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Beyond Proton Pump Inhibitors: Vonoprazan as a New Standard in Helicobacter pylori Eradication

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Abstract

Helicobacter pylori remains a significant global health burden, driving chronic gastritis, peptic ulcer disease, and gastric cancer. Conventional proton pump inhibitor (PPI)-based eradication therapies have shown declining efficacy due to rising antimicrobial resistance, variable acid suppression, and adherence challenges. Vonoprazan, a first-in-class potassium-competitive acid blocker (P-CAB), offers rapid, potent, and sustained acid inhibition independent of meal timing or CYP2C19 metabolism. Clinical trials and meta-analyses demonstrate superior or non-inferior eradication rates compared to PPI-based regimens, particularly in clarithromycin-resistant infections, with favourable safety and tolerability profiles. Real-world studies support its effectiveness, adherence benefits, and cost-effectiveness across healthcare systems. Vonoprazan-based dual, triple, and quadruple therapies are increasingly integrated into regional and international guidelines, with fixed-dose formulations and paediatric programmes under development. Future directions include broader global access, long-term safety monitoring, and exploration of novel delivery platforms. Overall, vonoprazan represents a paradigm shift in H. pylori management, providing a reliable alternative to PPIs and addressing key limitations of current eradication strategies.

Keywords

Helicobacter pylori, Proton pump inhibitor, Potassium-competitive acid blocker

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1. Introduction

1.1 Global burden and prevalence of H. pylori

H. pylori is a helical, Gram-negative organism that establishes itself in the stomach and affects around half of people worldwide. The burden is highly unequal: meta-analytic data indicate ~43.9% prevalence in adults and ~35.1% in children/teens globally, rising to ~53% in the African and Eastern Mediterranean regions and generally falling below 40% across most of Europe. Country-specific estimates reveal striking disparities-higher rates in parts of Asia and Latin America and much lower prevalence in Western Europe and North America-driven by crowding, sanitation, and access to healthcare [1].

1.2 Clinical sequelae of chronic infection

While many people carry the bacterium without symptoms, H. pylori is the leading cause of chronic active gastritis and peptic ulcer disease [2] and is also linked to gastric MALT lymphoma [3]. The organism is classified by WHO/IARC as a Group I carcinogen for non-cardio gastric cancer [4]. The Correa cascade describes the typical path to gastric cancer: chronic gastritis, then atrophy, intestinal metaplasia, dysplasia, and finally adenocarcinoma [5]. Both direct effects (e.g., epigenetic alterations and genomic instability) and indirect effects (persistent inflammation and oxidative stress) drive malignant transformation. Worldwide, gastric cancer still ranks among the major causes of cancer mortality; most non-cardia cases are attributable to H. pylori, with Asia carrying the greatest burden [6,7]. Eradication reduces ulcer recurrence and lowers gastric cancer risk, especially in high-incidence settings [2,8]. Yet, policy must remain context-specific, given possible protective associations against oesophageal adenocarcinoma and some allergic diseases [9].

1.3 Falling eradication rates with PPI therapies

Standard clarithromycin-based triple therapy (proton pump inhibitor [PPI] + amoxicillin + clarithromycin) has shown decreasing effectiveness in many regions, frequently dropping below historical intention-to-treat targets [2,10]. Rising clarithromycin and metronidazole resistance, variable adherence, and imperfect acid control (notably night-time acid breakthrough) contribute to failure [10,11,12,13]. Bismuth-containing quadruple therapy and tailored approaches can restore efficacy but at the cost of higher pill burden, more complex dosing, and increased adverse effects [10,14,15,16].

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1.4 Need for novel acid-suppressive agents

PPIs are prodrugs requiring acid-dependent activation in parietal-cell canaliculi and dosing 30-60 minutes before meals; real-world timing errors, CYP2C19 polymorphisms, and nighttime acid breakthrough all reduce reliability [10,13,17]. Long-term hypochlorhydria is associated with Clostridioides difficile infection and malabsorption of magnesium, calcium, iron, and vitamin B12, with downstream risks such as fractures and anaemia [18-22]. Rare idiosyncratic events (e.g., acute interstitial nephritis, chronic kidney disease) and observational links to cardiovascular outcomes or dementia remain debated but warrant caution [23]. Sustained hypergastrinemia may drive ECL-cell hyperplasia and fundic gland polyps, with uncertain neoplastic implications. Potential drug-drug interactions (e.g., with clopidogrel) have been scrutinised, though definitive clinical impact is inconsistent [24]. Reformulated PPIs, immediate-release or dual delayed-release, deliver only modest improvements [25].

1.5 Vonoprazan at a glance - first-in-class P-CAB

Vonoprazan is a first-in-class, potassium-competitive, reversible inhibitor of the gastric H+/K+ - ATPase that does not require acid activation [26,27]. It provides rapid onset and sustained, high-grade acid suppression with reliable intragastric pH control, including at night. Food-timing independence and consistent effect across CYP2C19 phenotypes enhance real-world performance [27]. It is orally administered, has a roughly working-day half-life, and is metabolised predominantly via CYP3A. After its initial approval in Japan in 2015 to treat acid-related disorders, vonoprazan-containing therapies for H. pylori were subsequently authorised in multiple nations, notably in the United States in 2022 [28]. Clinically, it serves as the backbone for dual (vonoprazan + high-dose amoxicillin), triple (vonoprazan + amoxicillin + clarithromycin), and bismuth-quadruple variants, with strong performance in clarithromycin-resistant settings [29].

2. Mechanism of Action & Pharmacology

2.1 Mechanistic

Vonoprazan is a potassium-competitive acid blocker (P-CAB) that reduces gastric acid by reversibly binding the parietal-cell H+/K+ - ATPase (proton pump). Unlike PPIs, it neither requires acid activation nor causes irreversible inhibition; by competing directly with potassium across all catalytic states, it delivers a faster onset and more sustained acid suppression. Pharmacological data suggest vonoprazan

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is ~350-fold more potent than the PPIs at inhibiting the proton pump. Being lipophilic and a weak base with a high pKa, it concentrates within the highly acidic parietal-cell canaliculi to levels far above plasma, sustaining its suppressive effect. Without the need for pre-activation in acidic conditions [30,31].

2.2 Pharmacokinetics

After oral administration, vonoprazan is rapidly absorbed, with peak plasma concentrations typically achieved within 1-2 hours (Tmax) after a single dose; at steady state, Tmax may extend slightly to about 3 hours. Exposure (Cmax and AUC) increases in a near-linear to slightly supra-proportional manner across therapeutic doses. Accumulation is minimal, with steady-state levels by day 3-4 of continuous therapy [32].

- **Food effect:** Food does not meaningfully alter pharmacokinetics. High-fat meals modestly increase Cmax (~5%) and AUC (~15%) and delay Tmax to ~ 5 hours; these differences are not clinically significant, supporting administration with or without food [33].
- **Distribution:** Vonoprazan shows extensive distribution, with an apparent volume of distribution of several hundred litres, greater than ten times total body volume, indicating broad tissue penetration. Plasma protein binding ~ 85 - 88 %, not saturable at therapeutic concentrations. A relatively high pKa (~9.0) facilitates rapid protonation and accumulation within parietal-ce canaliculi [34].
- **Metabolism:** Metabolism occurs primarily via hepatic CYP3A4 and CYP2C19, with additional contributions from CYP2B6, CYP2C9, and CYP2D6; no known metabolites are pharmacologically active. Vonoprazan can weakly inhibit P-glycoprotein, though this appears clinically insignificant [34].
- **Elimination:** The terminal elimination half-life averages 7-9 hours, allowing for once-daily dosing. Excretion occurs predominantly through the renal route (~ 65- 70%), with the remainder via faeces (~39%). Only a small proportion of the unchanged drug is recovered: <10% in urine and <2% in faeces [28,34].
- **Drug-drug interactions:** Both in vitro and in vivo data suggest that vonoprazan inhibits multiple CYP isoenzymes- namely CYP3A4, CYP2C9, CYP2D6, and CYP2B6. Clinical evaluation using midazolam (a CYP3A substrate) demonstrated weak inhibition, with a < 2-fold increase in midazolam exposure. Physiologically- based pharmacokinetic modelling predicts 50-80% reductions in vonoprazan exposure with strong CYP3A inducers, while strong CYP3A inhibitors such as poziotinib can increase exposure, warranting caution and possible dose adjustment. Vonoprazan may also inhibit CYP2C19 in vivo, as shown by its effect on progaunil; clinically, this

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interaction has been linked to increased tacrolimus concentrations, indicating a need for therapeutic drug monitoring when combined [28,34].

- **Regimen interactions:** With H. pylori triple therapy (vonoprazan+ amoxicillin + clarithromycin), vonoprazan exposure (AUC and Cmax) increased by ~ 1.8-fold, while clarithromycin increased by ~1.5 - 1.6 fold. No significant PK changes occurred with vonoprazan-amoxicillin-metronidazole. In elderly patients using low-dose aspirin (LDA) and NSAIDs, vonoprazan showed minimal pharmacokinetic interaction and did not impair LDA-induced platelet aggregation inhibition [34].

2.3 Pharmacodynamics

Vonoprazan exhibits dose-dependent inhibition of gastric acid secretion, with both 24-hour and nocturnal intragastric pH-holding times positively correlated with systemic exposure (AUC). In healthy H. pylori-negative volunteers, vonoprazan 20mg achieved a faster and more pronounced increase in intragastric pH compared with lansoprazole 30mg, and its effect was comparable to famotidine 20mg. Following repeated administration, maximal acid suppression is reached within seven days, with near-complete pH control reported at 40mg in Japanese and UK volunteers. Importantly, vonoprazan maintains its antisecretory efficacy regardless of the CYP2C19 genotype, thereby avoiding the variability in acid suppression often observed with PPIs and contributing to consistent therapeutic effects across diverse patient populations [32,34,35].

3. Vonoprazan-Based Eradication Regimens

3.1 First-line regimens

First-line options centre on vonoprazan and include a triple combination with amoxicillin and clarithromycin (supported by phase 3 data in US/EU populations and meta-analyses) [10,36], a high-dose dual combination with amoxicillin (validated in randomised trials and meta-analyses) [36,37], and bismuth-containing quadruple variants evaluated as effective alternatives, particularly in high-resistance settings [28,38].

3.2 Second-/rescue-line options

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For second- or rescue-line therapy, vonoprazan can be combined with metronidazole or sutafloxacin, or used within bismuth-substituted regimens; Japanese RCTs and reviews support these frameworks after failure of clarithromycin-based therapy [10,38,39].

3.3 Treatment duration

Common course lengths are 7, 10, or 14 days, with regimen-specific evidence underpinning each (e.g., 7-dual/triple, 10-day vonoprazan-based courses, and 14-day regimens used in international phase 3 trials) [28,36,37].

3.4 Regional guideline positions

- **Japan (JGES 2023):** Strongly recommends vonoprazan triple or dual as first-line; bismuth quadruple as a key rescue option [10].
- **American College of Gastroenterology (draft 2023):** Recognises vonoprazan as a viable alternative to PPIs, with strong evidence in resistant infections [10].
- **European Society of Gastrointestinal Endoscopy (2024):** States P-CAB regimens are non-inferior or superior to PPI-based triple therapy, with greater benefits in resistant infections [2].

3.5 Fixed-dose co-formulations in development

- Fixed-dose packs combining vonoprazan + amoxicillin + clarithromycin [28].
- Fixed-dose packs combining vonoprazan+ amoxicillin [28].

4. Clinical Efficacy

4.1 Randomised controlled trials & meta-analyses

- Pooled Asian RCTs (n ~3,000) showed 92% with vonoprazan triple versus 80% with PPI triple (OR 2.42; 95% CI 1.66-3.53) [40].
- International multicentre trial: vonoprazan triple 81% vs 69% with lansoprazole triple therapy [36].
- Clarithromycin-susceptible infection: vonoprazan triple therapy >95% [36].
- Dual therapy (international): 77% overall [36].

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- In East Asia, among clarithromycin-resistant cases, bismuth-based quadruple regimens achieve eradication rates above 90% [38].

4.2 Impact of clarithromycin resistance

- Dual therapy in resistant cases: 66-70%, vs 32% with lansoprazole triple (resistant strains) [36].
- Triple therapy in susceptible strains: >95% [36].

4.3 Head-to-head vs PPI regimens

- Vonoprazan triple 81% vs 69% with lansoprazole triple therapy (international) [36].
- Pooled comparison: 92% vs 80% (OR 2.42; 95% CI 1.66-3.53) [36].

5. Safety and Tolerability

5.1 Adverse Event Profile

Across pooled analyses and pharmacovigilance data, vonoprazan demonstrates a safety profile broadly comparable to proton pump inhibitors [41,42]. The overall incidence of adverse events is around 20%, with drug-related events at 1%, and discontinuations at 1%, the majority being mild in severity [32,42]. Higher adverse event rates have been noted in peptic ulcer disease, likely reflecting the complexity of the condition and the need for longer treatment courses, while eradication regimens for H. pylori tend to show more drug-related events due to the addition of antibiotics and bismuth [28,42]. Extended therapy beyond eight weeks is associated with an increase in adverse events, but tolerability remains consistent across Asian and non-Asian populations as well as between adults and adolescents [32,42]. Biochemical changes associated with potent acid suppression, such as elevated serum gastric and pepsinogen I levels, occur more frequently with vonoprazan than with PPIs [32,43]. Long-term follow-up from the VISION study confirmed these changes and reported histological findings such as parietal and foveolar cell hyperplasia, but no cases of gastric epithelial malignancy or neuroendocrine tumours. Rates of G-cell and ECL-cell hyperplasia remained low, and the overall safety profile was comparable to lansoprazole, with mild infections such as nasopharyngitis and bronchitis being most frequent [43]. Real-world safety data have not identified unexpected signals relative to PPIs, and long-term PPI-associated risks such as C. difficile infection, osteoporosis, and vitamin deficiencies have not been observed with vonoprazan to date, although continued monitoring remains important [41-43].

5.2 Laboratory and ECG Safety

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Preclinical evaluation of vonoprazan raised concerns about possible interaction with the hERG potassium channel; however, a controlled study using both therapeutic and supratherapeutic doses confirmed no clinically meaningful effect on QT prolongation [44]. Rare reports of QT interval changes have occurred in the presence of drug-drug interactions, particularly with CYP3A4 substrates, highlighting the need for caution when vonoprazan is combined with agents that influence this pathway [28,45]. Laboratory abnormalities such as transient elevations in liver enzymes remain uncommon, and systematic analyses have not identified new systemic safety concerns across therapeutic indications. The VISION trial reinforced the long-term safety of vonoprazan, showing that gastrin levels stabilised after an initial rise, chromogranin A increases were of uncertain clinical significance, and there were no gastric neuroendocrine tumours or malignant changes. Gastric polyp rates were comparable to those observed with PPIs [43].

In terms of reproductive safety, evidence remains limited. Animal studies suggest possible embryofetal and hepatic risks at high exposures, and human data are insufficient. The drug is not recommended during pregnancy or breastfeeding, and a pregnancy-exposure registry has been established to monitor outcomes [28,46].

5.3 Discontinuation and Adherence Rates Compared with PPIs

Clinical trials consistently demonstrate that vonoprazan is well tolerated, with low discontinuation rates and strong adherence comparable to or better than those observed with PPIs. Discontinuations due to adverse events generally remain at or below 2%, and the majority of events leading to withdrawal are mild in nature [32,42]. Studies in duodenal ulcer and gastro-oesophageal reflux disease report very low treatment withdrawals, while maintenance therapy also shows minimal discontinuation, not exceeding 2-3% across treatment arms [32]. Trails in H. pylori eradication regimens confirm similarly high adherence, with per-protocol completion rates exceeding 90% and no major differences in tolerability compared with PPI-based regimens [42]. Together, these findings indicate that vonoprazan offers both strong adherence and a favourable discontinuation profile, reinforcing its suitability for long-term clinical use [32,42,43].

6. Patient-Centric Considerations

6.1 Dosing simplicity and adherence

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Adherence is central to outcomes with acid-suppressive therapy. Conventional PPIs often require twice-daily dosing and, in refractory cases, an additional bedtime dose to counter nocturnal acid breakthrough; this higher pill burden is associated with lower adherence, whereas once-daily schedules across oral therapies show a ~20-25% higher likelihood of full compliance than twice-daily regimens [47]. Vonoprazan supports once-daily dosing without sacrificing efficacy: a longer half-life (7-9 hours vs 1-2 hours for PPIs) and acid stability allow rapid absorption and sustained intragastric pH control [32,34]. In a randomised, crossover trial in healthy volunteers, vonoprazan 20mg once daily achieved significantly higher 24-hour pH-holding times than rabeprazole 20 mg or 40 mg given once daily, including superior nocturnal pH maintenance [48]. For gastro-oesophageal reflux disease, this translates into faster symptom relief and superior healing rates for high-grade erosive oesophagitis compared with PPIs [49]. Overall, the ability to maintain high intragastric pH with a simplified once-daily regimen supports better adherence, fewer missed doses, and improved patient satisfaction [47,48].

6.2 Cost-effectiveness across health systems

Economic evaluations from Japan and China indicate a favourable value for vonoprazan vs conventional PPIs [49,50]. In Japan, from the public healthcare perspective, among patients on low-dose aspirin for secondary cardiovascular prevention, vonoprazan was dominant over esomeprazole (less costly and more effective) and cost-effective versus lansoprazole, with ICERs below commonly used willingness-to-pay thresholds [49]. Findings were robust to one-way and remained favourable even with low aspirin adherence; against generic lansoprazole, the ICER was ~1 million JPY/QALY [49]. These findings align with post-hoc Phase III data showing superior prevention of recurrent aspirin-associated gastrointestinal bleeding with vonoprazan, implying downstream economic benefits through fewer serious events, shorter hospitalisation, and improved quality of life [49]. In China, an RO model spanning acute treatment and maintenance showed vonoprazan to be effective and cost-saving versus conventional PPIs, particularly in severe disease; longer-term models… similarly favoured a vonoprazan-first strategy on QALYs and cost [50]. Limitations include the absence of direct head-to-head trials against all PPIs, reliance on meta-analyses with limited Chinese cohorts, and exclusion of adverse-event costs, although sensitivity analyses were stable. For H. pylori eradication, comparisons of 10-day versus 14-day vonoprazan-amoxicillin dual therapy showed the 10-day regimen slightly below a 90% eradication benchmark yet more cost-effective at usual willingness-to-pay thresholds, with the 14-day course becoming preferable at higher willingness-to-pay thresholds; smoking status and previous eradication failure materially influence cost-effectiveness [51]. Overall, across public systems in Japan and China, vonoprazan is generally more cost-effective. Then, standard PPIs, driven by stronger acid

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inhibition and reduced bleeding risk, while in private or mixed systems, reduced hospitalisation and better quality of life can offset higher acquisition costs; remaining key gaps remain: long-term real-world economic data, wider head-to-head comparisons with multiple PPIs, and models that explicitly include adverse-event costs [49-52].

6.3 Patient-reported outcomes in H. pylori

A Japanese prospective study of 233 patients with endoscopically diagnosed atrophic gastritis (184 H. pylori-positive) assessed quality of life (QoL) before and after eradication using SF-8. Improvements were observed in both physical (PCS) and mental (MSC) scores after treatment, irrespective of eradication success or baseline symptoms, with the greatest gains in those with lower pre-treatment QoL. Asymptomatic H. pylori-positive patients also improved, suggesting infection may impair well-being even without overt symptoms [52].

Unlike earlier reports restricted to successful eradication, this study used an intention-to-treat approach and still found QoL gains; serology mirrored clinical course, with drops in pepsinogen I/II and a rise in the PGI/II ratio consistent with mucosal healing [52].

7. Future Directions

7.1 Ongoing and planned clinical trials

Vonoprazan has progressed from Japan-only use to broader adoption, with US approvals for H. pylori regimens and erosive oesophagitis and active long-term safety follow-up programmes [28,43]. Trails in Western populations show vonoprazan-based dual and triple regimens are effective for H. pylori, including clarithromycin-resistant subgroups [36]. Regulators have requested paediatric programmes (stepwise PK/safety and efficacy), and a paediatric GERD study is registered. Together, these point to continued global roll-out with age expansions and real-world data complementing RCTs (SEC, PMDA, ClinicalTrails.gov) [28,36,43,53].

7.2 Role in rescue/second-line algorithms and antibiotic-sparing combinations

Where clarithromycin resistance is common or unknown, guidelines increasingly prioritise bismuth quadruple therapy as first-line. Within this landscape, vonoprazan can function as the acid-suppression backbone in clarithromycin-free salvage regimens and as part of antibiotic-sparing strategies (e.g.,

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vonoprazan-amoxicillin dual) to reduce macrolide exposure without sacrificing efficacy in appropriate patients [10]. Pivotal USEU data support both approaches by showing vonoprazan triple/dual non-inferiority overall and higher cure rates than a PPI-based triple in clarithromycin-resistant infections (PMDA) [36].

7.3 Co-packaged or fixed-dose vonoprazan

In the US, co-packaged "Dual Pak" and "Triple Pak" kits (pre-blistered vonoprazan with amoxicillin ± clarithromycin) are available to simplify instructions and day-to-day execution, although they are not single fixed-dose tablets [28,54]. Looking ahead, a fixed-dose vonoprazan-amoxicillin tablet could further streamline use and reduce dispensing errors; formulation work would need to address stability and dose flexibility across body weight and renal function.

7.4 Novel drug-delivery platforms

- **Gastro-retentive systems:** Purpose-built floating or controlled-release matrices/micro-devices that extend gastric residence could maintain high intragastric pH with fewer daily doses and enable once-daily VA regimens in harder-to-treat settings.
- **Transdermal/microneedles:** A steady, CYP-sparing systemic vonoprazan exposure via patch or microneedles could reduce drug-drug interaction concerns and simplify multi-day courses.
- **Status and gaps:** These are forward-looking concepts (no peer-reviewed vonoprazan delivery studies yet). Key unknowns include human PK targets for non-oral routes, manufacturability (scalable, moisture-resistant formulations), device cost, and regulatory paths for combination products; early feasibility should prioritise PK bridging and user-centred design before efficacy trials.

7.5 Research gaps

- **Long-term safety:** Five-year maintenance data in GERD show no malignant epithelial changes and broadly PPI-like safety, but ongoing surveillance of hypergastrenemia-related histology, polyps, and endocrine-cell findings is prudent - especially with longer, repeated courses in H. pylori programmes (IJBC Pharmacology). Beyond the stomach: Whether potent, sustained acid control benefits conditions with acid-dependent components (e.g., laryngophageal reflux subsets) remains to be tested.

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- **Access and implementation:** As approvals expand, cost, kit availability, and local resistance patterns will shape real-world impact; pragmatic studies comparing adherence and persistence versus twice-daily PPI strategies would be valuable (PMDA).

8. Conclusion

For H. pylori eradication, vonoprazan provides rapid, potent, and sustained acid suppression without acid-dependent activation, delivering reliable intragastric pH control and consistently higher cure rates than PPI-based comparators across dual (vonoprazan-amoxicillin), triple (vonoprazan-amoxicillin-clarithromycin), and bismuth-containing regimens, including in clarithromycin-resistant settings. Its safety is broadly PPI-like (mostly mild adverse events, expected rises in gastrin/pepsinogen I, no clinically meaningful QT prolongation, low discontinuation), while once-daily, food-timing-independent dosing supports adherence and public-payer analyses suggest favourable cost-effectiveness. Clinically, prefer vonoprazan when high-grade acid suppression and regimen simplicity are priorities, clarithromycin resistance is likely (using dual or bismuth-based options), or prior PPI therapy has failed; exercise caution with high amoxicillin resistance or penicillin allergy, clinically important CYP3A interactions (for example, drugs requiring monitoring such as tacrolimus), and during pregnancy or lactation, and maintain surveillance for hypergastrenemia-related histology and polyps with prolonged or repeated courses. Looking ahead, wider access, co-packaged kits (and potential fixed-dose combinations), paediatric programmes, long-term follow-up, and exploration of gastro-retentive and transdermal/microneedle delivery could further streamline therapy, guided by antibiotic stewardship and local susceptibility data.

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