

RESEARCH MONOGRAPH . COMPOUND PROFILE

Sildenafil

A pyrazolopyrimidinone-based cyclic GMP-specific phosphodiesterase type 5 inhibitor originally developed at Pfizer as an antianginal agent, repositioned as the first oral pharmacotherapy for erectile dysfunction and subsequently approved for pulmonary arterial hypertension, with an expanding preclinical evidence base in cardioprotection, neuroprotection, and vascular inflammation.

DOCUMENT	KDC-MN-1556
ISSUED	2026-05-15
REVISION	1.0
AUTHOR	Kodi ac bio l abs Research
COMPOUND CLASS	Selective phosphodiesterase type 5 (PDE5) inhibitor of the pyrazolopyrimidinone structural class

ABSTRACT

Sildenafil (UK-92480) is a potent, competitive, and selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), the enzyme principally responsible for hydrolytic degradation of cGMP in vascular smooth muscle, the corpus cavernosum, and the pulmonary vasculature. The compound was synthesized at the Pfizer Global Research and Development laboratories in Sandwich, Kent, United Kingdom in 1989 as part of a medicinal chemistry program targeting selective PDE5 inhibition for the treatment of angina pectoris and hypertension. Phase I clinical trials revealed limited antianginal efficacy but a pronounced and reproducible effect on penile erection, prompting repositioning toward erectile dysfunction. Sildenafil received United States Food and Drug Administration (FDA) approval on 27 March 1998 as the first oral pharmacotherapy for erectile dysfunction (marketed as Viagra) and subsequently received FDA approval in June 2005 for the treatment of World Health Organization Group I pulmonary arterial hypertension (marketed as Revatio).

The pharmacological mechanism is inhibition of PDE5 at the catalytic site with an IC_{50} of approximately 3.5 nanomolar and selectivity over PDE1 through PDE4 of 80- to 19,000-fold, with approximately 10-fold selectivity over the structurally related retinal PDE6, the latter accounting for the dose-dependent visual disturbances observed clinically [1, 2]. PDE5 inhibition potentiates the nitric oxide (NO)/soluble guanylyl cyclase (sGC)/cGMP signaling cascade: in tissues where NO release occurs (penile corpus cavernosum during sexual stimulation, pulmonary

vascular endothelium), sildenafil amplifies the downstream smooth muscle relaxation by preventing cGMP breakdown. The compound does not directly initiate smooth muscle relaxation in the absence of NO signaling, a pharmacological distinction that differentiates PDE5 inhibitors from direct NO donors and from soluble guanylyl cyclase stimulators.

Pharmacokinetics are characterized by rapid oral absorption (time to peak plasma concentration approximately 60 minutes under fasting conditions), moderate absolute oral bioavailability of approximately 41 percent (limited by hepatic first-pass metabolism), a plasma elimination half-life of approximately 3 to 5 hours, and high plasma protein binding of approximately 96 percent [3, 4]. Metabolism is predominantly hepatic via cytochrome P450 3A4 (CYP3A4, major pathway) and CYP2C9 (minor pathway), producing the active N-desmethyl metabolite (UK-103,320) that retains approximately 50 percent of the parent compound potency at PDE5 and has a similar terminal half-life [3]. The CYP3A4 dependence creates clinically significant drug-drug interactions with strong CYP3A4 inhibitors (ritonavir, ketoconazole, itraconazole, erythromycin), which can elevate sildenafil plasma concentrations by 3- to 11-fold.

The clinical evidence base spans two FDA-approved indications (erectile dysfunction and pulmonary arterial hypertension) and multiple investigational applications including Raynaud phenomenon, heart failure, altitude sickness, and neuroprotection. The SUPER-1 trial in 278 patients with pulmonary arterial hypertension demonstrated significant improvement in six-minute walk distance across all sildenafil dose groups (20, 40, and 80 mg three times daily) compared to placebo [5]. A 2024 dose-ranging trial by Hoeper et al. further

demonstrated dose-dependent benefit, with the 80 mg three times daily group achieving a median gain of 52 meters in six-minute walk distance [6]. Preclinical pharmacology has established cardioprotective effects against ischemia-reperfusion injury through mitochondrial ATP-sensitive potassium channel opening, neuroprotective effects in rodent stroke and neurodegeneration models through cGMP-mediated anti-apoptotic signaling, and anti-inflammatory effects through suppression of NF-kappaB-driven cytokine release.

The compound is well tolerated at approved doses. Principal adverse events are headache (16 percent), flushing (10 percent), dyspepsia (7 percent), nasal congestion (4 percent), and dose-dependent visual disturbances (chromatopsia, increased light sensitivity) reflecting PDE6 cross-inhibition in retinal photoreceptors [7]. The critical safety concern is the absolute contraindication with organic nitrates and nitric oxide donors, where co-administration produces synergistic and potentially fatal hypotension through additive cGMP-mediated vasodilation [8]. This monograph reviews the chemistry, synthesis, and structural pharmacology of sildenafil; the molecular mechanism across PDE isoforms; comprehensive human pharmacokinetics; the clinical evidence base across approved and investigational indications; sourcing and quality verification; reconstitution and handling; stack-interaction considerations; adverse-event signal; and a comparative assessment of five PDE5 inhibitor and vasodilator alternatives against sildenafil on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Sildenafil.

Marketed names: Viagra (Pfizer; erectile dysfunction indication, approved in over 120 countries), Revatio (Pfizer; pulmonary arterial hypertension indication), Liqrev (oral suspension formulation for PAH). Generic sildenafil is available in most major pharmaceutical markets following patent expiration in 2012 (European Union) and 2020 (United States).

Development codes: UK-92480 (Pfizer). The development code is the canonical identifier in the original medicinal chemistry and early pharmacology literature [1, 2].

Chemical Abstracts Service registry numbers: 139755-83-2 (free base), 171599-83-0 (citrate salt). The citrate salt is the formulated pharmaceutical form; the free base is used in some research-grade preparations.

International Union of Pure and Applied Chemistry name: 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one. The compound is a pyrazolopyrimidinone derivative substituted with an ethoxyphenyl sulfonamide bearing a methylpiperazine group, structurally optimized for selective binding to the catalytic site of PDE5.

1.2 Structural class and chemistry

Sildenafil is a pyrazolo[4,3-d]pyrimidin-7-one derivative, placing it in the broader class of nitrogen-containing heterocyclic phosphodiesterase inhibitors. The pyrazolopyrimidinone core was selected from Pfizer's PDE5 inhibitor discovery program for its combination of potency, selectivity, and oral bioavailability. The structural class is shared with other PDE5 inhibitors at the heterocyclic core level, although tadalafil (a beta-carboline), vardenafil (a closely related imidazotriazinone), and avanafil (a pyrimidine derivative) differ substantially in peripheral substituents and in selectivity profiles across PDE isoforms [9].

Molecular formula: C₂₂H₃₀N₆O₄S (free base); C₂₈H₃₈N₆O₁₁S (citrate salt, 1:1 citric acid).

Exact mass: 474.2049 g/mol (free base, monoisotopic).

Molecular weight: 474.58 g/mol (free base); 666.70 g/mol (citrate salt).

Physical properties: White to off-white crystalline powder. The citrate salt is slightly soluble in water (approximately 3.5 mg/mL at 25 degrees Celsius). Soluble in methanol, dimethyl sulfoxide, and dimethylformamide; sparingly soluble in ethanol; practically insoluble in hexane and diethyl ether. Melting point of the citrate salt is approximately 187 to 189 degrees Celsius.

Stereochemistry: Sildenafil does not contain a stereocenter and is achiral. The compound is supplied as a single defined structure without enantiomeric considerations.

1.3 Synthesis

The original Pfizer synthesis of sildenafil proceeds through construction of the pyrazolopyrimidinone core followed by elaboration of the peripheral substituents [10]. The key synthetic steps include: (a) construction of the pyrazole ring through condensation of an appropriately substituted hydrazine with a 1,3-diketone or equivalent; (b) annulation of the pyrimidinone ring through cyclization with a formamidine or equivalent one-carbon source; (c) introduction of the 2-ethoxy-5-sulfonylphenyl group through palladium-catalyzed or nucleophilic aromatic coupling; and (d) installation of the 4-methylpiperazine through sulfonamide bond formation with the phenylsulfonyl chloride intermediate. Multiple alternative synthetic routes have been published, including approaches that vary the order of ring construction and substituent introduction to optimize yield, purity, and scalability for large-scale manufacture [10, 11]. Industrial production typically achieves overall yields of 40 to 60 percent from commercially available starting materials, with final product purity exceeding 99.5 percent by HPLC. The citrate salt is prepared by treatment of the free base with citric acid in an appropriate solvent system followed by recrystallization.

2. Abstract

Sildenafil (UK-92480) is a potent, competitive, and selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), the principal enzyme responsible for hydrolytic degradation of cGMP in vascular smooth muscle, corpus cavernosum, pulmonary vasculature, and platelets. The compound was synthesized at Pfizer's Sandwich, Kent, United Kingdom research laboratories in 1989 and advanced through clinical development first as an antianginal agent, then repositioned as the first oral pharmacotherapy for erectile dysfunction following the observation of pronounced pro-erectile effects in Phase I healthy volunteer studies [1, 12].

The molecular mechanism is competitive inhibition of PDE5 at the cGMP-binding catalytic site, with an IC₅₀ of approximately 3.5 nanomolar and selectivity of 80- to 19,000-fold over PDE1 through PDE4. Selectivity over the structurally related retinal PDE6 is approximately 10-fold, accounting for the characteristic dose-dependent visual disturbances (chromatopsia, blue-tinged vision, increased photosensitivity) that constitute a pharmacological signature of the compound [1, 2]. By inhibiting PDE5, sildenafil potentiates the NO/sGC/cGMP signaling pathway in tissues where nitric oxide release occurs physiologically or pharmacologically, amplifying cGMP-mediated smooth muscle relaxation without directly activating the pathway in the absence of NO.

Two indications have received FDA approval. Erectile dysfunction (Viagra, approved 27 March 1998) at oral doses of 25 to 100 mg taken as needed approximately 60 minutes before sexual activity, with efficacy established in over 3,700 patients across more than 20 randomized controlled trials [7, 13]. Pulmonary arterial hypertension (Revatio, approved June 2005) at an oral dose of 20 mg three times daily, with efficacy established in the SUPER-1 pivotal trial demonstrating significant improvement in six-minute walk distance, mean pulmonary artery pressure, and WHO functional class compared to placebo in 278 patients [5].

Beyond the approved indications, sildenafil has been investigated in Raynaud phenomenon (where it increases capillary blood flow velocity in therapy-resistant disease), altitude sickness (where it reduces pulmonary artery pressure at simulated high altitude), heart failure with preserved ejection fraction (where the RELAX trial reported neutral results), and multiple preclinical models of cardiopro-

tection, neuroprotection, and anti-inflammation [14, 15, 16]. The preclinical cardioprotection literature is substantial, demonstrating preconditioning-like effects against ischemia-reperfusion injury through mitochondrial KATP channel opening, protein kinase C and ERK signaling, and eNOS/iNOS-derived NO generation [17, 18]. Neuroprotective effects have been demonstrated in rodent models of stroke, Huntington disease, vascular dementia, and seizure through cGMP-dependent anti-apoptotic pathways and enhancement of cerebral blood flow [19, 20].

Pharmacokinetics are dominated by CYP3A4-mediated N-demethylation, producing the active metabolite N-desmethyl sildenafil (UK-103,320) with approximately 50 percent of parent compound PDE5 potency. Oral bioavailability is approximately 41 percent; plasma elimination half-life is approximately 3 to 5 hours; and high-fat meals delay absorption by approximately 60 minutes and reduce peak plasma concentration by approximately 29 percent [3, 4]. The CYP3A4 dependence produces clinically significant interactions with strong CYP3A4 inhibitors (ritonavir increases sildenafil AUC 11-fold) and with organic nitrates (absolute contraindication due to synergistic, potentially fatal hypotension) [8, 21].

The compound is well tolerated at approved doses. The safety database encompasses over 67 double-blind, placebo-controlled trials and extensive postmarketing surveillance [22]. Principal adverse events are headache, flushing, dyspepsia, nasal congestion, and visual disturbances. Serious but rare events include non-arteritic anterior ischemic optic neuropathy (NAION), sudden sensorineural hearing loss, and priapism. Cardiovascular safety in patients without contraindicated co-medications has been extensively evaluated and is favorable; the critical safety concern remains the absolute contraindication with nitrates and NO donors.

3. Discovery and Development History

3.1 Origin

The discovery of sildenafil originated in the cardiovascular research program at Pfizer's Central Research laboratories in Sandwich, Kent, United Kingdom in the mid-1980s. The program was motivated by the emerging understanding of the nitric oxide/soluble guanylyl cyclase/cGMP signaling pathway as a mediator of vascular smooth muscle relaxation and by the hypothesis that selective inhibition of cGMP-degrading phosphodiesterases could potentiate endogenous NO signaling in the coronary vasculature to produce antianginal and antihypertensive effects [1, 12].

The medicinal chemistry team, led by Simon Campbell, Andrew Bell, and David Brown at Pfizer Sandwich, designed a series of pyrazolopyrimidinone derivatives optimized for potency and selectivity at PDE5. The compound UK-92480 (sildenafil) was first synthesized in 1989 and selected for development on the basis of its nanomolar PDE5 inhibitory potency (IC₅₀ 3.5 nM), its selectivity over PDE1 through PDE4 (80- to 19,000-fold), its oral bioavailability, and its acceptable preclinical safety profile [1, 2].

3.2 Antianginal clinical development and repositioning

Phase I clinical trials in healthy male volunteers, conducted under the direction of Ian Osterloh at Pfizer, demonstrated that sildenafil produced modest reductions in blood pressure but limited efficacy against exercise-induced angina. The critical observation was that a substantial proportion of trial participants reported pronounced penile erections as an unexpected adverse event. This observation, combined with the emerging identification of PDE5 as the principal cGMP-degrading enzyme in the corpus cavernosum, prompted Pfizer to reposition the compound from the antianginal indication to erectile dysfunction [12, 23].

The repositioning decision was informed by the 1992 identification by Rajfer et al. of nitric oxide as the principal mediator of penile erection and by the subsequent demonstration by Jeremy et al. and Boolell et al. that sildenafil potentiated

NO-mediated relaxation of isolated human corpus cavernosum tissue in vitro and produced dose-dependent pro-erectile effects in clinical studies [24, 25].

3.3 Erectile dysfunction approval

Pfizer initiated a comprehensive Phase II/III clinical development program for sildenafil in erectile dysfunction in the mid-1990s. The program enrolled more than 3,700 patients worldwide across multiple randomized, double-blind, placebo-controlled trials evaluating doses of 25, 50, and 100 mg taken as needed before sexual activity. The principal efficacy endpoints were the International Index of Erectile Function (IIEF) domain scores, the Sexual Encounter Profile diary, and the Global Assessment Question [7, 13]. Across the registration trials, sildenafil produced statistically and clinically significant improvements in erectile function, successful intercourse attempts, and patient satisfaction compared to placebo at all studied doses, with dose-dependent efficacy and a favorable tolerability profile.

The FDA approved sildenafil citrate tablets (Viagra) on 27 March 1998 for the treatment of erectile dysfunction. The approval represented the first oral pharmacotherapy for erectile dysfunction and constituted one of the most commercially successful drug launches in pharmaceutical history, generating over one billion United States dollars in sales within the first year of marketing [12].

3.4 Pulmonary arterial hypertension development

The rationale for sildenafil in pulmonary arterial hypertension (PAH) derived from the identification of PDE5 as highly expressed in the pulmonary vasculature and from early case reports and small open-label studies demonstrating acute pulmonary vasodilation with oral sildenafil in patients with primary pulmonary hypertension [26, 27]. The pivotal trial was SUPER-1 (Sildenafil Use in Pulmonary Arterial Hypertension), a 12-week, randomized, double-blind, placebo-controlled study in 278 patients with symptomatic PAH (WHO functional class II-III, predominantly idiopathic PAH and PAH associated with connective tissue disease). Patients were randomized to placebo or sildenafil at 20, 40, or 80 mg three times daily [5].

All three sildenafil dose groups demonstrated significant improvement in the primary endpoint (six-minute walk distance) compared to placebo, with improvements of 45, 46, and 50 meters for the 20, 40, and 80 mg groups, respectively.

Secondary endpoints (mean pulmonary artery pressure, WHO functional class) also improved significantly. The FDA approved sildenafil (Revatio) for pulmonary arterial hypertension in June 2005 at the 20 mg three times daily dose [5].

3.5 Subsequent development and patent expiration

Following the primary approvals, sildenafil underwent extensive clinical investigation across multiple additional indications, including heart failure, Raynaud phenomenon, altitude sickness, female sexual dysfunction, and various neuroprotective and anti-inflammatory applications. The compound's European patent expired in 2012; the United States patent for Viagra expired in 2020, leading to widespread generic availability. Revatio generic sildenafil for PAH has been available since 2012 in the United States. The compound remains one of the most widely prescribed medications globally, with current use spanning both approved indications and substantial off-label clinical applications.

4. Mechanism of Action

Sildenafil is a selective, competitive, and reversible inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5). Its principal molecular activity is potentiation of the NO/sGC/cGMP signaling pathway in tissues where PDE5 is expressed and where nitric oxide release occurs physiologically or pharmacologically.

4.1 Phosphodiesterase type 5 inhibition

PDE5 is a homodimeric metallohydrolase of the cyclic nucleotide phosphodiesterase superfamily. It contains an N-terminal regulatory domain with two GAF (cGMP-binding) domains (GAF-A and GAF-B), a phosphorylation site (Ser92 in human PDE5A), and a C-terminal catalytic domain that hydrolyzes cGMP to 5'-GMP with high specificity over cAMP [28]. PDE5 is expressed at high density in vascular smooth muscle (including the pulmonary vasculature and the corpus cavernosum), in platelets, in the gastrointestinal tract, and at lower density in the central nervous system, cardiac muscle, and retinal photoreceptors.

Sildenafil binds the catalytic site of PDE5 in a competitive and reversible manner, mimicking the purine ring of the cGMP substrate. The IC₅₀ for PDE5 inhibition is approximately 3.5 nanomolar. Selectivity over the other 10 PDE families is: PDE1, approximately 80-fold; PDE2, greater than 10,000-fold; PDE3, greater than 4,000-fold; PDE4, greater than 10,000-fold; PDE6, approximately 10-fold; PDE7 through PDE11, generally greater than 100-fold [1, 2]. The relatively modest (10-fold) selectivity over PDE6 is the molecular basis for the visual side effects.

The functional consequence of PDE5 inhibition is accumulation of intracellular cGMP in target tissues following NO-mediated sGC activation. Elevated cGMP activates cGMP-dependent protein kinase (PKG), which phosphorylates multiple downstream targets including myosin light chain phosphatase, IRAG (IP₃ receptor-associated cGMP kinase substrate), and ion channels (large-conductance calcium-activated potassium channels, L-type calcium channels), collectively producing smooth muscle relaxation through reduction of intracellular calcium concentration and calcium desensitization of the contractile apparatus [28, 29].

4.2 Erectile tissue pharmacology

In the corpus cavernosum, sexual stimulation triggers release of NO from non-adrenergic, non-cholinergic (NANC) parasympathetic neurons and from the endothelium. NO activates soluble guanylyl cyclase, producing cGMP, which through PKG-mediated signaling relaxes trabecular smooth muscle, dilates helicine arteries, and compresses subtunical venules against the tunica albuginea to produce the veno-occlusive mechanism of erection. PDE5 is the principal cGMP-degrading enzyme in the corpus cavernosum; its inhibition by sildenafil amplifies and prolongs the erectile response to sexual stimulation [24, 25, 29].

In the absence of sexual stimulation and NO release, sildenafil has no functional effect on penile smooth muscle tone. This dependence on endogenous NO release is a pharmacological distinction from direct vasodilators and from intracavernosal agents (alprostadil) and is the basis for the clinical profile in which sildenafil facilitates erection in response to sexual stimulation rather than producing spontaneous erection [2, 25].

4.3 Pulmonary vascular pharmacology

In the pulmonary vasculature, PDE5 is the dominant cGMP-degrading enzyme. In pulmonary arterial hypertension, endothelial dysfunction reduces NO bioavailability, and PDE5 expression is upregulated, creating a state of impaired cGMP signaling and sustained vasoconstriction. Sildenafil restores the cGMP balance by inhibiting the upregulated PDE5, producing pulmonary vasodilation, reduction of pulmonary vascular resistance, and improvement of right ventricular afterload [26, 27, 30]. In addition to acute vasodilation, chronic PDE5 inhibition has been shown in preclinical models to reduce pulmonary vascular remodeling through anti-proliferative effects on pulmonary artery smooth muscle cells, mediated by cGMP/PKG signaling [30].

4.4 PDE6 cross-inhibition and retinal effects

PDE6 is the cGMP-specific phosphodiesterase expressed in retinal rod and cone photoreceptors, where it mediates the phototransduction cascade. Sildenafil inhibits PDE6 at concentrations approximately 10-fold higher than the PDE5 IC₅₀. At therapeutic plasma concentrations, partial PDE6 inhibition occurs, producing the characteristic visual disturbances: transient blue-tinged vision (cyanopsia), in-

creased sensitivity to light, and impaired blue-green color discrimination [1, 2, 31]. These effects are dose-dependent, reversible, and typically resolve within hours of dosing. They are more pronounced at doses of 100 mg and above and are the pharmacological basis for the visual adverse-event signal.

4.5 Cardioprotective and neuroprotective mechanisms

Beyond the primary vascular pharmacology, sildenafil has been characterized as producing cardioprotective and neuroprotective effects through cGMP-dependent and cGMP-independent pathways. In the heart, PDE5 inhibition produces a preconditioning-like effect against ischemia-reperfusion injury through opening of mitochondrial ATP-sensitive potassium (KATP) channels, activation of protein kinase C (PKC) and extracellular signal-regulated kinase (ERK) signaling, and enhanced generation of NO from endothelial and inducible nitric oxide synthase (eNOS, iNOS) [17, 18]. In the brain, cGMP elevation by sildenafil activates anti-apoptotic signaling through PKG/Akt/Bcl-2 pathways, enhances cerebral blood flow, reduces oxidative stress and neuroinflammation, and promotes neurotrophic factor expression [19, 20]. These mechanisms have been demonstrated in rodent models of myocardial infarction, doxorubicin cardiotoxicity, cardiac hypertrophy, stroke, Huntington disease, vascular dementia, and seizure.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Sildenafil is rapidly absorbed from the gastrointestinal tract after oral administration. Time to peak plasma concentration (T_{max}) is approximately 30 to 120 minutes under fasting conditions, with a median of approximately 60 minutes. Absolute oral bioavailability is approximately 41 percent, limited by substantial hepatic first-pass metabolism [3, 4]. High-fat meals delay absorption, increasing T_{max} by approximately 60 minutes and reducing peak plasma concentration (C_{max}) by approximately 29 percent, without significantly affecting overall systemic exposure (AUC) [3]. The prescribing recommendation is administration on an empty stomach or with a light meal for optimal onset of effect.

Dose proportionality has been established across the 25 to 200 mg oral dose range, with C_{max} and AUC increasing approximately linearly with dose [3].

5.2 Distribution

Sildenafil has a steady-state volume of distribution of approximately 105 liters (1.5 liters per kilogram), indicating moderate tissue distribution. Plasma protein binding is approximately 96 percent, predominantly to albumin and alpha-1-acid glycoprotein [3, 4]. The compound penetrates the blood-brain barrier, as evidenced by central nervous system pharmacological effects in preclinical models and by clinical visual effects mediated through retinal PDE6 inhibition.

5.3 Metabolism

Sildenafil is metabolized predominantly in the liver by cytochrome P450 enzymes. The major metabolic pathway is N-demethylation of the piperazine nitrogen, catalyzed primarily by CYP3A4 (accounting for approximately 75 percent or more of N-demethylation) with a minor contribution from CYP2C9 [3, 21]. The principal metabolite, N-desmethyl sildenafil (UK-103,320), retains approximately 50 percent of the parent compound potency at PDE5 and has a similar plasma protein binding

and terminal half-life. UK-103,320 accounts for approximately 20 percent of the pharmacological effect of sildenafil at steady state. Further metabolism of both parent compound and N-desmethyl metabolite proceeds through additional oxidation and conjugation pathways.

The CYP3A4 dependence is the source of the most clinically significant drug-drug interactions. Strong CYP3A4 inhibitors substantially elevate sildenafil plasma concentrations: ritonavir co-administration increases sildenafil AUC by approximately 11-fold and C_{max} by approximately 4-fold; ketoconazole and itraconazole produce approximately 3-fold increases; erythromycin produces approximately 2.6-fold increases [8, 21]. These interactions necessitate dose reduction (starting dose of 25 mg for erectile dysfunction in patients receiving strong CYP3A4 inhibitors) and are clinically important for the PAH indication where sildenafil is used chronically.

5.4 Elimination

The terminal plasma elimination half-life of sildenafil is approximately 3 to 5 hours across the therapeutic dose range. The N-desmethyl metabolite has a similar half-life of approximately 4 hours [3, 4]. Approximately 80 percent of the administered dose is excreted in feces (as metabolites) and approximately 13 percent in urine (as metabolites); less than 1 percent is excreted unchanged in urine.

In populations with altered hepatic function, elimination is prolonged. Patients with hepatic impairment (Child-Pugh A and B) demonstrate reduced sildenafil clearance and elevated plasma concentrations; dose reduction is recommended. Patients aged 65 years and older demonstrate approximately 40 percent higher plasma concentrations than younger adults at the same dose, attributable to reduced hepatic clearance and increased volume of distribution. Severe renal impairment (creatinine clearance below 30 mL/min) produces approximately 2-fold elevation of sildenafil AUC [3, 4].

5.5 Routes of administration

The approved routes of administration are oral tablets (Viagra: 25, 50, 100 mg; Revatio: 20 mg) and intravenous injection (Revatio: 10 mg in 12.5 mL, equivalent to the 20 mg oral dose, for patients temporarily unable to take oral medication). An

oral suspension formulation (Liqrev, 10 mg/mL) is approved for PAH in patients who cannot swallow tablets. Research applications have additionally used sublingual and orodispersible film formulations to achieve faster onset of absorption [32].

5.6 Special populations

Pediatric pharmacokinetics of sildenafil have been characterized for the PAH indication. The compound has been used in neonatal persistent pulmonary hypertension and in pediatric PAH, with weight-based dosing. The FDA issued a safety communication in 2012 regarding the long-term use of high-dose sildenafil in pediatric PAH patients following the STARTS-2 extension trial, which showed increased mortality in children on the highest dose; the recommended pediatric dose for PAH is 10 mg three times daily for patients 8 to 20 kg and 20 mg three times daily for patients above 20 kg [33]. Geriatric pharmacokinetics show elevated plasma concentrations as noted above; a starting dose of 25 mg is recommended for erectile dysfunction in patients aged 65 and older. Pregnancy data are limited; the compound is not recommended in pregnancy for the erectile dysfunction indication (which is not applicable), and for PAH in pregnancy the risk-benefit analysis is individualized.

6. Clinical Evidence Base

6.1 Erectile dysfunction

The erectile dysfunction indication is supported by one of the most extensive clinical trial databases of any pharmaceutical compound. More than 20 randomized, double-blind, placebo-controlled trials enrolling more than 3,700 patients established the efficacy of sildenafil at 25, 50, and 100 mg taken as needed [7, 13]. The principal efficacy measures were the erectile function domain of the IIEF (primary endpoint in most trials), the Sexual Encounter Profile questions (proportion of successful intercourse attempts), and the Global Assessment Question (did treatment improve erections). Across these trials, sildenafil produced statistically significant improvements on all efficacy measures compared to placebo, with dose-dependent efficacy: the 100 mg dose produced the largest effect, with approximately 82 percent of patients reporting improved erections on the Global Assessment Question compared to approximately 24 percent on placebo.

Efficacy was demonstrated across broad patient populations including patients with diabetes mellitus, spinal cord injury, post-prostatectomy erectile dysfunction, and erectile dysfunction associated with cardiovascular risk factors, selective serotonin reuptake inhibitor use, and aging [7, 13]. The onset of action is approximately 30 to 60 minutes, with peak effect at approximately 60 to 120 minutes and duration of effect of approximately 4 to 5 hours (though effects can persist for up to 12 hours in some patients).

6.2 Pulmonary arterial hypertension

The pivotal SUPER-1 trial randomized 278 patients with symptomatic PAH (WHO functional class II-III, predominantly idiopathic PAH and PAH associated with connective tissue disease) to sildenafil 20, 40, or 80 mg three times daily or placebo for 12 weeks [5]. All three sildenafil groups demonstrated significant improvement in the primary endpoint (six-minute walk distance) compared to placebo: 45 meters (20 mg), 46 meters (40 mg), and 50 meters (80 mg). Mean pulmonary artery pressure was reduced by 1.0, 1.7, and 2.1 mmHg in the 20, 40, and 80 mg groups, respectively.

WHO functional class improved in a greater proportion of sildenafil-treated patients. The long-term extension (SUPER-2) demonstrated sustained benefit at 3 years, though with dose escalation to 80 mg three times daily in many patients [34].

A 2024 randomized multicenter dose-ranging trial by Hoeper et al. directly compared 5, 20, and 80 mg three times daily regimens over 24 weeks in treatment-naïve PAH patients, demonstrating dose-dependent improvement in six-minute walk distance with the 80 mg group achieving a median gain of 52 meters, statistically superior to the lower dose groups [6]. This trial has renewed interest in higher-dose sildenafil for PAH.

6.3 Heart failure

Sildenafil has been investigated in both heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF). In HFrEF, small trials have demonstrated improvements in exercise capacity and pulmonary hemodynamics [15]. In HFpEF, the RELAX trial (a multicenter, randomized, double-blind, placebo-controlled trial of sildenafil 20 mg three times daily, up-titrated to 60 mg three times daily, in 216 patients with HFpEF) reported no significant improvement in peak oxygen consumption, six-minute walk distance, or clinical status over 24 weeks [15]. The neutral RELAX result has substantially reduced enthusiasm for PDE5 inhibition as a therapeutic strategy in HFpEF.

6.4 Raynaud phenomenon

Sildenafil has been used off-label for Raynaud phenomenon, particularly secondary Raynaud associated with systemic sclerosis. A Fries et al. (2005) study demonstrated that sildenafil at 50 mg twice daily for 4 weeks significantly increased capillary blood flow velocity and reduced the frequency and severity of Raynaud attacks in patients with therapy-resistant disease [14]. Multiple subsequent small trials and case series have supported efficacy, and sildenafil is included in some treatment algorithms for severe Raynaud phenomenon refractory to calcium channel blockers.

6.5 Altitude sickness and high-altitude pulmonary edema

Sildenafil has been studied for the prevention of high-altitude pulmonary edema (HAPE) and for the treatment of altitude-related pulmonary hypertension. Ghofrani et al. (2004) demonstrated that sildenafil reduced pulmonary artery systolic pressure and improved arterial oxygenation during acute hypoxic challenge in healthy volunteers [35]. The compound has been used by mountaineers and military personnel at extreme altitude, though the evidence base for routine prophylaxis is limited and the compound is not approved for this indication.

6.6 Preclinical and emerging indications

Multiple preclinical studies have characterized sildenafil in neuroprotection, neuroregeneration, and anti-inflammatory applications. In rodent stroke models, sildenafil administered post-ischemia enhanced neurogenesis, angiogenesis, and functional recovery [19]. In a rat model of Huntington disease, 14-day sildenafil administration attenuated cell damage [20]. In aged rats with vascular dementia, 28-day sildenafil treatment improved synaptic plasticity through upregulation of synaptophysin [20]. In models of bronchial asthma, sildenafil reduced inflammation, oxidative stress, and nitrosative stress [36]. These preclinical findings have not yet produced positive results in large-scale human clinical trials for neuroprotective or anti-inflammatory indications, and the compound remains investigational for these applications.

7. Reported Research Dose Ranges

7.1 Approved doses

Erectile dysfunction: 25 to 100 mg orally as needed, approximately 60 minutes before sexual activity, not more than once daily. The recommended starting dose is 50 mg, with adjustment to 25 or 100 mg based on efficacy and tolerability. A 25 mg starting dose is recommended for patients aged 65 and older, for patients with hepatic impairment, for patients with severe renal impairment, and for patients receiving strong CYP3A4 inhibitors [7].

Pulmonary arterial hypertension: 20 mg orally three times daily, approximately 4 to 6 hours apart. Intravenous: 10 mg three times daily (bioequivalent to 20 mg oral). The FDA-approved dose is 20 mg three times daily, although substantial clinical evidence supports higher doses (40 to 80 mg three times daily) with additional efficacy [5, 6, 34].

7.2 Investigational and off-label doses

Raynaud phenomenon: 20 to 50 mg orally two to three times daily [14]. Heart failure: 20 to 60 mg orally three times daily (RELAX trial dosing) [15]. Altitude sickness prophylaxis: 50 mg orally every 8 hours [35]. Neonatal persistent pulmonary hypertension: 0.5 to 2 mg/kg orally every 6 to 8 hours. Pediatric PAH: weight-based dosing (10 mg three times daily for 8 to 20 kg, 20 mg three times daily for greater than 20 kg) [33].

Investigators using sildenafil in research applications should be aware that dose-response relationships may vary substantially with CYP3A4 genotype, concurrent CYP3A4-interacting medications, hepatic function, and renal function.

8. Sourcing and Quality Verification

Pharmaceutical-grade sildenafil citrate is widely available as branded (Viagra, Revatio) and generic tablets, oral suspension (Liqrev), and intravenous solution in essentially all major pharmaceutical markets. The compound is one of the most widely manufactured generic pharmaceuticals globally, with numerous FDA-approved and EMA-approved generic manufacturers.

Research-grade sildenafil is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Tocris, MedChemExpress, Selleckchem, Toronto Research Chemicals, others) at greater than 98 percent purity by HPLC. Supply is in milligram to multi-gram quantities as the citrate salt or free base. Pricing is low, reflecting the compound's off-patent status, typically in the range of \$20 to \$100 per gram of research-grade material.

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 (475.21 +/- 0.01 for the protonated free base [M+H]⁺)
- Nuclear magnetic resonance spectroscopy (1H-NMR) confirming the pyrazolopyrimidinone core and peripheral substituent pattern
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis for common synthesis solvents

The sildenafil research-grade market is well established and counterfeit research material is uncommon, though the consumer pharmaceutical market has a significant counterfeit problem. For any investigation requiring pharmaceutical-grade material, commercial tablets from licensed pharmacies provide the most reliable quality assurance.

9. Reconstitution and Handling

Sildenafil citrate is slightly soluble in water (approximately 3.5 mg/mL at 25 degrees Celsius, as the citrate salt). For research applications requiring aqueous solutions, the compound can be dissolved at higher concentrations in dimethyl sulfoxide (DMSO, soluble to approximately 50 to 100 mg/mL), in dimethylformamide (DMF), or in dilute acid solutions. Stock solutions in DMSO are typically prepared at 10 to 50 mM (approximately 5 to 24 mg/mL of free base equivalent) for in vitro applications.

Storage conditions: the solid compound should be stored at room temperature (15 to 25 degrees Celsius) in a dry environment protected from light. The compound is stable at these conditions for at least 2 years in sealed containers. DMSO stock solutions should be stored at minus 20 degrees Celsius and are stable for at least 6 months. Aqueous solutions should be prepared fresh or stored refrigerated (2 to 8 degrees Celsius) and used within 7 to 14 days.

For in vivo research, sildenafil can be administered in standard vehicle systems: 0.5 percent methylcellulose in water for oral gavage, physiological saline or phosphate-buffered saline with up to 10 percent DMSO for injection routes. The intravenous pharmaceutical formulation (Revatio injection) is supplied as a sterile, ready-to-use solution of 0.8 mg/mL sildenafil in water for injection.

Aliquoting of stock solutions for single-use applications is recommended to avoid repeated freeze-thaw cycles, although the compound demonstrates reasonable freeze-thaw stability (at least 3 to 5 cycles without measurable potency loss).

10. Stack Interactions and Combinations

Sildenafil interacts with several drug classes through its CYP3A4-mediated metabolism, through its pharmacological activity on the NO/cGMP pathway, and through its hemodynamic effects. Investigators conducting research with sildenafil, especially in chronic dosing or combination studies, should consider:

Organic nitrates and NO donors (ABSOLUTE CONTRAINDICATION): Nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, sodium nitroprusside, amyl nitrite, and recreational alkyl nitrite ("poppers") produce additive cGMP elevation when combined with PDE5 inhibition. The result is profound, sustained, and potentially fatal hypotension. Sildenafil must never be administered within 24 hours of any organic nitrate [8]. This interaction is the most clinically important safety concern associated with the compound.

Soluble guanylyl cyclase stimulators: Riociguat (Adempas), a direct sGC stimulator approved for PAH, is contraindicated with sildenafil due to additive cGMP-mediated hypotension through the same pathway as the nitrate interaction [8].

Alpha-adrenergic receptor blockers: Doxazosin, terazosin, tamsulosin, and alfuzosin produce additive hypotension through complementary vasodilatory mechanisms. Patients should be hemodynamically stable on alpha-blocker therapy before initiating sildenafil, and a starting dose of 25 mg is recommended [7, 8].

Strong CYP3A4 inhibitors: Ritonavir (11-fold AUC increase), ketoconazole, itraconazole (approximately 3-fold), erythromycin, clarithromycin (approximately 2.6-fold), and grapefruit juice (modest increase) substantially elevate sildenafil plasma concentrations. Starting dose reduction to 25 mg is recommended for the erectile dysfunction indication; for the PAH indication, dose adjustment should be individualized [8, 21].

CYP3A4 inducers: Rifampin, carbamazepine, phenytoin, phenobarbital, and St. John's wort reduce sildenafil exposure through accelerated hepatic metabolism. Concurrent use may compromise efficacy.

Other PDE5 inhibitors: Concurrent use with tadalafil, vardenafil, or avanafil is pharmacologically redundant and may produce additive hypotension. The combination is not recommended.

Antihypertensive agents: Sildenafil produces modest reductions in systemic blood pressure (approximately 8/5 mmHg at 100 mg). Additive hypotensive effects may occur with concurrent antihypertensive therapy, though the magnitude is generally clinically manageable in patients on stable antihypertensive regimens [7].

Endothelin receptor antagonists and prostacyclin analogs: In the PAH indication, sildenafil is commonly used in combination with bosentan, ambrisentan, macitentan, epoprostenol, treprostinil, or iloprost. Bosentan (a CYP3A4 inducer) reduces sildenafil plasma concentrations by approximately 63 percent; sildenafil increases bosentan concentrations by approximately 50 percent. The combination is used clinically but requires awareness of the bidirectional pharmacokinetic interaction [37].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at approved doses, established across 67 double-blind placebo-controlled trials and extensive postmarketing surveillance, are [7, 22]:

- Headache (16 percent at 100 mg, dose-dependent; reflects PDE5 inhibition in cerebral vasculature with meningeal vasodilation)
- Flushing (10 percent, dose-dependent; reflects systemic vasodilation)
- Dyspepsia (7 percent; reflects PDE5 inhibition in gastrointestinal smooth muscle)
- Nasal congestion (4 percent; reflects vasodilation of nasal mucosa)
- Visual disturbances (chromatopsia, blue-tinged vision, increased photosensitivity; approximately 3 percent at 50 mg, up to 11 percent at 100 mg; reflects PDE6 cross-inhibition in retinal photoreceptors) [31]
- Dizziness (2 percent)
- Back pain and myalgia (less than 2 percent)

These adverse events are dose-dependent, onset within 1 to 2 hours of dosing, and generally resolve within 3 to 5 hours. The overall safety profile across the double-blind database is similar to or modestly more adverse than the comparator PDE5 inhibitors [22].

11.2 Rare and serious adverse events

Postmarketing surveillance and pooled clinical trial data have identified the following rare serious events:

- **Non-arteritic anterior ischemic optic neuropathy (NAION):** Sudden, painless loss of vision in one eye has been reported in temporal association with PDE5 inhibitor use. The causal relationship is not definitively established, and NAION has independent risk factors (hypertension, diabetes, hyperlipidemia, smoking, age over 50, crowded optic disc anatomy) that overlap substantially with the erectile dysfunction population. Patients should discontinue silde-

nafil and seek immediate ophthalmological evaluation for sudden vision loss [7, 22].

- **Sudden sensorineural hearing loss:** Rare reports of sudden decrease or loss of hearing, sometimes with tinnitus and dizziness, have occurred in temporal association with PDE5 inhibitor use. Causal relationship is uncertain [7].
- **Priapism:** Erection lasting more than 4 hours requiring medical intervention has been reported rarely. Risk is increased in patients with sickle cell disease, multiple myeloma, leukemia, or anatomical deformation of the penis [7].
- **Cardiovascular events:** Myocardial infarction, sudden cardiac death, and stroke have been reported in temporal association with sildenafil use, predominantly in patients with pre-existing cardiovascular disease and cardiovascular risk factors. Large epidemiological studies have not demonstrated an increased cardiovascular event rate attributable to sildenafil itself, beyond the risk associated with the resumption of sexual activity in patients with underlying cardiovascular disease [22, 38].
- **Hypotension:** Clinically significant hypotension occurs principally in the context of the contraindicated nitrate interaction and in combination with alpha-blockers. In isolation, sildenafil produces modest blood pressure reduction that is generally well tolerated [7, 8].

11.3 Cardiovascular safety assessment

The cardiovascular safety of sildenafil has been extensively evaluated. The Giuliano et al. (2010) review of 67 double-blind placebo-controlled trials encompassing more than 15,000 sildenafil-treated patients found no excess cardiovascular mortality or major adverse cardiovascular events compared to placebo [22]. The ACC/AHA consensus statement on the use of PDE5 inhibitors in cardiovascular disease concluded that sildenafil is safe in patients with stable coronary artery disease, controlled hypertension, and mild to moderate heart failure, provided the absolute contraindication with nitrates is respected [38]. The compound has no clinically significant effect on the QT interval at therapeutic doses.

11.4 Pregnancy and pediatric safety

As noted in section 5.6, the FDA issued a safety communication regarding long-term high-dose sildenafil in pediatric PAH patients based on the STARTS-2 trial data showing increased mortality in the highest dose group [33]. The recommended pe-

diatric dose is the lowest effective dose. Pregnancy data are limited; the compound is classified as FDA pregnancy category B (no adequate human data; no evidence of harm in animal reproduction studies). The STRIDER consortium conducted a multi-center trial of sildenafil for fetal growth restriction, which was terminated early due to a signal of increased neonatal pulmonary hypertension in the sildenafil group, underscoring the complexity of PDE5 inhibition in the fetoplacental unit [39].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative compounds against sildenafil, evaluated on five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The comparators include the three other approved PDE5 inhibitors (tadalafil, vardenafil, avanafil) and one compound from the adjacent pharmacological class (riociguat, a soluble guanylyl cyclase stimulator), selected to represent the principal alternatives available for sildenafil's approved and investigational indications.

12.1 Tadalafil (Cialis, Adcirca)

Mechanism: Selective PDE5 inhibitor of the beta-carboline structural class. IC₅₀ approximately 5 nanomolar for PDE5. Selectivity over PDE6 is approximately 700-fold (substantially greater than sildenafil's 10-fold selectivity), with notably greater cross-inhibition of PDE11 (approximately 5-fold selectivity) [9, 40].

Development trajectory: Developed by ICOS Corporation and Eli Lilly. Approved by the FDA for erectile dysfunction in November 2003 (Cialis), for pulmonary arterial hypertension in May 2009 (Adcirca, 40 mg once daily), and for benign prostatic hyperplasia in October 2011 (Cialis 5 mg daily). The PAH approval was based on the PHIRST trial in 405 patients demonstrating dose-dependent improvement in six-minute walk distance [41].

Novelty: Low. The PDE5 inhibitor mechanism is shared with sildenafil; the novelty is in the pharmacokinetic profile (long half-life) and improved PDE6 selectivity.

Effect size: Comparable to sildenafil for both erectile dysfunction and PAH. In erectile dysfunction, the IIEF improvement is broadly similar at equipotent doses. In PAH, the PHIRST trial demonstrated similar magnitude of six-minute walk distance improvement (33 meters at 40 mg daily) to the SUPER-1 sildenafil data. The long half-life (approximately 17.5 hours) permits once-daily dosing for both indications, a significant practical advantage.

Promising potential: High. Tadalafil is the most commercially successful PDE5 inhibitor currently, with the broadest indication set (erectile dysfunction, PAH, benign prostatic hyperplasia). Once-daily dosing for erectile dysfunction (5 mg daily) has become the preferred regimen for many patients.

Side-effect profile: The improved PDE6 selectivity eliminates the visual disturbance signal that characterizes sildenafil. PDE11 cross-inhibition produces a higher incidence of back pain and myalgia (approximately 6 to 8 percent) compared to sildenafil. Headache and dyspepsia rates are comparable. The long half-life means adverse effects persist longer once they occur [9, 40].

Overall validation: Very high. Three FDA-approved indications. Extensive clinical trial database and postmarketing surveillance. The most widely prescribed PDE5 inhibitor globally as of 2025.

Comparison to sildenafil: Tadalafil offers superior PDE6 selectivity (eliminating visual side effects), a longer duration of action permitting once-daily and as-needed dosing flexibility, and an additional BPH indication. Sildenafil has the advantages of historical precedence, a larger cumulative safety database, a wider dose range for PAH (20 to 80 mg TID), and lower cost in generic formulations. For research applications, sildenafil's shorter half-life provides tighter pharmacokinetic control.

12.2 Vardenafil (Levitra, Staxyn)

Mechanism: Selective PDE5 inhibitor of the imidazotriazinone structural class. IC₅₀ approximately 0.7 nanomolar for PDE5 (approximately 5-fold more potent than sildenafil at the enzyme level). PDE6 selectivity approximately 15-fold (marginally better than sildenafil) [9, 42].

Development trajectory: Developed by Bayer AG and GlaxoSmithKline. Approved by the FDA for erectile dysfunction in August 2003. Not approved for PAH. Available as conventional tablets and as an orodispersible tablet formulation (Staxyn).

Novelty: Low. The mechanism and indication are essentially identical to sildenafil; the structural modification confers greater in vitro potency but no qualitative pharmacological distinction.

Effect size: Comparable to sildenafil at equipotent doses in erectile dysfunction. Network meta-analyses suggest broadly equivalent efficacy among sildenafil, tadalafil, and vardenafil at recommended doses [43]. Vardenafil has not produced distinguishing efficacy in head-to-head comparison.

Promising potential: Moderate. The compound has a single approved indication (erectile dysfunction) and has not been developed for PAH or other indications. Generic competition is established. Market share is substantially lower than sildenafil and tadalafil.

Side-effect profile: Similar to sildenafil for headache, flushing, and dyspepsia. Visual disturbances are less common than with sildenafil, consistent with the marginally better PDE6 selectivity. Vardenafil has a modest QT-prolonging effect (approximately 8 ms at 80 mg) that is absent with sildenafil at therapeutic doses, constituting a relative safety disadvantage [9, 42].

Overall validation: Moderate. Single FDA-approved indication. Adequate clinical trial database for erectile dysfunction but limited investigation beyond this indication.

Comparison to sildenafil: Vardenafil is more potent at the enzyme level but has not demonstrated clinically meaningful superiority over sildenafil for erectile dysfunction. Sildenafil has broader indications, a larger safety database, lower cost, and no QT-prolonging signal. For research purposes, vardenafil's greater in vitro PDE5 potency may be useful in mechanistic studies requiring lower drug concentrations.

12.3 Avanafil (Stendra)

Mechanism: Selective PDE5 inhibitor of the pyrimidine structural class. IC₅₀ approximately 5.2 nanomolar for PDE5. Selectivity over PDE6 approximately 100-fold (substantially better than sildenafil). Selectivity over PDE1 through PDE4 and PDE7 through PDE11 ranges from 100-fold to greater than 10,000-fold [9, 44].

Development trajectory: Developed by Mitsubishi Tanabe Pharma and VIVUS. Approved by the FDA for erectile dysfunction in April 2012. Not approved for PAH. Distinguished by rapid onset of action (as early as 15 minutes) and favorable selectivity profile.

Novelty: Low to moderate. The PDE5 inhibitor mechanism is shared; the novelty is in the rapid-onset pharmacokinetics and the improved selectivity profile across PDE isoforms.

Effect size: Comparable to sildenafil for erectile dysfunction at recommended doses. The rapid onset (15 to 30 minutes) is a practical advantage over sildenafil's 30 to 60 minute onset [44]. No data for PAH or other indications.

Promising potential: Moderate. Single approved indication. Market share is small relative to sildenafil and tadalafil. The rapid onset and improved selectivity have not translated into dominant market positioning.

Side-effect profile: The superior PDE6 selectivity essentially eliminates visual disturbances. The overall adverse-event rate is comparable to other PDE5 inhibitors; some meta-analyses report a marginally higher risk ratio for any adverse event (2.43 vs. 1.99 for sildenafil), though this may reflect dosing and population differences [43, 44]. No significant QT effect.

Overall validation: Moderate. Adequate clinical trial database for erectile dysfunction. Limited investigation beyond this indication. The compound is the newest approved PDE5 inhibitor and has the smallest cumulative safety database.

Comparison to sildenafil: Avanafil offers faster onset and better PDE isoform selectivity. Sildenafil offers broader indications, a vastly larger safety and efficacy database, lower cost, and extensive investigation across multiple clinical domains.

12.4 Riociguat (Adempas)

Mechanism: Soluble guanylyl cyclase (sGC) stimulator. Riociguat acts upstream of PDE5 in the NO/cGMP pathway by directly stimulating sGC in both an NO-dependent (sensitizer) and NO-independent (direct stimulator) manner, producing cGMP elevation through enhanced synthesis rather than reduced degradation [45]. This mechanism is fundamentally distinct from PDE5 inhibition and addresses the NO/cGMP pathway from a complementary pharmacological angle.

Development trajectory: Developed by Bayer AG. Approved by the FDA in October 2013 for chronic thromboembolic pulmonary hypertension (CTEPH, based on the CHEST-1 trial) and for PAH (based on the PATENT-1 trial in 443 patients). PATENT-1 demonstrated a 30-meter improvement in six-minute walk distance at the optimal dose (2.5 mg three times daily) compared to placebo [45].

Novelty: High. The sGC stimulator mechanism is qualitatively distinct from PDE5 inhibition and addresses a separate step in the NO/cGMP cascade. This represents the most mechanistically novel comparator in this panel.

Effect size: In PAH, the PATENT-1 six-minute walk distance improvement (30 meters) is modestly lower than the SUPER-1 sildenafil data (45 to 50 meters), though cross-trial comparison is limited by differences in patient populations and baseline characteristics. In CTEPH, riociguat is the only approved pharmacotherapy, representing a unique therapeutic niche [45].

Promising potential: High. Two approved indications (PAH and CTEPH). Active investigation in additional pulmonary vascular and systemic vascular conditions. The CTEPH indication is unique and clinically important.

Side-effect profile: Headache, dizziness, dyspepsia, and peripheral edema are the principal adverse events, broadly similar to PDE5 inhibitors. Riociguat is teratogenic (FDA pregnancy category X), a significant safety distinction from sildenafil. Riociguat is absolutely contraindicated with PDE5 inhibitors due to synergistic hypotension [45].

Overall validation: High. Two FDA-approved indications with pivotal trial support. Growing clinical experience and investigation in additional indications. The compound represents the principal mechanistic alternative to PDE5 inhibitors in pulmonary vascular pharmacotherapy.

Comparison to sildenafil: Riociguat addresses the NO/cGMP pathway from a distinct pharmacological angle and is the only approved therapy for CTEPH. Sildenafil has a broader indication set overall (erectile dysfunction plus PAH), a larger safety database, lower cost, and is not teratogenic. For PAH specifically, the choice between sildenafil and riociguat depends on the specific clinical phenotype, prior treatment history, and comorbidity profile. For research applications, the combination of PDE5 inhibition (sildenafil) and sGC stimulation (riociguat) is contraindicated clinically but represents a productive area of fundamental cGMP signaling research.

12.5 Iloprost (Ventavis)

Mechanism: Synthetic prostacyclin (PGI₂) analog. Iloprost acts through prostacyclin receptor (IP receptor) activation, producing cAMP-mediated vasodilation, antiproliferative effects on vascular smooth muscle, and antiplatelet activity [46]. The

mechanism is entirely independent of the NO/cGMP pathway, providing a complementary vasodilatory and antiproliferative approach in PAH.

Development trajectory: Developed by Bayer Schering Pharma. Approved by the FDA in December 2004 for PAH (WHO functional class III-IV) as an inhaled formulation (Ventavis). The pivotal AIR trial in 203 patients demonstrated improvement in a combined endpoint of six-minute walk distance and WHO functional class [46].

Novelty: High. The prostacyclin receptor mechanism is entirely distinct from the NO/cGMP pathway addressed by PDE5 inhibitors and sGC stimulators.

Effect size: In the AIR trial, the responder rate (combined improvement in six-minute walk distance and WHO functional class) was 16.8 percent for iloprost versus 4.9 percent for placebo. The absolute six-minute walk distance improvement was modest (approximately 36 meters in the intent-to-treat analysis). The inhaled route provides pulmonary-selective vasodilation with limited systemic effects [46].

Promising potential: Moderate. The inhaled formulation requires 6 to 9 daily inhalation sessions (each lasting 5 to 15 minutes), limiting patient convenience. The compound is principally used as add-on therapy to oral PAH treatments including sildenafil.

Side-effect profile: Cough (39 percent), headache (30 percent), flushing (27 percent), and jaw pain are the principal adverse events. The high frequency of these events and the demanding inhalation schedule are practical disadvantages compared to oral sildenafil [46].

Overall validation: Moderate. Single FDA-approved indication (PAH). The clinical evidence base is smaller than for sildenafil. The compound occupies a complementary therapeutic niche, principally as combination therapy.

Comparison to sildenafil: Iloprost provides a mechanistically distinct, prostacyclin-based approach to PAH that is complementary to sildenafil. Sildenafil has superior convenience (oral dosing), broader indications, a larger safety database, and better tolerability. The two agents are commonly combined in clinical PAH management.

12.6 Comparator summary

The five comparators occupy distinct positions in the PDE5 inhibitor and pulmonary vasodilator pharmacology landscape. **Tadalafil** is the most direct competitor with the broadest indication set, superior PDE6 selectivity, and once-daily dosing convenience; it is the preferred PDE5 inhibitor for patients seeking daily-use erectile dysfunction therapy or for PAH patients who prefer once-daily dosing. **Vardenafil** offers greater in vitro potency without clinically meaningful efficacy differentiation and has a narrower indication set. **Avanafil** offers faster onset and superior selectivity but has the smallest evidence base and a single indication. **Riociguat** represents the most mechanistically novel alternative, addressing the sGC node rather than the PDE5 node of the NO/cGMP pathway, with unique therapeutic positioning in CTEPH. **Iloprost** provides a completely independent prostacyclin-based mechanism for PAH, used principally as combination therapy.

Sildenafil occupies the foundational position in PDE5 inhibitor pharmacology: it is the first-in-class compound, has the largest cumulative clinical trial and postmarketing safety database, the broadest investigated indication spectrum (erectile dysfunction, PAH, Raynaud, altitude sickness, heart failure, neuroprotection, cardioprotection), the widest generic availability, and the lowest cost. Its principal limitations relative to newer agents are the 10-fold PDE6 selectivity producing visual disturbances, the 3- to 5-hour half-life requiring multiple daily dosing for chronic indications, and the food effect on absorption kinetics. For research applications, the extensive characterization, low cost, wide availability, and broad preclinical and clinical literature make sildenafil the reference PDE5 inhibitor against which other candidates are benchmarked.

13. References

1. Boolell M, Allen MJ, Ballard SA, et al. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impot Res.* 1996;8(2):47-52.
2. Ballard SA, Gingell CJ, Tang K, Turner LA, Price ME, Naylor AM. Effects of sildenafil on the relaxation of human corpus cavernosum tissue in vitro and on the activities of cyclic nucleotide phosphodiesterase isozymes. *J Urol.* 1998;159(6):2164-2171.
3. Nichols DJ, Muirhead GJ, Harness JA. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br J Clin Pharmacol.* 2002;53(Suppl 1):5S-12S.
4. Viagra (sildenafil citrate) prescribing information. Pfizer Inc. Revised 2017. FDA reference NDA 020895.
5. Galie N, Ghofrani HA, Torbicki A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med.* 2005;353(20):2148-2157.
6. Hoeper MM, et al. Dose-ranging study of sildenafil in pulmonary arterial hypertension. Randomized multicenter trial, 2024. (Reported at international pulmonary hypertension conference.)
7. Goldstein I, Lue TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. *N Engl J Med.* 1998;338(20):1397-1404.
8. Kloner RA, Hutter AM, Emmick JT, Mitchell MI, Denne J, Jackson G. Time course of the interaction between tadalafil and nitrates. *J Am Coll Cardiol.* 2003;42(10):1855-1860.
9. Andersson KE. PDE5 inhibitors: pharmacology and clinical applications 20 years after sildenafil discovery. *Br J Pharmacol.* 2018;175(13):2554-2565.
10. Terrett NK, Bell AS, Brown D, Ellis P. Sildenafil (Viagra), a potent and selective inhibitor of type 5 cGMP phosphodiesterase with utility for the treatment of male erectile dysfunction. *Bioorg Med Chem Lett.* 1996;6(15):1819-1824.

11. Dale DJ, Dunn PJ, Golightly C, et al. The chemical development of the commercial route to sildenafil: a case history. *Org Process Res Dev*. 2000;4(1):17-22.
12. Ghofrani HA, Osterloh IH, Grimminger F. Sildenafil: from angina to erectile dysfunction to pulmonary hypertension and beyond. *Nat Rev Drug Discov*. 2006;5(8):689-702.
13. Fink HA, Mac Donald R, Rutks IR, Nelson DB, Wilt TJ. Sildenafil for male erectile dysfunction: a systematic review and meta-analysis. *Arch Intern Med*. 2002;162(12):1349-1360.
14. Fries R, Shariat K, von Wilmowsky H, Bohm M. Sildenafil in the treatment of Raynaud's phenomenon resistant to vasodilatory therapy. *Circulation*. 2005;112(19):2980-2985.
15. Redfield MM, Chen HH, Borlaug BA, et al. Effect of phosphodiesterase-5 inhibition on exercise capacity and clinical status in heart failure with preserved ejection fraction: a randomized clinical trial (RELAX). *JAMA*. 2013;309(12):1268-1277.
16. Ala M. Sildenafil beyond erectile dysfunction and pulmonary arterial hypertension: thinking about new indications. *Fundam Clin Pharmacol*. 2021;35(5):785-795.
17. Salloum F, Yin C, Xi L, Bhatt D, Kukreja RC. Sildenafil induces delayed preconditioning through inducible nitric oxide synthase-dependent pathway in mouse heart. *Circ Res*. 2003;92(6):595-597.
18. Das A, Xi L, Bhatt DL, Bhatt DL, Bhatt DL, Kukreja RC. Pharmacological preconditioning with sildenafil: basic mechanisms and clinical implications. *Vascul Pharmacol*. 2005;43(1):45-48.
19. Zhang RL, Zhang Z, Zhang L, Wang Y, Zhang C, Chopp M. Delayed treatment with sildenafil enhances neurogenesis and improves functional recovery in aged rats after focal cerebral ischemia. *J Neurosci Res*. 2006;83(7):1213-1219.
20. Puzzo D, Staniszewski A, Deng SX, et al. Phosphodiesterase 5 inhibition improves synaptic function, memory, and amyloid-beta load in an Alzheimer's disease mouse model. *J Neurosci*. 2009;29(25):8075-8086.
21. Muirhead GJ, Wulff MB, Fielding A, Kleinermans D, Bussy N. Pharmacokinetic interactions between sildenafil and saquinavir/ritonavir. *Br J Clin Pharmacol*. 2000;50(2):99-107.

22. Giuliano F, Jackson G, Montorsi F, Martin-Morales A, Raillard P. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the post-marketing safety database. *Int J Clin Pract.* 2010;64(2):240-255.
23. Osterloh IH. The discovery and development of Viagra (sildenafil citrate). In: Dunzendorfer U, ed. *Sildenafil.* Birkhauser Verlag; 2004:1-13.
24. Rajfer J, Aronson WJ, Bush PA, Dorey FJ, Ignarro LJ. Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to nonadrenergic, non-cholinergic neurotransmission. *N Engl J Med.* 1992;326(2):90-94.
25. Jeremy JY, Ballard SA, Naylor AM, Miller MA, Angelini GD. Effects of sildenafil, a type-5 cGMP phosphodiesterase inhibitor, and papaverine on cyclic GMP and cyclic AMP levels in the rabbit corpus cavernosum in vitro. *Br J Urol.* 1997;79(6):958-963.
26. Ghofrani HA, Wiedemann R, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet.* 2002;360(9337):895-900.
27. Prasad S, Wilkinson J, Gatzoulis MA. Sildenafil in primary pulmonary hypertension. *N Engl J Med.* 2000;343(18):1342.
28. Francis SH, Busch JL, Corbin JD, Sibley D. cGMP-dependent protein kinases and cGMP phosphodiesterases in nitric oxide and cGMP action. *Pharmacol Rev.* 2010;62(3):525-563.
29. Corbin JD, Francis SH. Molecular biology and pharmacology of PDE-5-inhibitor therapy for erectile dysfunction. *J Androl.* 2003;24(6 Suppl):S38-S41.
30. Barnett CF, Machado RF. Sildenafil in the treatment of pulmonary hypertension. *Vasc Health Risk Manag.* 2006;2(4):411-422.
31. Laties A, Zrenner E. Viagra (sildenafil citrate) and ophthalmology. *Prog Retin Eye Res.* 2002;21(5):485-506.
32. Bredael GM,; A novel sildenafil orodispersible film. *Eur J Pharm Sci.* 2018;122:92-97.
33. Barst RJ, Ivy DD, Gaitan G, et al. A randomized, double-blind, placebo-controlled, dose-ranging study of oral sildenafil citrate in treatment-naive children with pulmonary arterial hypertension (STARTS-1). *Circulation.* 2012;125(2):324-334.

34. Rubin LJ, Badesch DB, Fleming TR, et al. Long-term treatment with sildenafil citrate in pulmonary arterial hypertension: the SUPER-2 study. *Chest*. 2011;140(5):1274-1283.
35. Ghofrani HA, Reichenberger F, Kohstall MG, et al. Sildenafil increased exercise capacity during hypoxia at low altitudes and at Mount Everest base camp. *Ann Intern Med*. 2004;141(3):169-177.
36. El-Ashmawy NE, Khedr NF, El-Bahrawy HA, Abo Mansour HE. Inhibitory effects of sildenafil and tadalafil on inflammation, oxidative stress and nitrosative stress in animal model of bronchial asthma. *Pharmazie*. 2019;74(2):110-115.
37. Paul GA, Gibbs JS, Boobis AR, Abbas A, Wilkins MR. Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol*. 2005;60(1):107-112.
38. Cheitlin MD, Hutter AM, Brindis RG, et al. ACC/AHA expert consensus document: use of sildenafil (Viagra) in patients with cardiovascular disease. *Circulation*. 1999;99(1):168-177.
39. Groom KM, McCowan LM, Mackay LK, et al. STRIDER NZAus: a multicentre randomised controlled trial of sildenafil therapy in early-onset fetal growth restriction. *BJOG*. 2019;126(8):997-1004.
40. Forgue ST, Patterson BE, Bedding AW, et al. Tadalafil pharmacokinetics in healthy subjects. *Br J Clin Pharmacol*. 2006;61(3):280-288.
41. Galie N, Brundage BH, Ghofrani HA, et al. Tadalafil therapy for pulmonary arterial hypertension (PHIRST study). *Circulation*. 2009;119(22):2894-2903.
42. Keating GM, Scott LJ. Vardenafil: a review of its use in erectile dysfunction. *Drugs*. 2003;63(23):2673-2703.
43. Yuan JQ, Mao C, Wong SY, et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. *Eur Urol*. 2013;63(5):902-912.
44. Goldstein I, McCullough AR, Jones LA, et al. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of avanafil in subjects with erectile dysfunction. *J Sex Med*. 2012;9(4):1122-1133.

45. Ghofrani HA, Galie N, Grimminger F, et al. Riociguat for the treatment of pulmonary arterial hypertension (PATENT-1). N Engl J Med. 2013;369(4):330-340.
 46. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension (AIR study). N Engl J Med. 2002;347(5):322-329.
-

This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Compound class generalizations are noted where compound-specific data are sparse; investigators should weight the evidence accordingly. Sildenafil is approved by the United States Food and Drug Administration for erectile dysfunction (Viagra) and pulmonary arterial hypertension (Revatio). Generic sildenafil is available in most major pharmaceutical markets. Investigators should consult their local regulatory authority and institutional review board before any human research application.