U.S. Preventive Services Task Force<sup>101</sup> and the U.K. National Health Service Centre for Reviews and Dissemination<sup>102</sup>

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