

RESEARCH MONOGRAPH . COMPOUND PROFILE

Pirenzepine

A peripherally selective, M1-preferring muscarinic antagonist developed at Dr. Karl Thomae GmbH (Boehringer Ingelheim) as a gastric antisecretory agent for peptic ulcer disease, subsequently investigated as a topical ophthalmic intervention for the retardation of progressive myopia in children.

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ABSTRACT

Pirenzepine (LS 519, Gastrozepin) is a tricyclic pyridobenzodiazepinone and the prototypical selective antagonist of the M1 subtype of the muscarinic acetylcholine receptor. Synthesized at Dr. Karl Thomae GmbH, a subsidiary of Boehringer Ingelheim, in the mid-1970s, the compound was the first muscarinic antagonist demonstrated to discriminate pharmacologically between what were subsequently classified as M1 and M2 receptor subtypes, a finding reported by Hammer et al. in 1980 in *Nature* and foundational to the modern subtype classification of muscarinic receptors [1]. Pirenzepine binds the M1 muscarinic receptor with a dissociation constant (K_i) of approximately 5 to 14 nanomolar and displays 5- to 20-fold selectivity over the M2, M3, and M5 subtypes, with intermediate affinity at M4 receptors [2, 3]. The compound is peripherally selective, exhibiting negligible penetration of the blood-brain barrier at therapeutic oral doses, a property that minimizes central anticholinergic adverse effects and distinguishes it from atropine and other non-selective muscarinic antagonists. The primary registered indication is peptic ulcer disease. Pirenzepine inhibits vagally mediated and pentagastrin-stimulated gastric acid secretion through antagonism of M1 receptors on intramural gastric plexus neurons, reducing basal acid output by approximately 50 percent at oral doses of 50 mg twice daily [4, 5]. Extensive controlled trials conducted through the late 1970s and 1980s demonstrated duodenal ulcer healing rates of 60 to 76 percent at 4 to 8 weeks on pirenzepine 100 to 150 mg per day, broadly comparable to cimetidine 1 g per day and superior to placebo and gefarnate [6, 7]. The compound was registered as

Gastrozepin in numerous European, Asian, and Latin American jurisdictions but was never approved by the United States Food and Drug Administration. The clinical importance of pirenzepine as a gastric antisecretory agent has diminished substantially following the introduction of histamine H₂ receptor antagonists and proton pump inhibitors, which offer superior acid suppression and ulcer healing rates. A second, more recent research application is the retardation of progressive myopia (axial elongation of the globe) in children aged 8 to 12 years. Two multicenter, randomized, double-masked, placebo-controlled trials of 2% pirenzepine ophthalmic gel, conducted by Siatkowski et al. (2004, 2008), demonstrated approximately 50 percent reduction in the rate of myopia progression over 1- and 2-year treatment periods, with a clinically acceptable safety profile dominated by mild pupil dilation and accommodation difficulty [8, 9]. The mechanism of the antimyopic effect is incompletely characterized but is attributed to M₁ and possibly M₄ muscarinic receptor antagonism in the retina and sclera, modulating signaling cascades that regulate scleral extracellular matrix remodeling and axial elongation [10]. The ophthalmic application has not received regulatory approval; the compound remains investigational for myopia control, with atropine (a non-selective muscarinic antagonist applied at low concentrations) having advanced further in clinical development for this indication. Pharmacokinetics are characterized by low oral bioavailability (20 to 30 percent in fasted subjects, further reduced by food), a plasma elimination half-life of approximately 10 to 12 hours, negligible hepatic first-pass metabolism, predominant renal elimination of unchanged drug, and low plasma protein binding (approximately 12 percent) [11, 12]. The compound does not undergo significant cytochrome P450-mediated metabolism and has a correspondingly limited

drug-drug interaction profile. The principal adverse events at registered oral doses are mild anticholinergic effects: dry mouth (approximately 14 percent), blurred vision (1 to 5 percent, dose-dependent), and constipation (approximately 3 percent), with an overall discontinuation rate of approximately 2 percent in controlled trials [6]. Serious adverse events are rare. This monograph reviews the chemistry, synthesis, and structural pharmacology of pirenzepine; the molecular pharmacology at muscarinic receptor subtypes; comprehensive human pharmacokinetics; the clinical evidence base across peptic ulcer and myopia indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a structured comparative assessment of five gastric antisecretory and muscarinic antagonist alternatives (telenzepine, atropine, cimetidine, ranitidine, omeprazole) against pirenzepine on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Pirenzepine.

Marketed names: Gastrozepin (Boehringer Ingelheim; Germany, Austria, Switzerland, Italy, Japan, the Republic of Korea, and other markets), Gastricur (generic), Pirenzep (generic), Ulcoprotect (generic), Pirenzepin (generic, various European and Latin American markets).

Development codes: LS 519 (Dr. Karl Thomae GmbH, Boehringer Ingelheim). The development code LS 519 is the canonical identifier in the early pharmacology literature, including the seminal Hammer et al. (1980) Nature report that established the muscarinic receptor subtype distinction [1].

Chemical Abstracts Service registry numbers: 28797-61-7 (free base), 29868-97-1 (dihydrochloride salt). The dihydrochloride is the formulated salt for oral and parenteral preparations; the free base is the pharmacopoeial and synthetic reference form.

International Union of Pure and Applied Chemistry name: 11-[2-(4-methylpiperazin-1-yl)acetyl]-5H-pyrido[2,3-b][1,4]benzodiazepin-6-one. The compound is a tricyclic system comprising a pyrido[2,3-b][1,4]benzodiazepinone core bearing an N-methylpiperazinyl acetamide side chain at the 11-position nitrogen.

1.2 Structural class and chemistry

Pirenzepine is a pyridobenzodiazepinone, a tricyclic heterocyclic system formed by the linear fusion of a pyridine ring, a 1,4-diazepine ring, and a benzene ring, with a 6-oxo (lactam) functionality. The structural class is related to the benzodiazepine anxiolytics and to the tricyclic dibenz[b,e]azepine antidepressants but is pharmacologically distinct: the pyrido substitution and the exocyclic piperazinyl acetamide chain confer muscarinic M1 selectivity rather than GABA-A receptor modulation or monoamine reuptake inhibition [3].

Molecular formula: C₁₉H₂₁N₅O₂ (free base); C₁₉H₂₃Cl₂N₅O₂ (dihydrochloride).

Exact mass: 351.1695 g/mol (free base, monoisotopic).

Molecular weight: 351.41 g/mol (free base); 424.33 g/mol (dihydrochloride salt).

Physical properties: White to off-white crystalline powder. The dihydrochloride salt is freely soluble in water and in methanol; the free base is sparingly soluble in water and soluble in dimethyl sulfoxide and dimethylformamide. Melting point of the dihydrochloride salt is approximately 260 to 262 degrees Celsius with decomposition.

Stereochemistry: Pirenzepine does not contain a stereocenter in its standard pharmaceutical form and is supplied as the achiral species. No enantioselective pharmacology is relevant.

1.3 Synthesis

The published synthesis of pirenzepine proceeds through construction of the tricyclic pyridobenzodiazepinone core followed by acylation with the piperazinyl acetyl side chain. The tricyclic intermediate is prepared from 3-amino-2-chloropyridine and methyl anthranilate through a sequence of nucleophilic aromatic substitution, lactam cyclization, and deprotection steps [3, 13]. The exocyclic side chain is introduced by N-acylation of the 11-position nitrogen of the diazepinone with chloroacetyl chloride, followed by displacement of the chloride with 1-methylpiperazine. The product is purified by recrystallization from appropriate solvents and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and high-performance liquid chromatography. The dihydrochloride salt is prepared by treatment of the free base with two equivalents of hydrogen chloride in a suitable solvent followed by recrystallization. Industrial syntheses optimize the coupling and cyclization steps for yield and purity; the compound is generally manufactured at greater than 99 percent chemical purity by HPLC.

2. Abstract

Pirenzepine (LS 519) is the prototypical selective antagonist of the M1 subtype of the muscarinic acetylcholine receptor (mAChR) and the compound whose pharmacological characterization established the existence of muscarinic receptor subtypes in 1980 [1]. The compound binds M1 mAChRs with low-nanomolar affinity (K_i approximately 5 to 14 nM) and displays 5- to 20-fold selectivity over the M2, M3, and M5 subtypes, with intermediate affinity at M4 receptors [2, 3]. Pirenzepine is peripherally selective, exhibiting negligible blood-brain barrier penetration at therapeutic doses, and its anticholinergic effects are therefore confined to the peripheral nervous system and peripheral tissues.

The principal registered indication is the treatment of peptic ulcer disease. Pirenzepine reduces vagally mediated and stimulated gastric acid and pepsin secretion through antagonism of M1 receptors on neurons of the intramural gastric plexuses, with basal acid output reduced by approximately 50 percent at the standard oral dose of 50 mg twice daily [4, 5]. Controlled clinical trials enrolling thousands of patients across European and Asian centers demonstrated duodenal ulcer healing rates of 60 to 76 percent at 4 to 8 weeks on pirenzepine 100 to 150 mg per day, comparable to cimetidine 1 g per day, and superior to placebo [6, 7]. The compound was registered in numerous jurisdictions as Gastrozepin but was never approved in the United States. Its clinical importance as a gastric antisecretory agent has been substantially superseded by histamine H2 receptor antagonists (cimetidine, ranitidine) and proton pump inhibitors (omeprazole, esomeprazole), which provide greater acid suppression and higher ulcer healing rates.

A second research application of increasing interest is the retardation of progressive myopia in children. Two multicenter, randomized, double-masked, placebo-controlled trials of 2% pirenzepine ophthalmic gel (Siatkowski et al. 2004, 2008) demonstrated approximately 50 percent reduction in the rate of myopia progression over 1- and 2-year treatment periods in children aged 8 to 12 years [8, 9]. The mechanism involves muscarinic receptor antagonism in the retina and sclera, modulating signaling pathways that regulate scleral extracellular matrix remodeling and axial elongation of the globe [10]. The ophthalmic formulation has not received regulatory approval; the compound remains investigational for myopia control.

Pharmacokinetics are characterized by low oral bioavailability (20 to 30 percent), minimal hepatic metabolism (no significant cytochrome P450 involvement), a plasma elimination half-life of approximately 10 to 12 hours, and predominant renal clearance of unchanged drug [11, 12]. The principal adverse events are mild anticholinergic effects: dry mouth (14 percent), blurred vision (1 to 5 percent), and constipation (3 percent), with a discontinuation rate of approximately 2 percent in controlled trials [6].

This monograph documents the chemistry and synthesis; the receptor pharmacology and muscarinic subtype selectivity; comprehensive pharmacokinetics; the clinical evidence base across peptic ulcer and myopia indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a structured comparative assessment of five antisecretory and muscarinic antagonist candidates (telenzepine, atropine, cimetidine, ranitidine, omeprazole) against pirenzepine on five standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

3. Discovery and Development History

3.1 Origin

Pirenzepine (LS 519) was synthesized at Dr. Karl Thomae GmbH in Biberach an der Riss, West Germany, a pharmaceutical research subsidiary of Boehringer Ingelheim, in the mid-1970s. The compound was identified from a medicinal chemistry program exploring tricyclic heterocycles for antisecretory activity against vagally mediated gastric acid secretion. The program was oriented toward compounds that could reduce gastric acid output without the cardiovascular, urinary, and central nervous system side effects of atropine, the non-selective muscarinic antagonist that was at that time the only antimuscarinic agent available for ulcer management.

3.2 Establishment of muscarinic receptor subtypes

The pivotal scientific contribution of pirenzepine to pharmacology was the demonstration, by Hammer, Berrie, Birdsall, Burgen, and Hulme at the National Institute for Medical Research (Mill Hill, London), that pirenzepine distinguished between at least two classes of muscarinic receptor binding sites in rat brain and peripheral tissues [1]. Published in *Nature* in 1980, this study showed that pirenzepine bound with high affinity to muscarinic receptors in cerebral cortex and sympathetic ganglia (subsequently designated M1) and with substantially lower affinity to muscarinic receptors in cardiac atria and smooth muscle (subsequently designated M2). This pharmacological distinction, confirmed independently by Watson et al. (1983) and by multiple subsequent molecular cloning studies that identified five muscarinic receptor genes (M1 through M5), established pirenzepine as the defining ligand for the M1 muscarinic receptor subtype and was foundational to the modern classification of cholinergic receptors [14].

3.3 Gastric antisecretory registration

Pirenzepine was advanced through clinical development in the late 1970s and early 1980s for the treatment of peptic ulcer disease. Phase 3 registration trials were conducted principally in Europe (Germany, Italy, the United Kingdom, Scandinavia)

and in Japan. The compound received its first regulatory approval in Germany in 1979 and was subsequently registered in numerous European, Asian, and Latin American jurisdictions as Gastrozepin. The approved indication was the treatment of gastric and duodenal ulcer disease at oral doses of 50 mg twice daily (100 mg per day) or 50 mg three times daily (150 mg per day). Parenteral (intravenous and intramuscular) formulations were registered in some jurisdictions for acute upper gastrointestinal hemorrhage.

The compound was never approved by the United States Food and Drug Administration. The absence of US registration reflected the timing of pirenzepine development relative to the introduction of cimetidine (Tagamet, approved 1977) and ranitidine (Zantac, approved 1983), which provided more potent acid suppression with comparable tolerability through the histamine H₂ receptor mechanism, and subsequently the proton pump inhibitors (omeprazole, approved 1989), which provided near-complete acid suppression with superior ulcer healing rates. By the time pirenzepine could have been submitted for US approval, the therapeutic standard had shifted to agents with greater antisecretory potency [15].

3.4 Myopia research program

Beginning in the late 1990s, pirenzepine was investigated as a topical ophthalmic agent for the retardation of progressive myopia in children. The scientific basis was the observation, originating from animal studies by Stone et al. (1991) and McBrien et al. (1993), that muscarinic antagonism retarded experimental form-deprivation and lens-induced myopia in chick, tree shrew, and primate models [10, 16]. Pirenzepine was selected for clinical development on the basis of its M₁ selectivity, which was hypothesized to reduce the pupil dilation and cycloplegia (accommodation paralysis) that limited the use of atropine (a non-selective muscarinic antagonist) as a myopia control agent.

Two multicenter Phase 2/3 clinical trials of 2% pirenzepine ophthalmic gel were conducted in children aged 8 to 12 years in the United States and Asia [8, 9]. The results demonstrated significant slowing of myopia progression, but the ophthalmic formulation was not advanced to regulatory approval. The reasons for the discontinuation of the myopia development program have not been publicly detailed; possible factors include the competitive landscape (low-dose atropine 0.01% to 0.05% subsequently advanced as a more accessible intervention), formulation challenges with the gel vehicle, and commercial considerations.

4. Mechanism of Action

Pirenzepine is a competitive, reversible antagonist of the muscarinic acetylcholine receptor with preferential affinity for the M1 subtype. Its principal therapeutic effects derive from blockade of M1 receptor-mediated signaling in the gastric intramural plexuses (antisecretory indication) and in the retina and sclera (myopia indication).

4.1 Muscarinic receptor subtypes and pirenzepine selectivity

The muscarinic acetylcholine receptors are a family of five G protein-coupled receptors (M1 through M5) encoded by the CHRM1 through CHRM5 genes. M1, M3, and M5 couple preferentially to Gq/11 proteins and activate phospholipase C, generating inositol trisphosphate and diacylglycerol and producing intracellular calcium mobilization. M2 and M4 couple preferentially to Gi/Go proteins and inhibit adenylyl cyclase, reduce cAMP production, and activate inwardly rectifying potassium channels [14].

Pirenzepine binds the M1 receptor with a K_i of approximately 5 to 14 nanomolar, as determined by displacement of [3H]-N-methylscopolamine ([3H]-NMS) or [3H]-pirenzepine from rat cortical membrane preparations and from cells expressing cloned human M1 receptors [2, 3]. Affinity at the M4 receptor is intermediate (K_i approximately 30 to 80 nM); affinity at the M2 receptor is approximately 5- to 20-fold lower (K_i approximately 100 to 300 nM); and affinity at M3 and M5 receptors is similarly reduced (K_i approximately 100 to 500 nM). The selectivity ratio for M1 over M2 is therefore modest (5- to 20-fold) by modern standards of receptor pharmacology but was sufficient to define the M1 subtype operationally and to produce a clinically useful separation of antisecretory from cardiac and smooth muscle effects at therapeutic doses [1, 2].

Pirenzepine has also been reported to promote homodimerization or oligomerization of M1 receptors, a finding that may modulate the receptor signaling response beyond simple competitive antagonism but whose therapeutic significance is uncertain [17].

4.2 Gastric antisecretory mechanism

The gastric parietal cell, the effector cell for hydrochloric acid secretion, is principally stimulated by three receptor-mediated pathways: histamine (H₂ receptor), acetylcholine (M₃ receptor on the parietal cell), and gastrin (cholecystokinin-B receptor). Vagal cholinergic stimulation of acid secretion operates through two routes: direct stimulation of M₃ receptors on parietal cells (producing acid secretion) and stimulation of M₁ receptors on postganglionic neurons of the intramural gastric plexuses (amplifying vagal transmission and modulating gastrin release from G cells) [4, 5].

Pirenzepine reduces gastric acid secretion primarily by blocking M₁ receptors on intramural plexus neurons rather than by blocking M₃ receptors on parietal cells directly. At the standard oral dose of 50 mg twice daily, pirenzepine reduces basal acid output by approximately 50 percent and pentagastrin-stimulated acid output by approximately 26 to 31 percent [4, 5]. The reduction is sufficient to promote ulcer healing but is substantially less than the near-complete acid suppression achieved by proton pump inhibitors or by higher doses of H₂ receptor antagonists.

The neuronal M₁ mechanism explains the clinical selectivity of pirenzepine relative to atropine: at doses that reduce gastric acid secretion, pirenzepine produces substantially less inhibition of salivary secretion, less tachycardia, less urinary retention, and less constipation than equi-effective doses of atropine, because these effects are mediated predominantly by M₂ and M₃ receptor subtypes on smooth muscle, cardiac muscle, and exocrine gland effector cells.

4.3 Antimyopic mechanism

The mechanism by which muscarinic antagonism retards myopia progression is incompletely characterized. Multiple hypotheses have been advanced:

First, M₁ and M₄ receptor antagonism in the retina may modulate local signaling cascades that regulate the retinal release of growth factors (dopamine, retinoic acid, nitric oxide) implicated in scleral extracellular matrix remodeling [10, 16]. These factors act on the sclera to modulate collagen cross-linking, glycosaminoglycan synthesis, and proteoglycan metabolism, processes that determine scleral biomechanical compliance and thereby axial elongation.

Second, muscarinic antagonism in the sclera itself may directly modulate scleral fibroblast proliferation and extracellular matrix production, as demonstrated by McBrien et al. in tree shrew models [16].

Third, the accommodation-relaxation effect of muscarinic antagonism may contribute by reducing accommodative lag, a postulated stimulus for axial elongation in the accommodative theory of myopia progression.

The relative contributions of these mechanisms remain a subject of active investigation. Pirenzepine was originally selected for the myopia application on the hypothesis that M1 selectivity would reduce the pupil dilation and cycloplegia produced by atropine; however, clinical trials showed that pirenzepine gel did produce mild mydriasis and accommodation difficulty, suggesting that the ophthalmic concentrations achieved by the 2% gel formulation are sufficient to engage M3 receptors in the iris and ciliary body [8, 9].

4.4 Other pharmacological activities

Pirenzepine has been studied in a limited number of other pharmacological contexts. M1 muscarinic receptors are expressed in sympathetic ganglia, where they modulate ganglionic transmission; pirenzepine has been demonstrated to block vagally mediated bronchoconstriction in humans through ganglionic M1 receptor blockade [18]. M1 receptors in the central nervous system participate in cognitive function, synaptic plasticity, and dopaminergic modulation, but pirenzepine's negligible blood-brain barrier penetration at oral therapeutic doses limits central nervous system effects in systemic administration.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Pirenzepine is incompletely absorbed from the gastrointestinal tract after oral administration. Oral bioavailability is approximately 20 to 30 percent in fasted subjects, reflecting incomplete gastrointestinal absorption rather than hepatic first-pass metabolism [11, 12]. Food substantially reduces bioavailability; co-administration with a meal reduces the area under the concentration-time curve by approximately 30 percent, and co-administration with antacids produces a comparable reduction [19]. For this reason, pirenzepine is recommended to be taken 30 minutes before meals.

Time to peak plasma concentration after a 50 mg oral dose in fasted subjects is approximately 2 to 3 hours. Maximum plasma concentration after a 50 mg oral dose is approximately 25 to 30 nanograms per milliliter [11].

5.2 Distribution

Pirenzepine has a moderate volume of distribution (approximately 1.2 to 1.7 liters per kilogram), reflecting distribution into extravascular tissues but limited penetration of lipophilic compartments. Plasma protein binding is low, approximately 12 percent, predominantly to albumin [6, 12]. The compound does not significantly cross the blood-brain barrier, a property attributed to the quaternary nitrogen-like character of the protonated piperazine ring at physiological pH and to the hydrophilic tricyclic core. Central nervous system concentrations after systemic administration are negligible, and central anticholinergic effects (confusion, sedation, memory impairment) are rarely observed at therapeutic doses.

5.3 Metabolism

Pirenzepine undergoes minimal hepatic metabolism. No significant first-pass hepatic extraction occurs, and the low oral bioavailability is attributable to incomplete gastrointestinal absorption rather than presystemic metabolism [11]. The

compound is not a significant substrate of cytochrome P450 enzymes, and no metabolites of clinical significance have been identified. The absence of CYP-mediated metabolism is the basis for the minimal drug-drug interaction profile of pirenzepine. The compound is neither an inducer nor an inhibitor of the major CYP isoforms at therapeutic concentrations.

5.4 Elimination

Renal excretion of unchanged drug is the principal elimination pathway. The mean renal clearance of approximately 110 milliliters per minute approximates the glomerular filtration rate, indicating that pirenzepine is eliminated predominantly by glomerular filtration without significant tubular secretion or reabsorption [11]. The harmonic mean elimination half-life after a single oral dose is approximately 10.2 hours, increasing modestly to approximately 12.4 hours with multiple dosing, consistent with mild accumulation on repeated administration at the standard 12-hour dosing interval [11, 12].

In patients with chronic renal insufficiency, pirenzepine elimination is prolonged and dose adjustment is appropriate. The half-life extends to approximately 18 to 22 hours in patients with moderate renal impairment (creatinine clearance 20 to 50 mL/min) and to approximately 25 to 35 hours in patients on maintenance hemodialysis [20]. Hepatic impairment does not significantly alter pirenzepine pharmacokinetics, consistent with the negligible hepatic metabolism.

5.5 Routes of administration

Three principal routes have been used clinically:

Oral: 50 mg tablets, administered twice daily (100 mg per day) or three times daily (150 mg per day), taken 30 minutes before meals. This is the standard registered route for peptic ulcer disease.

Parenteral (intravenous, intramuscular): 10 mg ampoules, administered by slow intravenous injection or intramuscular injection, used in some jurisdictions for acute upper gastrointestinal hemorrhage and perioperative antisecretory prophylaxis.

Ophthalmic: 2% pirenzepine gel, applied topically to the conjunctival sac twice daily in the myopia clinical trials. This formulation has not been commercially marketed.

5.6 Special populations

Pediatric pharmacokinetics for the ophthalmic route have been characterized in the context of the myopia trials; systemic absorption from the 2% ophthalmic gel is low, and measurable plasma concentrations were not consistently detected in the pediatric trial populations [8]. Geriatric pharmacokinetics are similar to adult values except in the context of age-related renal impairment. Pregnancy and lactation data are limited; the compound has been rated pregnancy category B in some jurisdictions (no evidence of human harm, no evidence of animal teratogenicity at multiples of the human dose).

6. Clinical Evidence Base

6.1 Peptic ulcer disease: duodenal ulcer

The principal clinical evidence for pirenzepine in peptic ulcer disease derives from extensive controlled trials conducted in the late 1970s and 1980s, predominantly in European and Japanese centers.

The Carmine and Brogden (1985) review in *Drugs*, which remains the most comprehensive published assessment of pirenzepine clinical pharmacology, summarized the evidence from over 30 controlled trials [6]. In duodenal ulcer, pirenzepine at oral doses of 100 to 150 mg per day produced endoscopically confirmed healing rates of 60 to 76 percent at 4 to 8 weeks, compared to approximately 35 to 45 percent on placebo. The response was dose-related: 100 mg per day (50 mg twice daily) was superior to placebo, and 150 mg per day (50 mg three times daily) produced modestly higher healing rates with a higher incidence of anticholinergic adverse effects [6, 7].

Comparative trials against cimetidine (Tagamet, 200 mg three times daily plus 400 mg at bedtime, total 1000 mg per day) showed pirenzepine healing rates that were generally not statistically different from cimetidine, though numerical healing rates with cimetidine were consistently slightly higher (73 to 83 percent vs. 60 to 76 percent for pirenzepine at comparable timepoints) [6, 21]. Pirenzepine was superior to gefarnate (300 mg per day) in multiple comparative trials.

6.2 Peptic ulcer disease: gastric ulcer

In gastric ulcer, controlled trial data are more limited. Available studies showed healing rates at 4 to 8 weeks of approximately 50 to 70 percent on pirenzepine 100 to 150 mg per day, compared to 50 to 80 percent on cimetidine at standard doses [6]. The differences were not statistically significant in any individual trial.

6.3 Peptic ulcer disease: maintenance therapy

Pirenzepine at reduced doses (50 to 100 mg per day) was studied as maintenance therapy to prevent ulcer recurrence after initial healing. Recurrence rates at 12 months were approximately 20 to 30 percent on pirenzepine maintenance versus 50 to 60 percent on placebo, a significant reduction [6]. However, the introduction of H2 receptor antagonist maintenance therapy (ranitidine 150 mg at bedtime) and subsequently proton pump inhibitor maintenance and *Helicobacter pylori* eradication therapy rendered pirenzepine maintenance therapy obsolete.

6.4 Myopia progression in children

Two multicenter, randomized, double-masked, placebo-controlled, parallel-group trials evaluated 2% pirenzepine ophthalmic gel applied twice daily to both eyes in children aged 8 to 12 years with progressive myopia.

The Siatkowski et al. (2004) 1-year trial enrolled 174 children at 13 US sites and randomized them 2:1 to pirenzepine gel or placebo [8]. At 1 year, mean myopia progression (change in cycloplegic spherical equivalent refraction) was 0.26 diopters in the pirenzepine group versus 0.53 diopters in the placebo group, a 51 percent reduction ($P < 0.001$). Axial elongation was similarly reduced. The safety profile was acceptable; the most common adverse events were mild pupil dilation (reported in approximately 10 to 15 percent of pirenzepine-treated subjects) and mild accommodation difficulty. No serious ocular adverse events were reported.

The Siatkowski et al. (2008) 2-year trial enrolled 353 children at 14 US and Asian sites and randomized them 2:1 to pirenzepine gel or placebo [9]. At 2 years, pirenzepine reduced the rate of myopia progression by approximately 50 percent compared to placebo, with the treatment effect sustained through the second year. The safety and tolerability profile was consistent with the 1-year trial; no new safety signals emerged.

A network meta-analysis by Huang et al. (2016), evaluating 16 interventions for myopia control in children, ranked pirenzepine as effective for both refraction and axial length outcomes, though less effective than atropine (which produced greater myopia retardation but at the cost of more substantial mydriasis and cycloplegia) [22].

6.5 Other investigated indications

Pirenzepine has been studied in limited fashion for the suppression of omeprazole-induced hypergastrinemia. Omeprazole and other proton pump inhibitors produce secondary hypergastrinemia (elevated plasma gastrin) through the loss of acid-mediated negative feedback on antral G cells. Pirenzepine, by blocking M1-mediated gastrin release, was demonstrated to reduce omeprazole-induced hypergastrinemia in a small clinical study [23]. This application has not been pursued clinically.

7. Reported Research Dose Ranges

7.1 Approved doses

Peptic ulcer disease (gastric and duodenal ulcer): 50 mg twice daily (100 mg per day) as the standard registered dose, with some jurisdictions approving 50 mg three times daily (150 mg per day). Tablets are taken 30 minutes before meals. Duration of treatment for acute ulcer healing is typically 4 to 8 weeks. Maintenance therapy (where used) is 50 mg once or twice daily.

Parenteral: 10 mg by slow intravenous injection or intramuscular injection, typically every 8 to 12 hours, for acute upper gastrointestinal hemorrhage or perioperative antisecretory prophylaxis.

7.2 Investigational doses

Myopia control: 2% pirenzepine ophthalmic gel, applied to the conjunctival sac of each eye twice daily. The dose delivered per application is approximately 30 to 50 micrograms per eye. Treatment duration in clinical trials was 1 to 2 years.

Hypergastrinemia suppression: 50 mg twice daily (concurrent with proton pump inhibitor therapy) in investigational protocols.

Investigators acquiring research-grade pirenzepine should treat these dose ranges as reference points and should characterize pharmacokinetics and tolerability in their specific study populations and routes of administration.

8. Sourcing and Quality Verification

Pharmaceutical-grade pirenzepine (Gastrozepin brand or licensed generic) is available in jurisdictions where the compound is registered for peptic ulcer disease. Pharmaceutical sourcing is feasible in Germany, Italy, Japan, the Republic of Korea, and other marketed territories. The pharmaceutical-grade material is supplied as 25 mg or 50 mg oral tablets and as 10 mg parenteral ampoules.

Research-grade pirenzepine dihydrochloride is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Tocris Bioscience, Cayman Chemical, MedChemExpress, Selleckchem, Santa Cruz Biotechnology, Abcam, LGC Standards) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the dihydrochloride salt; the free base is also available from selected suppliers. Pricing is moderate, in the range of \$30 to \$150 per gram of research-grade material at the time of monograph preparation.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (352.18 for the protonated free base $[M+H]^+$, or the dihydrochloride salt mass as appropriate)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis (gas chromatography of common synthesis solvents)

The research-grade pirenzepine market is well established. The compound has been commercially available for decades as a pharmacological tool and as a radioligand precursor ($[^3H]$ -pirenzepine); counterfeit material is uncommon. On-receipt analytical confirmation is nonetheless appropriate for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Pirenzepine dihydrochloride is freely soluble in water at room temperature. For research applications, the compound is supplied as a crystalline powder and is reconstituted as needed. Stock solutions are typically prepared at 10 to 100 mM in water, phosphate-buffered saline, or dimethyl sulfoxide for in vitro applications. For in vivo research, solutions in normal saline or phosphate-buffered saline are standard.

Refrigerated storage (2 to 8 degrees Celsius) of the solid is recommended; the compound is stable at room temperature under dry conditions for extended periods but should be protected from prolonged exposure to light and moisture. Aqueous stock solutions should be stored at 2 to 8 degrees Celsius and used within 14 to 30 days of preparation. Dimethyl sulfoxide stock solutions are stable at minus 20 degrees Celsius for at least 6 months.

Aliquoting of stock solutions for single-use is recommended to avoid freeze-thaw cycles. The compound is stable through at least 3 to 5 freeze-thaw cycles in aqueous solution without measurable loss of potency.

For ophthalmic research formulations, the 2% pirenzepine gel used in the myopia clinical trials was formulated in a carbomer-based gel vehicle for topical ocular application. The specific formulation details are proprietary; investigators seeking to replicate the ophthalmic application should consult the trial methodology publications for vehicle composition guidance [8, 9].

10. Stack Interaction Considerations

Pirenzepine has a limited drug-drug interaction profile, reflecting its minimal hepatic metabolism and its selective receptor pharmacology. Investigators conducting research with pirenzepine, especially in chronic dosing regimens or in combination with other research compounds, should consider:

Anticholinergic agents: Concurrent use with other muscarinic antagonists (atropine, scopolamine, glycopyrrolate, ipratropium, tiotropium, oxybutynin, tolterodine) produces additive anticholinergic effects. The combination increases the risk of dry mouth, constipation, urinary retention, and (with agents that penetrate the blood-brain barrier) central anticholinergic syndrome. Concurrent use is pharmacologically redundant for the antisecretory effect and is not recommended.

Cholinergic agents: Acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine, pyridostigmine, neostigmine) produce pharmacological opposition to pirenzepine at muscarinic receptors. The clinical consequence depends on the relative receptor occupancy; at therapeutic doses, pirenzepine may partially attenuate the gastrointestinal and secretory effects of acetylcholinesterase inhibitors.

H2 receptor antagonists and proton pump inhibitors: Concurrent use with cimetidine, ranitidine, famotidine, omeprazole, esomeprazole, or lansoprazole produces additive acid suppression. The combination has been studied (pirenzepine plus omeprazole for hypergastrinemia) but is not standard clinical practice. No pharmacokinetic interaction is expected, as pirenzepine is not a CYP substrate and does not compete for renal tubular secretion with these agents.

Antacids: Concurrent administration with aluminum- and magnesium-containing antacids reduces pirenzepine oral bioavailability by approximately 30 percent, reflecting reduced gastrointestinal absorption [19]. A dosing interval of at least 1 hour between pirenzepine and antacid administration is recommended.

CYP substrates: Pirenzepine does not inhibit or induce the major cytochrome P450 isoforms (CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4) at therapeutic concentrations. No CYP-mediated drug-drug interactions are expected or reported.

Drugs affecting renal function: Because pirenzepine is eliminated predominantly by glomerular filtration, drugs that reduce glomerular filtration rate (nonsteroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) may modestly increase pirenzepine exposure. The effect is clinically significant only in the context of pre-existing renal impairment.

Ophthalmic combinations: For the myopia indication, concurrent use of pirenzepine ophthalmic gel with other topical ophthalmic muscarinic agents (atropine, cyclopentolate, tropicamide) would produce additive mydriasis and cycloplegia. Concurrent use with topical ophthalmic cholinergic agonists (pilocarpine) would produce pharmacological opposition.

11. Adverse Events and Safety

11.1 Common adverse events (oral administration)

The principal adverse events at registered oral doses (100 to 150 mg per day) are mild anticholinergic effects:

- Dry mouth (approximately 14 percent at 100 to 150 mg per day). This is the most frequently reported adverse event and reflects residual M3 receptor antagonism on salivary glands at therapeutic doses.
- Blurred vision (approximately 1 percent at 100 mg per day, increasing to approximately 5.6 percent at 150 mg per day). The dose-dependence of this effect reflects the dose-limited selectivity of pirenzepine; at 150 mg per day, sufficient plasma concentrations are achieved to engage M3 receptors in the ciliary muscle, producing mild cycloplegia.
- Constipation (approximately 3 percent).
- Diarrhea (approximately 3 percent).
- Headache (approximately 2 percent).
- Mental confusion (approximately 1.5 percent, principally in elderly patients and likely reflecting minimal blood-brain barrier penetration at higher doses or in patients with compromised barrier function) [6, 7].

The overall discontinuation rate attributable to adverse events in controlled trials was approximately 2 percent, substantially lower than the discontinuation rate observed with atropine at equi-effective antisecretory doses [6].

11.2 Adverse events (ophthalmic administration)

In the myopia clinical trials with 2% pirenzepine ophthalmic gel, the principal adverse events were:

- Mild pupil dilation (mydriasis), reported in approximately 10 to 15 percent of treated subjects
- Mild difficulty with near accommodation
- Mild ocular surface irritation attributable to the gel vehicle

No serious ocular adverse events (corneal toxicity, elevated intraocular pressure, retinal effects) were reported in either the 1-year or 2-year trials [8, 9]. Systemic adverse events from ophthalmic administration were not observed, consistent with negligible systemic absorption from the gel formulation.

11.3 Rare and serious adverse events

Serious adverse events attributable to pirenzepine are rare. The following have been reported in postmarketing surveillance and in large controlled trial databases:

- Urinary retention (rare, principally in elderly men with benign prostatic hyperplasia)
- Tachycardia (rare at registered doses; more common at higher doses or in patients concurrently receiving other anticholinergic agents)
- Allergic hypersensitivity reactions including skin rash (rare)
- Paralytic ileus (extremely rare, reported in individual cases with concurrent opioid use)

No hepatotoxicity, nephrotoxicity, hematological toxicity, or cardiotoxicity (QT prolongation, arrhythmia) has been attributed to pirenzepine at therapeutic doses. The compound does not produce the clinically significant cardiac arrhythmias observed with some other anticholinergic agents (e.g., disopyramide).

11.4 Dose-limited selectivity

The M1 selectivity of pirenzepine is dose-limited. At 100 mg per day (50 mg twice daily), the plasma concentrations achieved are sufficient to produce selective M1 antagonism with minimal M2 and M3 engagement. At 150 mg per day, M3 engagement becomes clinically apparent (increased blurred vision, increased dry mouth). At doses exceeding 150 mg per day (studied in some early pharmacokinetic trials), the selectivity advantage is progressively lost and the adverse-event profile approaches that of a non-selective muscarinic antagonist [6].

11.5 Pregnancy and lactation

Human pregnancy data are limited. Animal reproductive toxicology studies have not demonstrated teratogenicity at multiples of the human dose. The compound is rated pregnancy category B in some jurisdictions. Use during pregnancy and lactation is generally not recommended unless the potential benefit outweighs the potential risk.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five antisecretory and muscarinic antagonist candidates against pirenzepine, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five candidates were selected to represent the principal therapeutic alternatives and mechanistic comparators for pirenzepine's two clinical applications (gastric antisecretion and muscarinic antagonism for myopia control).

12.1 Telenzepine

Mechanism: Selective M1 muscarinic receptor antagonist; the pyrido[1,2-a]benzodiazepinone structural analog of pirenzepine with approximately 4- to 25-fold greater M1 affinity and improved M1/M2 selectivity ratio. K_i at M1 approximately 0.8 to 3 nanomolar, with approximately 10- to 50-fold selectivity over M2 [24, 25].

Development trajectory: Developed by Byk Gulden (subsequently Altana Pharma, now Nycomed/Takeda) as a next-generation selective muscarinic antagonist for peptic ulcer disease. Advanced through Phase 2 and limited Phase 3 clinical development in Europe in the late 1980s. The compound demonstrated greater antisecretory potency than pirenzepine on a milligram-per-milligram basis and comparable ulcer healing rates at lower doses (3 to 6 mg per day). The development program was discontinued, reportedly for commercial reasons related to the competitive dominance of H2 receptor antagonists and proton pump inhibitors rather than for safety or efficacy failures.

Novelty: Low to moderate. The mechanism is an incremental improvement on pirenzepine (same receptor target, same structural class, greater potency and selectivity). No novel mechanistic insight.

Effect size: The antisecretory effect on a molar basis is greater than pirenzepine (approximately 4- to 25-fold more potent). Ulcer healing rates in Phase 2 trials were comparable to pirenzepine and cimetidine at substantially lower doses. Clinical

data are limited relative to pirenzepine.

Promising potential: Low. Development is terminated. The compound is available as a research-grade reagent and as a pharmacological tool but has no registered indication and no active development program.

Side-effect profile: The improved M1/M2 selectivity theoretically predicts a superior side-effect profile relative to pirenzepine. Available clinical data (limited) suggest comparable tolerability at equi-effective doses, with dry mouth and visual disturbance as the principal adverse events.

Overall validation: Low to moderate. The compound has produced limited clinical efficacy data that support the concept of selective M1 antagonism for acid suppression but has not advanced to registration or large-scale clinical validation.

Comparison to pirenzepine: Telenzepine is the more potent and more selective M1 antagonist but has substantially less clinical validation, no registered indication, and no active development program. Pirenzepine has the advantage of extensive clinical trial data, registered indications, an established safety database, and broad commercial availability. For research applications requiring maximal M1 selectivity, telenzepine is the superior pharmacological tool; for clinical translation, pirenzepine has the operational advantage.

12.2 Atropine

Mechanism: Non-selective muscarinic receptor antagonist, binding M1 through M5 with approximately equal affinity (K_i approximately 0.5 to 2 nanomolar at all subtypes) [14]. Competitive, reversible antagonism at all muscarinic receptor subtypes. Full blood-brain barrier penetration at systemic doses.

Development trajectory: Atropine is the oldest and most extensively characterized muscarinic antagonist, in clinical use for over 150 years. It is registered for numerous indications including preoperative antisecretory prophylaxis, bradycardia, organophosphate poisoning, and (as low-concentration ophthalmic drops) cycloplegia and mydriasis for examination. In the past decade, low-dose atropine (0.01% to 0.05% ophthalmic solution) has emerged as the most extensively studied pharmacological intervention for myopia control in children, supported by the ATOM (Atropine for the Treatment of Myopia) series of randomized controlled trials conducted in Singapore [26, 27].

Novelty: None. The compound is over a century old and is the prototypical muscarinic antagonist.

Effect size: For gastric acid suppression, atropine is effective but requires doses that produce substantial systemic anticholinergic effects (tachycardia, dry mouth, urinary retention, constipation, central nervous system effects). For myopia control, low-dose atropine (0.01%) reduces myopia progression by approximately 50 to 60 percent over 2 years; higher concentrations (0.5% to 1%) produce greater retardation (up to 77 percent reduction) but with unacceptable mydriasis and cycloplegia in children [26, 27].

Promising potential: High for the myopia indication. Low-dose atropine has advanced further in clinical development than pirenzepine for myopia control, with multiple large randomized controlled trials completed and regulatory submissions in progress in several jurisdictions. For gastric antisecretion, atropine has been functionally replaced by H2 antagonists and proton pump inhibitors.

Side-effect profile: Substantially less favorable than pirenzepine for systemic administration, owing to non-selective engagement of all muscarinic subtypes and blood-brain barrier penetration. For ophthalmic myopia application, low-dose atropine (0.01%) produces minimal mydriasis and near-normal accommodation, a significant advantage; higher concentrations produce clinically significant photophobia and loss of near vision.

Overall validation: Very high. Atropine is one of the most extensively validated drugs in pharmacology. For the myopia indication, the ATOM trial series provides the strongest evidence base among muscarinic agents.

Comparison to pirenzepine: Atropine is the more potent muscarinic antagonist but lacks subtype selectivity. For peptic ulcer disease, pirenzepine is superior to atropine in selectivity and tolerability. For myopia control, low-dose atropine has advanced further clinically than pirenzepine ophthalmic gel and has a stronger evidence base, but pirenzepine's M1 selectivity was hypothesized to provide a more favorable ocular side-effect profile. The myopia trial data suggest that both compounds produce mild mydriasis at their effective ophthalmic concentrations, partially negating the selectivity advantage of pirenzepine.

12.3 Cimetidine

Mechanism: Competitive antagonist of the histamine H₂ receptor on gastric parietal cells. Reduces histamine-stimulated gastric acid secretion by blocking the histaminergic drive to the proton pump [28]. No muscarinic receptor activity.

Development trajectory: Developed by Sir James Black and colleagues at Smith, Kline and French (now GSK). First H₂ receptor antagonist approved (United Kingdom 1976, United States 1977 as Tagamet). Registered for duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, and Zollinger-Ellison syndrome. First blockbuster drug in the history of the pharmaceutical industry. Now available over-the-counter in many jurisdictions.

Novelty: None in the contemporary context, though cimetidine was revolutionary at the time of its introduction and transformed peptic ulcer management. The H₂ receptor antagonist class was the first targeted antisecretory approach.

Effect size: Superior to pirenzepine for gastric acid suppression. Cimetidine reduces basal acid output by approximately 70 to 80 percent (versus approximately 50 percent for pirenzepine). Duodenal ulcer healing rates at 4 weeks: approximately 70 to 85 percent on cimetidine 1 g per day versus approximately 60 to 76 percent on pirenzepine 100 to 150 mg per day [6, 21]. The difference is consistently in favor of cimetidine but is not always statistically significant in individual trials.

Promising potential: Low for new therapeutic development. Cimetidine has been largely supplanted by ranitidine and famotidine (more potent H₂ antagonists with fewer drug interactions) and by proton pump inhibitors for peptic ulcer management. Cimetidine retains some interest as an over-the-counter antacid and for its immunomodulatory properties.

Side-effect profile: Generally well tolerated. Principal adverse events include headache, dizziness, diarrhea, and muscle pain. Cimetidine is a moderate inhibitor of CYP1A2, CYP2C19, CYP2D6, and CYP3A4, producing clinically significant drug-drug interactions with warfarin, phenytoin, theophylline, and other CYP substrates. Cimetidine also has antiandrogenic effects (gynecomastia, impotence) at high doses owing to androgen receptor antagonism, a side effect absent from pirenzepine.

Overall validation: Very high. Cimetidine has an enormous clinical trial database and decades of postmarketing experience. It is one of the most extensively validated drugs in gastroenterology.

Comparison to pirenzepine: Cimetidine is the more effective antisecretory agent for peptic ulcer healing, with higher acid suppression, higher ulcer healing rates, and a more extensive evidence base. Pirenzepine has a simpler drug interaction profile (no CYP inhibition) and lacks the antiandrogenic effects of cimetidine. In the contemporary therapeutic landscape, both compounds have been substantially superseded by proton pump inhibitors. Pirenzepine retains a unique mechanistic distinction (M1 muscarinic antagonism) that supports its continued use as a pharmacological research tool.

12.4 Ranitidine

Mechanism: Competitive antagonist of the histamine H2 receptor on gastric parietal cells. Approximately 5- to 10-fold more potent than cimetidine at the H2 receptor [29]. No muscarinic receptor activity.

Development trajectory: Developed by Glaxo (now GSK) and approved in 1981 (United Kingdom) and 1983 (United States) as Zantac. Became the world's best-selling prescription drug in 1988. Registered for the same indications as cimetidine. In 2019 to 2020, ranitidine was withdrawn from markets worldwide after the detection of N-nitrosodimethylamine (NDMA), a probable human carcinogen, as a degradation product in ranitidine formulations [30]. The withdrawal was based on stability concerns rather than clinical safety data.

Novelty: None in the contemporary context. Ranitidine was a major pharmacological advance over cimetidine in the early 1980s (greater potency, fewer drug interactions, no antiandrogenic effects).

Effect size: Superior to pirenzepine. Ranitidine reduces basal acid output by approximately 80 to 90 percent. Duodenal ulcer healing rates at 4 weeks are approximately 75 to 90 percent on ranitidine 300 mg per day, consistently higher than pirenzepine [6].

Promising potential: Essentially none. The compound has been withdrawn from global markets due to the NDMA contamination issue. Famotidine has replaced ranitidine as the preferred H2 antagonist.

Side-effect profile: Prior to withdrawal, ranitidine was considered to have an excellent safety profile with fewer drug interactions and no antiandrogenic effects compared to cimetidine. The NDMA issue was a manufacturing and stability problem, not an intrinsic pharmacological safety concern.

Overall validation: Very high historically, though the NDMA-related withdrawal has ended the clinical use of the compound.

Comparison to pirenzepine: Ranitidine was the more effective antisecretory agent, with greater acid suppression and higher ulcer healing rates. Its global withdrawal due to NDMA contamination has removed it from the therapeutic landscape. Pirenzepine, while less effective as an antisecretory agent, does not share this stability concern and remains available (where registered) as a therapeutic option. The comparison is principally of historical and pharmacological interest.

12.5 Omeprazole

Mechanism: Irreversible inhibitor of the gastric hydrogen-potassium ATPase (proton pump) on parietal cells. Omeprazole is a prodrug that is acid-activated in the parietal cell canaliculus; the active sulfenamide covalently modifies cysteine residues on the proton pump, producing near-complete and sustained acid suppression [31].

Development trajectory: Developed by AB Hassle (Astra, now AstraZeneca). Approved 1988 (Europe), 1989 (United States) as Prilosec/Losec. First proton pump inhibitor. Registered for duodenal ulcer, gastric ulcer, gastroesophageal reflux disease, Zollinger-Ellison syndrome, and *Helicobacter pylori* eradication (in combination with antibiotics). The proton pump inhibitor class has become the dominant antisecretory class worldwide.

Novelty: None in the contemporary context, though omeprazole was revolutionary at its introduction and fundamentally changed the management of acid-related disorders.

Effect size: Substantially superior to pirenzepine. Omeprazole 20 mg per day reduces basal acid output by greater than 90 percent and produces duodenal ulcer healing rates of 90 to 100 percent at 4 weeks [31]. This represents approximately a 20- to 40-percentage-point improvement over pirenzepine and a 10- to 20-percentage-point improvement over H₂ receptor antagonists.

Promising potential: Low for new therapeutic development in the antiseecretory space (the class is mature and generic). Proton pump inhibitors remain the standard of care for acid-related disorders. Some recent interest in adverse effects of long-term PPI use (bone density, vitamin B12 deficiency, *Clostridium difficile* infection, hypomagnesemia) has generated limited interest in alternative antiseecretory strategies.

Side-effect profile: Generally well tolerated for short-term use. Long-term use has been associated with modest increases in the risk of osteoporotic fractures, community-acquired pneumonia, *Clostridium difficile*-associated diarrhea, hypomagnesemia, vitamin B12 deficiency, and chronic kidney disease, though the absolute risk increments are small [32]. Omeprazole is a moderate inhibitor of CYP2C19, producing drug-drug interactions with clopidogrel (clinically significant), diazepam, and phenytoin.

Overall validation: Extremely high. Omeprazole is one of the most extensively studied drugs in medicine, with thousands of clinical trials and decades of post-marketing experience. It is the reference standard for gastric antiseecretory therapy.

Comparison to pirenzepine: Omeprazole is overwhelmingly superior to pirenzepine for gastric acid suppression and ulcer healing. The clinical dominance of proton pump inhibitors is the principal reason that pirenzepine has been marginalized as a therapeutic antiseecretory agent. Pirenzepine retains value as a pharmacological research tool (the prototypical M1 muscarinic antagonist), as a topical ophthalmic candidate for myopia control (an application entirely outside the omeprazole mechanism), and in jurisdictions where proton pump inhibitors are not accessible. The two compounds are not mechanistic competitors; they act on different targets in the acid secretory pathway.

12.6 Comparator summary

The five compounds occupy distinct positions in the antisecretory and muscarinic antagonist landscape. **Telenzepine** is the more potent and selective M1 antagonist but has no registered indication, no active development, and limited clinical data; it serves principally as a research tool. **Atropine** is the non-selective muscarinic antagonist comparator, inferior to pirenzepine in systemic selectivity and tolerability for the antisecretory indication but substantially ahead of pirenzepine in clinical development for the myopia indication (as low-dose ophthalmic solution). **Cimetidine** was the first-generation H2 receptor antagonist that commercially dis-

placed pirenzepine in the 1980s; it produces greater acid suppression but has CYP-mediated drug interactions and antiandrogenic effects that pirenzepine lacks. **Ranitidine** was the second-generation H2 antagonist with superior potency, now withdrawn due to NDMA contamination. **Omeprazole** is the gold-standard proton pump inhibitor that renders pirenzepine (and to a substantial degree, H2 antagonists) therapeutically obsolete for gastric acid suppression.

Pirenzepine occupies a historically significant but therapeutically marginal position in the antisecretory landscape. Its enduring value is threefold: it is the prototypical M1 muscarinic receptor antagonist and a foundational pharmacological tool for receptor subtype classification; it is an investigational candidate for myopia control in children, representing a distinct mechanism (M1-selective muscarinic antagonism) from the non-selective atropine approach; and it is a well-characterized, well-tolerated compound with decades of human safety data that supports its use as a research reagent and as a clinical tool in settings where more potent antisecretory agents are not available or appropriate.

13. References

1. Hammer R, Berrie CP, Birdsall NJ, Burgen AS, Hulme EC. Pirenzepine distinguishes between different subclasses of muscarinic receptors. *Nature*. 1980;283(5742):90-92.
2. Hulme EC, Birdsall NJ, Buckley NJ. Muscarinic receptor subtypes. *Annu Rev Pharmacol Toxicol*. 1990;30:633-673.
3. Caulfield MP, Birdsall NJ. International Union of Pharmacology. XVII. Classification of muscarinic acetylcholine receptors. *Pharmacol Rev*. 1998;50(2):279-290.
4. Bianchi Porro G, Petrillo M. Pirenzepine in the management of peptic ulcer disease. *Scand J Gastroenterol Suppl*. 1982;72:201-207.
5. Hammer R, Giachetti A. Muscarinic receptor subtypes: M1 and M2 biochemical and functional characterization. *Life Sci*. 1982;31(26):2991-2998.
6. Carmine AA, Brogden RN. Pirenzepine. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in peptic ulcer disease and other allied diseases. *Drugs*. 1985;30(2):85-126.
7. Jaup BH. Pirenzepine. A review of clinical results. *Scand J Gastroenterol Suppl*. 1982;72:213-218.
8. Siatkowski RM, Cotter S, Miller JM, et al. Safety and efficacy of 2% pirenzepine ophthalmic gel in children with myopia: a 1-year, multicenter, double-masked, placebo-controlled parallel study. *Arch Ophthalmol*. 2004;122(11):1667-1674.
9. Siatkowski RM, Cotter SA, Crockett RS, et al. Two-year multicenter, randomized, double-masked, placebo-controlled, parallel safety and efficacy study of 2% pirenzepine ophthalmic gel in children with myopia. *J AAPOS*. 2008;12(4):332-339.
10. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces experimental myopia and eye enlargement via a nonaccommodative mechanism. *Invest Ophthalmol Vis Sci*. 1993;34(1):205-215.

11. Jaup BH, Blomstrand C. Oral pharmacokinetics of pirenzepine in man following single and multiple doses. *Int J Pharm.* 1986;34(1-2):57-62.
12. Carmine AA, Brogden RN. Pharmacokinetics and bioequivalence of different formulations of pirenzepine. *Int J Clin Pharmacol Ther Toxicol.* 1986;24(6):313-318.
13. Jacobson KA, Stiles GL, Ji XD. Functionalized congener approach to muscarinic antagonists: analogues of pirenzepine. *J Med Chem.* 1992;35(22):4105-4116.
14. Watson M, Yamamura HI, Roeske WR. A unique regulatory profile and regional distribution of [3H]-pirenzepine binding in the rat provide evidence for distinct M1 and M2 muscarinic receptor subtypes. *Life Sci.* 1983;32(26):3001-3011.
15. Bertaccini G, Coruzzi G. Pirenzepine: a useful model for the development of selective muscarinic antagonists. *Pharmacol Res Commun.* 1988;20(Suppl 4):1-10.
16. Stone RA, Lin T, Laties AM. Muscarinic antagonist effects on experimental chick myopia. *Exp Eye Res.* 1991;52(6):755-758.
17. Pramod AB, Foster J, Bhatt DL. Pirenzepine promotes the homodimerization of M1 muscarinic receptors. *Biochem Biophys Res Commun.* 2014;449(2):186-191.
18. Lammers JW, Minette P, McCusker MT, et al. The role of pirenzepine-sensitive (M1) muscarinic receptors in vagally mediated bronchoconstriction in humans. *Am Rev Respir Dis.* 1989;139(2):446-449.
19. Feurle GE, Baca I, Zierden E. Effect of food and antacids on the oral absorption of pirenzepine in man. *Int J Pharm.* 1986;34(1-2):121-126.
20. Czock D, Keller F, Rasche FM, et al. Oral pharmacokinetics of pirenzepine in patients with chronic renal insufficiency, failure, and maintenance haemodialysis. *Eur J Clin Pharmacol.* 1985;28(4):445-449.
21. Sonnenberg A, Dammann HG, Muller-Lissner S, et al. Treatment of duodenal ulcer with pirenzepine and cimetidine. *Gastroenterology.* 1984;87(2):378-382.
22. Huang J, Wen D, Wang Q, et al. Efficacy comparison of 16 interventions for myopia control in children: a network meta-analysis. *Ophthalmology.* 2016;123(4):697-708.
23. Inoue T, Kitagawa M, Hashimoto S, et al. Effects of pirenzepine on omeprazole-induced hypergastrinemia and acid suppression in peptic ulcer patients. *J Gastroenterol.* 1995;30(4):439-443.

24. Eltze M, Gonne S, Riedel R, et al. Pharmacological evidence for selective inhibition of gastric acid secretion by telenzepine, a new antimuscarinic drug. *Eur J Pharmacol.* 1985;112(2):211-224.
25. Turconi M, Nicola M, Quintero MG, et al. Synthesis of a new class of 2,3-dihydro-1H-pyrrolo[1,2-a]benzimidazol-1-ones as selective muscarinic M1 receptor antagonists. *J Med Chem.* 1990;33(8):2101-2108.
26. Chia A, Chua WH, Cheung YB, et al. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (Atropine for the Treatment of Myopia 2). *Ophthalmology.* 2012;119(2):347-354.
27. Yam JC, Jiang Y, Tang SM, et al. Low-concentration atropine for myopia progression (LAMP) study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops. *Ophthalmology.* 2019;126(1):113-124.
28. Black JW, Duncan WA, Durant CJ, et al. Definition and antagonism of histamine H₂-receptors. *Nature.* 1972;236(5347):385-390.
29. Baxter GS, Burton KJ, Clarke DE, et al. Ranitidine. A review of its pharmacology and clinical use. *Drugs.* 1983;25(5):455-471.
30. United States Food and Drug Administration. FDA requests removal of all ranitidine products (Zantac) from the market. FDA News Release, April 1, 2020.
31. Fellenius E, Berglindh T, Sachs G, et al. Substituted benzimidazoles inhibit gastric acid secretion by blocking (H⁺ + K⁺)ATPase. *Nature.* 1981;290(5802):159-161.
32. Vaezi MF, Yang YX, Howden CW. Complications of proton pump inhibitor therapy. *Gastroenterology.* 2017;153(1):35-48.

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