

## RESEARCH MONOGRAPH . COMPOUND PROFILE

# Tadalafil

*A long-acting beta-carboline-derived cyclic GMP phosphodiesterase inhibitor developed by ICOS and Eli Lilly for erectile dysfunction, subsequently approved for benign prostatic hyperplasia and pulmonary arterial hypertension, distinguished from other PDE5 inhibitors by a 17.5-hour plasma half-life, food-independent absorption, and emerging preclinical interest in neuroprotection and cognitive enhancement.*

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## ABSTRACT

Tadalafil is a selective inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), approved by the United States Food and Drug Administration for the treatment of erectile dysfunction (ED), the signs and symptoms of benign prostatic hyperplasia (BPH), and pulmonary arterial hypertension (PAH). Structurally a beta-carboline (pyrazinopyridoindole) derivative bearing a methylenedioxyphenyl substituent, tadalafil is chemically and pharmacologically distinct from the pyrimidinone-based PDE5 inhibitors sildenafil and vardenafil. The compound was originally synthesized at ICOS Corporation as IC351, advanced through clinical development in a joint venture with Eli Lilly and Company (Lilly ICOS LLC), and received its first regulatory approval in the European Union in November 2002 and in the United States in November 2003 under the trade name Cialis for the on-demand treatment of ED at 10 mg and 20 mg oral doses [1, 2].

The defining pharmacokinetic feature of tadalafil is its prolonged plasma elimination half-life of approximately 17.5 hours, roughly three to five times longer than the half-lives of sildenafil (3 to 5 hours) and vardenafil (4 to 5 hours), enabling a clinically meaningful therapeutic window of 24 to 36 hours from a single oral dose and supporting a once-daily 2.5 mg or 5 mg dosing regimen approved for both ED and BPH [3, 4]. Absorption is not affected by food, a further distinction from sildenafil and vardenafil, whose absorption is delayed by high-fat meals. Tadalafil is metabolized predominantly by hepatic cytochrome P450 3A4 (CYP3A4) to the pharmacologically inactive

methylcatechol glucuronide conjugate; approximately 61 percent of an administered dose is excreted in feces and 36 percent in urine [5].

The molecular mechanism is inhibition of PDE5, the enzyme responsible for hydrolysis of cGMP in vascular smooth muscle. In the corpus cavernosum, nitric oxide released during sexual stimulation activates soluble guanylate cyclase, which synthesizes cGMP from guanosine triphosphate; cGMP in turn activates protein kinase G, producing smooth muscle relaxation, vasodilation, and penile erection. By preventing cGMP degradation, tadalafil amplifies and sustains the nitric oxide signaling cascade. The same mechanism operates in the pulmonary vasculature (where PDE5 inhibition reduces pulmonary arterial pressure) and in the smooth muscle of the prostate, bladder neck, and urethra (where PDE5 inhibition alleviates lower urinary tract symptoms associated with BPH) [6, 7]. Tadalafil is more than 10,000-fold selective for PDE5 over PDE3 (cardiovascular), approximately 700-fold selective over PDE6 (retinal), but only approximately 40-fold selective over PDE11A, a dual-specificity phosphodiesterase expressed in skeletal muscle, prostate, testes, and other tissues. The relatively low PDE5/PDE11 selectivity ratio is the presumed molecular basis for the back pain and myalgia adverse events that occur at higher frequency with tadalafil than with the other PDE5 inhibitors [8, 9].

Clinical efficacy in ED has been established across multiple randomized, double-blind, placebo-controlled trials enrolling populations with mild through severe dysfunction, with overall response rates of 60 to 70 percent on validated questionnaires. The 40 mg once-daily dose for PAH produced a statistically significant 33-meter improvement in six-minute walk distance

over placebo in the PHIRST registration trial [10]. The 5 mg once-daily dose for BPH produced a statistically significant improvement in International Prostate Symptom Score (IPSS) of approximately 2 points over placebo across four pivotal 12-week trials [11]. Common adverse events include headache (approximately 15 percent at 20 mg), dyspepsia (approximately 10 percent), back pain (approximately 6 percent), myalgia (approximately 4 percent), nasal congestion, and flushing. The compound is absolutely contraindicated with organic nitrates (the combination produces severe, potentially fatal hypotension) and with soluble guanylate cyclase stimulators [12, 13]. Rare but serious postmarketing signals include nonarteritic anterior ischemic optic neuropathy (NAION), sudden sensorineural hearing loss, and priapism. The compound is not recommended in patients with recent myocardial infarction, unstable angina, uncontrolled hypertension, or in patients in whom sexual activity is medically inadvisable.

This monograph documents the chemistry, synthesis, and stereochemistry of tadalafil; the PDE5 inhibitory mechanism in molecular and physiological detail; the comprehensive human pharmacokinetic record; the preclinical pharmacology across vascular, urological, pulmonary, and neuroprotective domains; the clinical evidence base for all approved and investigational indications; sourcing and quality verification considerations; reconstitution and handling; stack-interaction implications for concurrent pharmacotherapy; adverse-event and safety signal characterization; and a structured comparative assessment of five PDE5 inhibitor alternatives (sildenafil, vardenafil, avanafil, mirodenafil, udenafil) against tadalafil on five competency standards: novelty, effect size, promising potential, side-effect profile, and overall validation.

# 1. Compound Identification

## 1.1 Names, synonyms, and registry identifiers

**International Nonproprietary Name:** Tadalafil.

**Marketed names:** Cialis (Eli Lilly; United States, European Union, Japan, Australia, and approximately 100 other jurisdictions for ED and BPH), Adcirca (Eli Lilly; United States, for PAH at the 20 mg twice-daily dose), Alyq (generic, PAH indication), Tadliq (Sanofi; FDA-approved oral suspension). Following patent expiration in 2017 (European Union) and 2018 (United States), multiple generic formulations are marketed globally.

**Development codes:** IC351 (ICOS Corporation). The development code is the canonical identifier in the early medicinal chemistry and pharmacology literature [1].

**Chemical Abstracts Service registry number:** 171596-29-5.

**International Union of Pure and Applied Chemistry name:** (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2-methyl-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione. The compound is a tetracyclic beta-carboline derivative incorporating a fused pyrazinone, piperazinedione, and indole ring system with a pendant methylenedioxyphenyl (piperonyl) substituent at the C-6 position.

## 1.2 Structural class and chemistry

Tadalafil is a beta-carboline (pyrazinopyridoindole) derivative, structurally unrelated to the pyrimidinone-based PDE5 inhibitors sildenafil and vardenafil. The structural class places it within the tryptophan-derived indole alkaloid family, specifically as a synthetic hydantoin-fused tryptoline bearing a 1,3-benzodioxole pharmacophore [14].

**Molecular formula:** C<sub>22</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>.

**Exact mass:** 389.1376 g/mol (monoisotopic).

**Molecular weight:** 389.40 g/mol.

**Physical properties:** White to off-white crystalline powder. Practically insoluble in water (less than 0.73 mg/L); soluble in dimethyl sulfoxide, dimethylformamide, and methanol; sparingly soluble in ethanol and ethyl acetate. Melting point is approximately 298 to 300 degrees Celsius. The compound is light-stable and non-hygroscopic under standard storage conditions.

**Stereochemistry:** Tadalafil possesses two stereocenters at C-6 and C-12a and is supplied as the single (6R,12aR)-trans diastereomer, which is the pharmacologically active form. The (6R,12aR) configuration is critical for PDE5 binding; the cis diastereomers and the (6S,12aS)-trans enantiomer exhibit substantially reduced inhibitory potency. Commercial and pharmaceutical-grade material is supplied as the single active diastereomer at greater than 99 percent diastereomeric excess. Investigators acquiring research-grade tadalafil should confirm stereochemical purity by chiral high-performance liquid chromatography [15].

## 1.3 Synthesis

The published synthesis of tadalafil proceeds through a Pictet-Spengler condensation as the key stereochemistry-defining step. D-Tryptophan methyl ester is condensed with piperonal (3,4-methylenedioxybenzaldehyde) under acidic conditions to yield the trans-beta-carboline intermediate with the (1R,3R) relative configuration (corresponding to (6R,12aR) in the final product numbering). The resulting tetrahydro-beta-carboline is then cyclized with chloroacetyl chloride followed by methylamine-mediated ring closure to form the piperazinedione ring, yielding tadalafil [16, 17]. Industrial process optimization has focused on the diastereoselectivity of the Pictet-Spengler step (the trans:cis ratio is typically 85:15 to 95:5 depending on solvent, acid catalyst, and temperature), the crystallization-based diastereomeric purification, and the removal of the unwanted cis isomer. Overall yields of 40 to 60 percent from D-tryptophan methyl ester are reported in optimized large-scale syntheses. The compound is manufactured in high stereochemical purity (greater than 99.5 percent diastereomeric excess) by recrystallization from appropriate solvent systems.

## 2. Abstract

Tadalafil (IC351, Cialis, Adcirca) is a potent, selective, long-acting inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5), developed by ICOS Corporation in collaboration with Eli Lilly and Company and approved by the United States Food and Drug Administration for three indications: erectile dysfunction (2003), pulmonary arterial hypertension (2009, as Adcirca), and benign prostatic hyperplasia with or without concurrent erectile dysfunction (2011) [1, 2, 6, 7].

The pharmacological mechanism is inhibition of PDE5, the enzyme that hydrolyzes cGMP in vascular and visceral smooth muscle. In the physiological context of nitric oxide (NO)-mediated vasodilation, PDE5 inhibition amplifies and prolongs the cGMP signal, producing smooth muscle relaxation in the corpus cavernosum (facilitating erection), in the pulmonary vasculature (reducing pulmonary arterial pressure), and in the prostate and bladder neck (alleviating lower urinary tract symptoms). The IC<sub>50</sub> of tadalafil for human recombinant PDE5 is approximately 1 to 5 nanomolar; selectivity over PDE1, PDE2, PDE3, PDE4, PDE7 through PDE10 exceeds 1000-fold; selectivity over PDE6 is approximately 700-fold; and selectivity over PDE11A is approximately 40-fold [8, 18].

The distinguishing pharmacokinetic features are a 17.5-hour plasma elimination half-life (enabling a 24 to 36 hour window of clinical effect from a single on-demand dose), food-independent absorption, and 94 percent plasma protein binding. The compound is metabolized predominantly by CYP3A4 to the inactive methylcatechol glucuronide; no active circulating metabolites have been identified. Peak plasma concentration is reached at approximately 2 hours; oral bioavailability has not been formally reported as a single numeric value but is estimated at approximately 36 to 50 percent based on population pharmacokinetic modeling [3, 5, 19].

Clinical efficacy in ED has been demonstrated in more than 20 randomized controlled trials, with response rates of 60 to 70 percent across severity strata. The PHIRST trial in PAH demonstrated a 33-meter improvement in six-minute walk distance at 40 mg daily [10]. Four pivotal BPH trials demonstrated a 2-point improvement in IPSS at 5 mg daily [11]. Common adverse events are headache, dyspepsia, back pain, myalgia, nasal congestion, and flushing. The absolute contraindication

with organic nitrates reflects the synergistic hypotensive mechanism of dual cGMP pathway amplification [12, 13]. Rare postmarketing safety signals include NAION, sudden hearing loss, and priapism.

Emerging preclinical research has characterized tadalafil as neuroprotective in rodent models of Alzheimer's disease, vascular dementia, and stroke, attributable to cGMP-mediated enhancement of cerebral blood flow, synaptic plasticity, and neuroinflammation suppression [20, 21]. Epidemiological studies have reported inverse associations between PDE5 inhibitor use and Alzheimer's disease risk, though confounding cannot be excluded. These findings remain investigational and have not produced registration-quality clinical evidence for cognitive indications.

## 3. Discovery and Development History

### 3.1 Origin

Tadalafil originated in a phosphodiesterase inhibitor program at ICOS Corporation, a biotechnology company based in Bothell, Washington. In 1993, ICOS initiated a medicinal chemistry effort directed at selective PDE5 inhibition, exploring a beta-carboline structural scaffold that was chemically distinct from the pyrimidinone series that had yielded sildenafil at Pfizer [1, 14]. The compound designated IC351 emerged from this series as a potent, selective PDE5 inhibitor with a notably long plasma half-life in preclinical species. The structural novelty (a tetracyclic indole-piperazinedione system rather than a substituted pyrimidinone) afforded a distinct intellectual property position and, subsequently, distinct pharmacokinetic and selectivity properties.

### 3.2 Partnership with Eli Lilly

In 1998, ICOS entered a 50/50 joint venture with Eli Lilly and Company (Lilly ICOS LLC) to develop and commercialize IC351 for ED. GlaxoWellcome had previously held a partnership position with ICOS but allowed the agreement to lapse in 1996, reportedly because the PDE5 inhibitor program did not align with its therapeutic focus areas [2]. The Lilly ICOS partnership provided the clinical development, regulatory, and commercial infrastructure for the Phase 2 and Phase 3 trial programs and for the global launch of the product.

### 3.3 Clinical development and ED approval

Phase 1 studies in healthy volunteers were initiated in 1995 and characterized the pharmacokinetic profile, including the long half-life and food-independent absorption. Phase 2 dose-ranging studies in men with ED were initiated in 1997 and established the 10 mg and 20 mg on-demand doses as the optimal therapeutic range. Multiple Phase 3 randomized, double-blind, placebo-controlled trials were conducted across North America, Europe, and Asia-Pacific, enrolling populations with ED of varying severity and etiology, including diabetes-associated ED, post-prostatectomy ED, and ED with concurrent BPH [22, 23].

The FDA initially delayed approval in April 2002, requesting additional studies, labeling revisions, and resolution of manufacturing issues. Tadalafil received European Union approval in November 2002 and United States FDA approval on November 21, 2003, for the on-demand treatment of ED at 10 mg and 20 mg oral doses under the trade name Cialis. The once-daily 2.5 mg and 5 mg dosing regimen for ED received FDA approval in January 2008, based on studies demonstrating continuous erectile readiness and improved scores on the International Index of Erectile Function (IIEF) with daily dosing [4, 24].

### 3.4 Expansion to PAH and BPH

The pulmonary arterial hypertension indication was developed on the basis of PDE5 expression in pulmonary vascular smooth muscle and the established mechanism of cGMP-mediated pulmonary vasodilation. The PHIRST (Pulmonary Arterial Hypertension and Response to Tadalafil) registration trial, a 16-week randomized, double-blind, placebo-controlled study in 405 patients with PAH, demonstrated a statistically significant 33-meter improvement in six-minute walk distance at the 40 mg daily dose [10]. Tadalafil received FDA approval for PAH in May 2009 under the trade name Adcirca at a dose of 40 mg once daily (two 20 mg tablets).

The BPH indication was based on the recognition that PDE5 is expressed in prostate smooth muscle, bladder detrusor muscle, and the vascular endothelium of the lower urinary tract. Four 12-week randomized, double-blind, placebo-controlled trials in men with BPH-related lower urinary tract symptoms demonstrated that tadalafil 5 mg once daily produced a statistically significant improvement in IPSS compared to placebo, with a mean treatment difference of approximately 1.5 to 2.5 points [11, 25]. FDA approval for BPH (and for the combination of BPH and ED) was granted in October 2011 at the 5 mg once-daily dose.

### 3.5 Patent expiration and generic availability

Tadalafil patent exclusivity expired in the European Union in November 2017 and in the United States in September 2018. Multiple generic formulations are now marketed globally, and the compound is among the most widely prescribed medications worldwide.

## 3.6 Acquisition of ICOS

Eli Lilly acquired ICOS Corporation in January 2007 for approximately \$2.3 billion, consolidating full ownership of the tadalafil franchise.

## 4. Mechanism of Action

Tadalafil is a competitive, reversible inhibitor of PDE5, the principal cGMP-hydrolyzing enzyme in vascular smooth muscle, pulmonary vascular smooth muscle, penile corpus cavernosum, and the lower urinary tract. The compound also inhibits PDE11A at concentrations approximately 40-fold higher than those required for PDE5 inhibition. These two molecular activities account for the therapeutic effects and the characteristic adverse-event profile.

### 4.1 PDE5 inhibition and the NO-cGMP pathway

PDE5 (phosphodiesterase type 5, encoded by the PDE5A gene) is a homodimeric enzyme that catalyzes the hydrolysis of the 3',5'-cyclic phosphodiester bond of cGMP to yield the inactive linear nucleotide 5'-GMP. The enzyme is expressed at high levels in corpus cavernosum smooth muscle, pulmonary arterial smooth muscle, vascular endothelium, platelets, and at lower levels throughout the central nervous system, kidney, and gastrointestinal tract [6, 18].

The physiological context for PDE5 function is the NO-cGMP vasodilatory cascade. Sexual stimulation triggers release of nitric oxide from nonadrenergic, noncholinergic (NANC) parasympathetic nerve terminals and from the vascular endothelium of the helicine arteries and sinusoidal spaces of the corpus cavernosum. Nitric oxide activates the heme-containing soluble guanylate cyclase (sGC), which catalyzes the conversion of guanosine triphosphate (GTP) to cGMP. The second messenger cGMP activates cGMP-dependent protein kinase (protein kinase G, PKG), which phosphorylates multiple downstream targets including myosin light chain phosphatase, large-conductance calcium-activated potassium channels, and inositol trisphosphate receptor-associated cGMP kinase substrate (IRAG). The net effect is cytoplasmic calcium reduction, smooth muscle relaxation, arteriolar dilation, increased sinusoidal blood inflow, compression of subtunical venules against the tunica albuginea (the corporal veno-occlusive mechanism), and tumescence progressing to rigid erection [6, 26].

PDE5 terminates this cascade by hydrolyzing cGMP. Tadalafil competitively inhibits PDE5 at the catalytic site with an IC<sub>50</sub> of approximately 1 to 5 nanomolar for human recombinant enzyme, preventing cGMP degradation and amplifying the

downstream signal. The inhibition is competitive (tadalafil occupies the cGMP-binding catalytic pocket) and reversible (inhibition is surmountable by increasing cGMP concentration and is terminated when tadalafil dissociates or is cleared). Because the mechanism requires upstream nitric oxide release, tadalafil does not produce erection in the absence of sexual stimulation [18].

## 4.2 PDE5 inhibition in the pulmonary vasculature

The same NO-cGMP-PDE5 pathway operates in pulmonary arterial smooth muscle. In PAH, endothelial dysfunction produces deficiency of NO, reduced cGMP, and unopposed vasoconstriction and vascular remodeling. PDE5 expression is upregulated in the pulmonary vasculature of PAH patients, further depleting the available cGMP pool. Tadalafil inhibits pulmonary vascular PDE5, restoring cGMP levels, promoting vasodilation, and potentially attenuating vascular smooth muscle proliferation and remodeling [7, 10]. The 40 mg dose approved for PAH produces substantially higher plasma concentrations than the 5 to 20 mg ED doses, reflecting the dose-response requirements of the pulmonary vascular bed.

## 4.3 PDE5 inhibition in the lower urinary tract

PDE5 is expressed in the smooth muscle of the prostate, bladder neck, urethra, detrusor muscle, and prostatic vasculature. The mechanism by which PDE5 inhibition alleviates BPH-related lower urinary tract symptoms (LUTS) is multifactorial and not fully resolved. Proposed contributing mechanisms include: (a) relaxation of prostate and bladder neck smooth muscle tone through cGMP-mediated calcium reduction; (b) improved pelvic blood flow and oxygenation through vasodilation; (c) reduction of afferent nerve signaling from the bladder through modulation of cGMP-dependent sensory pathways; and (d) anti-proliferative and anti-inflammatory effects on prostatic tissue mediated through the NO-cGMP-PKG cascade [11, 25, 27]. The clinical effect (approximately 2-point IPSS improvement over placebo) is modest compared to alpha-1 adrenergic antagonists (approximately 3 to 5 points) but is additive when combined with alpha-blockers or 5-alpha-reductase inhibitors.

## 4.4 PDE11A inhibition

PDE11A is a dual-specificity phosphodiesterase (hydrolyzing both cAMP and cGMP) expressed in skeletal muscle, prostate, testes, pituitary, liver, and kidney. Tadalafil inhibits PDE11A with approximately 40-fold lower potency than PDE5, a selectivity

ratio substantially lower than those of sildenafil (approximately 1000-fold) and vardenafil (approximately 9300-fold) [8, 9]. The functional consequences of PDE11A inhibition in humans are incompletely characterized. The leading clinical hypothesis is that PDE11A inhibition in skeletal muscle, by elevating intracellular cAMP and/or cGMP, produces the back pain and myalgia that occur in approximately 6 to 9 percent of tadalafil-treated patients and at lower frequency with the more PDE11-selective sildenafil and vardenafil [9, 28]. PDE11A expression in testes has raised theoretical fertility concerns, but clinical data from spermatogenesis studies have not demonstrated adverse effects on sperm parameters at therapeutic doses [29].

## 4.5 Selectivity profile summary

Tadalafil selectivity ratios (PDE5 IC<sub>50</sub> relative to other PDE family IC<sub>50</sub> values) are approximately: PDE1 (greater than 10,000-fold), PDE2 (greater than 10,000-fold), PDE3 (greater than 10,000-fold), PDE4 (greater than 10,000-fold), PDE6 (approximately 700-fold), PDE7 through PDE10 (greater than 10,000-fold), PDE11A (approximately 40-fold). The high selectivity over PDE3 (cardiovascular contractility enzyme) and PDE6 (retinal phototransduction enzyme) accounts for the low incidence of cardiovascular adverse events and visual disturbances relative to some other PDE5 inhibitors [8, 18].

## 5. Pharmacokinetics and Routes of Administration

### 5.1 Absorption

Tadalafil is absorbed from the gastrointestinal tract after oral administration with a median time to peak plasma concentration ( $T_{max}$ ) of approximately 2 hours (range 0.5 to 6 hours). At the 20 mg dose, mean peak plasma concentration ( $C_{max}$ ) is approximately 378 micrograms per liter (approximately 970 nanomolar). Absorption is not significantly affected by food; the 90 percent confidence intervals for  $C_{max}$  and area under the curve (AUC) ratios with and without food fall within bioequivalence limits. This food-independence is a meaningful clinical advantage over sildenafil and vardenafil, both of which show reduced or delayed absorption after high-fat meals [3, 5].

### 5.2 Distribution

The apparent volume of distribution ( $V_z/F$ ) is approximately 63 liters, indicating moderate tissue distribution beyond the plasma compartment. Plasma protein binding is 94 percent, predominantly to albumin, and is constant across the therapeutic concentration range. The compound crosses the blood-brain barrier; brain-to-plasma ratios in rodent pharmacokinetic studies indicate moderate central nervous system penetration, lower than sildenafil but sufficient to produce measurable cGMP elevation in hippocampal and cortical tissue [20, 21].

### 5.3 Metabolism

Tadalafil is metabolized predominantly in the liver by CYP3A4. The principal metabolic pathway is demethylenation of the methylenedioxyphenyl group to yield a catechol metabolite, which undergoes further methylation by catechol-O-methyltransferase (COMT) and glucuronidation to yield the methylcatechol glucuronide conjugate, the major circulating metabolite. The methylcatechol glucuronide is

pharmacologically inactive at PDE5 at concentrations achieved in plasma. No other circulating metabolites are present at pharmacologically relevant concentrations [5, 30].

CYP3A4 is the predominant CYP isoform; minor contributions from CYP2C9 and CYP1A2 have been identified in vitro but are not clinically significant. Tadalafil does not inhibit or induce CYP3A4 at therapeutic concentrations, differentiating it from some protease inhibitors and azole antifungals that produce bidirectional interactions [30].

## 5.4 Elimination

Mean oral clearance is approximately 2.5 liters per hour. The mean terminal elimination half-life is 17.5 hours in healthy subjects (range approximately 12 to 21 hours), the defining pharmacokinetic feature that distinguishes tadalafil from other PDE5 inhibitors. The half-life is sufficiently long to support a once-daily dosing regimen (2.5 mg or 5 mg) with steady-state plasma concentrations approximately 1.6-fold higher than single-dose concentrations [3, 19].

Excretion is predominantly fecal (approximately 61 percent of the administered dose, as metabolites) and renal (approximately 36 percent, as metabolites). Less than 0.1 percent of the administered dose is excreted unchanged in urine, confirming that elimination is metabolic rather than renal [5].

## 5.5 Routes of administration

Tadalafil is administered exclusively by the oral route. Available formulations include immediate-release tablets (2.5 mg, 5 mg, 10 mg, and 20 mg), a 20 mg tablet formulated for the PAH indication (Adcirca), and an oral suspension (Tadliq, 20 mg/mL). No parenteral, sublingual, or transdermal formulations are approved or in advanced clinical development.

## 5.6 Special populations

**Renal impairment:** No dose adjustment is required for mild or moderate renal impairment (creatinine clearance 31 to 80 mL/min). For severe renal impairment (creatinine clearance less than 30 mL/min), the maximum recommended on-demand

dose is 5 mg, and the once-daily regimen should be initiated at 2.5 mg. Tadalafil is not removed by hemodialysis [31].

**Hepatic impairment:** In mild hepatic impairment (Child-Pugh class A), exposure is not clinically significantly altered. In moderate hepatic impairment (Child-Pugh class B), the maximum recommended on-demand dose is 10 mg. The compound has not been studied in severe hepatic impairment (Child-Pugh class C) and is not recommended in this population [31].

**Elderly:** Healthy elderly subjects (65 years and older) show slightly higher AUC compared to younger subjects, but no dose adjustment is required based on age alone [19].

**CYP3A4 interaction context:** In subjects receiving potent CYP3A4 inhibitors (ketoconazole 400 mg daily), tadalafil AUC increased by 312 percent and C<sub>max</sub> by 22 percent. The maximum recommended dose in patients taking potent CYP3A4 inhibitors is 10 mg once every 72 hours (on-demand) or 2.5 mg daily (once-daily regimen). CYP3A4 inducers (rifampin) reduce tadalafil exposure substantially and may compromise efficacy [30, 31].

## 6. Preclinical Pharmacology

### 6.1 Erectile function models

In canine and rabbit models of erectile function, tadalafil produced dose-dependent enhancement of intracavernosal pressure responses to pelvic nerve stimulation, consistent with the PDE5 inhibitory mechanism. The onset and duration of effect in these models predicted the clinical pharmacokinetic profile [14]. In spontaneously hypertensive rats, chronic tadalafil administration partially reversed the endothelial dysfunction and impaired erectile responses associated with hypertension.

### 6.2 Pulmonary vascular pharmacology

In rodent and canine models of pulmonary hypertension induced by chronic hypoxia or monocrotaline, tadalafil reduced pulmonary arterial pressure, attenuated vascular remodeling (medial hypertrophy of pulmonary arterioles), and improved right ventricular function. The mechanism in these models involves cGMP-mediated vasodilation and, with chronic dosing, inhibition of smooth muscle proliferation through protein kinase G-mediated growth arrest pathways [7, 32].

### 6.3 Lower urinary tract pharmacology

In vitro studies of human and rat prostate tissue strips demonstrated that tadalafil produced concentration-dependent relaxation of phenylephrine-precontracted preparations, consistent with PDE5 inhibition in prostatic smooth muscle. In vivo studies in rat models of partial bladder outlet obstruction demonstrated that tadalafil reduced voiding frequency and increased functional bladder capacity [27].

### 6.4 Neuroprotection and cognitive pharmacology

Tadalafil has been characterized in multiple preclinical neuroprotection paradigms. Garcia-Barroso et al. (2013) demonstrated that tadalafil crosses the blood-brain barrier in mice and reverses cognitive dysfunction in the J20 transgenic mouse model of Alzheimer's disease, with improvements in spatial memory associ-

ated with reductions in tau pathology and hippocampal oxidative stress [20]. Chronic tadalafil treatment in aged mice increased hippocampal cGMP and CREB phosphorylation and improved performance in Morris water maze and novel object recognition tasks [21]. In rodent models of vascular dementia (bilateral common carotid artery occlusion) and focal cerebral ischemia, tadalafil improved neurological outcome scores and reduced infarct volume, attributable to enhanced cerebral blood flow, endothelial nitric oxide synthase upregulation, and suppression of neuroinflammatory cytokines [33, 34].

Epidemiological analyses of prescription databases have reported inverse associations between PDE5 inhibitor use (including tadalafil) and Alzheimer's disease diagnosis, with hazard ratios in the range of 0.60 to 0.80, though confounding by indication (ED medications prescribed to healthier populations) cannot be excluded [35]. These findings remain investigational and have not produced clinical trial evidence for cognitive indications.

## 6.5 Cardioprotective and anti-remodeling pharmacology

In rodent and canine models of cardiac ischemia-reperfusion injury, tadalafil reduced infarct size through a cGMP-PKG-dependent mechanism involving mitochondrial ATP-sensitive potassium channel opening. Chronic tadalafil treatment in models of pressure-overload cardiac hypertrophy (transverse aortic constriction) attenuated left ventricular hypertrophy and fibrosis. Clinical trials of tadalafil in heart failure with preserved ejection fraction (HFpEF) have produced mixed results, with the RELAX trial (a Phase 3 study of sildenafil in HFpEF) serving as the reference negative readout for the PDE5 inhibitor class in this indication [36].

## 7. Clinical Evidence Base

### 7.1 Erectile dysfunction

The pivotal registration trials for tadalafil in ED comprised multiple randomized, double-blind, placebo-controlled studies across North America, Europe, and Asia enrolling a total of more than 4,000 patients with ED of varying severity and etiology. Efficacy was assessed using the International Index of Erectile Function (IIEF) erectile function domain score and the Sexual Encounter Profile (SEP) diary.

At the 20 mg on-demand dose, mean IIEF-EF domain scores improved by approximately 7 to 9 points from baseline compared to approximately 1 to 2 points for placebo (treatment difference approximately 6 to 7 points). SEP Question 3 (successful intercourse completion) rates were approximately 64 to 73 percent for tadalafil 20 mg versus approximately 32 to 36 percent for placebo [22, 23]. Efficacy was maintained across subgroups including patients with diabetes mellitus (lower absolute response rates but statistically significant improvement over placebo), post-radical prostatectomy patients (bilateral nerve-sparing technique required for optimal response), and patients with concurrent BPH [37].

The 36-hour window of clinical effect was confirmed in time-course studies demonstrating that efficacy at 24 hours and 36 hours post-dose was significantly superior to placebo, distinguishing tadalafil from the 4 to 8 hour effective windows of sildenafil and vardenafil [4].

The once-daily dosing regimen (2.5 mg and 5 mg) was established in studies demonstrating that continuous daily dosing produced IIEF improvements comparable to on-demand dosing, with the added convenience of uncoupling dosing from sexual activity. The 5 mg daily dose was selected as the optimal balance of efficacy and tolerability [24].

### 7.2 Pulmonary arterial hypertension

The PHIRST (Pulmonary Arterial Hypertension and Response to Tadalafil) registration trial was a 16-week randomized, double-blind, placebo-controlled study in 405 patients with PAH (WHO functional class I to III) at four dose levels (2.5 mg, 10 mg,

20 mg, and 40 mg once daily) [10]. The primary endpoint was change from baseline in six-minute walk distance (6MWD). At 40 mg daily, tadalafil produced a mean placebo-corrected improvement in 6MWD of 33 meters (p less than 0.01), along with a statistically significant improvement in time to clinical worsening and a trend toward improvement in WHO functional class. The 20 mg dose produced a non-significant 27-meter improvement; the 2.5 mg and 10 mg doses were not significantly different from placebo.

The long-term open-label extension of PHIRST demonstrated sustained efficacy through 52 weeks of treatment. Tadalafil is recommended in international PAH treatment guidelines as a first-line oral therapy for WHO functional class II and III PAH, either as monotherapy or in combination with an endothelin receptor antagonist (ambrisentan, bosentan, macitentan) [38].

## 7.3 Benign prostatic hyperplasia

Four 12-week randomized, double-blind, placebo-controlled pivotal trials evaluated tadalafil 2.5 mg and 5 mg once daily in men with BPH-related LUTS (IPSS at least 13 at baseline). The pooled results demonstrated that tadalafil 5 mg daily produced a mean improvement in total IPSS of approximately 4.5 to 5.5 points from baseline, compared to approximately 2.5 to 3.5 points for placebo (treatment difference approximately 1.5 to 2.5 points, p less than 0.001 in each trial) [11, 25].

The IPSS improvement was significant across storage (irritative) and voiding (obstructive) symptom subscores. Maximum urinary flow rate (Qmax) improved by approximately 1.0 to 1.5 mL/sec with tadalafil 5 mg versus approximately 0.5 to 1.0 mL/sec with placebo in some but not all trials, and the Qmax effect was not as consistent as the subjective symptom improvement [39].

A study evaluating tadalafil 5 mg in combination with the alpha-1 adrenergic antagonist tamsulosin 0.4 mg demonstrated additive benefits on IPSS and patient-reported outcomes compared to either agent alone [40].

## 7.4 Investigational indications

**Duchenne muscular dystrophy:** Tadalafil was investigated for Duchenne muscular dystrophy (DMD) on the basis that PDE5 inhibition might improve skeletal muscle perfusion and attenuate ischemic muscle damage. A randomized, double-blind,

placebo-controlled Phase 3 trial in 331 ambulatory boys with DMD did not meet its primary endpoint (change in six-minute walk distance), and the DMD program was discontinued [41].

**Raynaud phenomenon:** Small clinical studies have reported that tadalafil improves digital blood flow and reduces the severity and frequency of Raynaud attacks, consistent with the vasodilatory mechanism [42].

**Heart failure:** PDE5 inhibitors have been investigated for heart failure with preserved and reduced ejection fraction. Results have been mixed; the class has not established clinical efficacy in heart failure [36].

**Cognitive impairment:** Preclinical and epidemiological evidence supports investigation of PDE5 inhibitors in cognitive impairment and dementia, but no registration-quality clinical trials have been completed for cognitive indications as of the date of this monograph [35].

## 8. Sourcing and Quality Verification

Pharmaceutical-grade tadalafil is widely available as branded (Cialis, Adcirca) and generic immediate-release tablets in 2.5 mg, 5 mg, 10 mg, and 20 mg strengths, as well as a 20 mg/mL oral suspension (Tadliq). Pharmaceutical sourcing is straightforward given the global availability of the compound following patent expiration.

Research-grade tadalafil is supplied by multiple chemical and pharmaceutical research suppliers (Sigma-Aldrich, Cayman Chemical, Tocris, MedChemExpress, Selleckchem, TCI Chemicals, Santa Cruz Biotechnology, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to multigram quantities. Pricing is moderate, 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 (390.1449 for the protonated molecule  $[M+H]^+$ ; 389.1376 monoisotopic for the neutral compound)
- Chiral or diastereomeric HPLC confirmation of stereochemical purity (greater than 99 percent diastereomeric excess of the (6R,12aR)-trans form)
- Nuclear magnetic resonance ( $^1H$  and  $^{13}C$ ) comparison against published spectral data
- Karl Fischer or loss-on-drying analysis for residual water
- Residual solvent analysis (gas chromatography) for common synthesis solvents

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, and others) provide independent confirmation of vendor certificates of analysis. Because tadalafil is among the most commonly counterfeited pharmaceutical compounds globally (a consequence of the high commercial value of the ED franchise), analytical verification is particularly important for lots obtained outside of established pharmaceutical and chemical supplier chains.

## 9. Reconstitution and Handling

Tadalafil is practically insoluble in water (less than 0.73 mg/L at ambient conditions). For in vitro research applications, the compound is dissolved in dimethyl sulfoxide (DMSO) at concentrations up to 50 to 100 mM (19.5 to 38.9 mg/mL) to prepare stock solutions. Stock solutions in DMSO are stable for at least 6 months at minus 20 degrees Celsius and for at least 12 months at minus 80 degrees Celsius when stored in sealed, light-protected vials with minimal headspace.

For in vivo animal studies where oral gavage is not feasible with tablet formulations, tadalafil can be prepared as a suspension in 0.5 percent methylcellulose in water, in a DMSO/PEG-400/water vehicle (typically 5 percent DMSO, 40 percent PEG-400, 55 percent water), or in a cyclodextrin-based formulation (hydroxypropyl-beta-cyclodextrin at 20 to 40 percent w/v in water) to achieve acceptable suspension or solubility for dosing [43].

The solid compound is stable at room temperature in dry conditions and should be stored at 2 to 25 degrees Celsius in a tightly sealed container protected from moisture. The compound is light-stable and non-hygroscopic. Aliquoting of DMSO stock solutions into single-use vials is recommended to avoid repeated freeze-thaw cycles. Stability to at least 3 freeze-thaw cycles has been demonstrated without measurable potency loss.

For the pharmaceutical oral tablet formulation, no reconstitution is required. Tablets should be stored at controlled room temperature (20 to 25 degrees Celsius) in the original packaging.

## 10. Stack Interactions and Combinations

Tadalafil interacts with several drug classes through its CYP3A4-mediated metabolism, its cGMP-elevating mechanism, and its hemodynamic effects. Investigators conducting research with tadalafil, especially in chronic dosing regimens or in combination with other compounds, should consider:

**Organic nitrates (ABSOLUTE CONTRAINDICATION):** Nitroglycerin, isosorbide dinitrate, isosorbide mononitrate, amyl nitrite, and other organic nitrate preparations are absolutely contraindicated with tadalafil. Nitrates are exogenous NO donors that directly activate guanylate cyclase and increase cGMP; the combination with PDE5 inhibition produces synergistic, potentially life-threatening hypotension. Clinical pharmacology studies demonstrated that tadalafil potentiated the hypotensive effect of nitroglycerin for at least 24 hours after dosing, consistent with the long half-life [12, 13].

**Soluble guanylate cyclase stimulators (CONTRAINDICATED):** Riociguat (Adempas) and other sGC stimulators are contraindicated for the same mechanistic reason as nitrates: additive cGMP elevation producing severe hypotension [12].

**Alpha-1 adrenergic antagonists:** Concurrent use with alpha-blockers (doxazosin, tamsulosin, alfuzosin, prazosin, terazosin) can produce additive blood pressure reduction. The prescribing information recommends that patients be hemodynamically stable on their alpha-blocker regimen before initiating tadalafil. The combination of tadalafil 5 mg daily with tamsulosin 0.4 mg is used clinically for concurrent ED and BPH and is generally well tolerated [40].

**CYP3A4 inhibitors:** Potent inhibitors (ketoconazole, itraconazole, ritonavir, saquinavir, nelfinavir, indinavir, clarithromycin, nefazodone) increase tadalafil exposure by up to 312 percent. The maximum recommended on-demand dose is 10 mg once every 72 hours; for once-daily dosing, 2.5 mg daily is the maximum [30, 31].

**CYP3A4 inducers:** Potent inducers (rifampin, phenytoin, carbamazepine, phenobarbital, St. John's wort) reduce tadalafil exposure substantially. Rifampin 600 mg daily reduced tadalafil AUC by 88 percent, effectively abolishing clinical effect. Concurrent use requires dose adjustment or consideration of an alternative PDE5 inhibitor with different metabolic routes [30].

**Antihypertensive agents:** Tadalafil has a mild blood pressure-lowering effect (approximately 1 to 2 mmHg systolic on average). Additive effects with other antihypertensive agents (ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics) are generally well tolerated but may produce symptomatic hypotension in susceptible individuals, particularly on initiation [31].

**Other PDE5 inhibitors:** Concurrent use with another PDE5 inhibitor is pharmacologically redundant and increases the risk of adverse events without additional efficacy. The combination is not recommended.

**Alcohol:** Concurrent ethanol and tadalafil may produce additive vasodilation and orthostatic hypotension. The prescribing information advises moderation in alcohol consumption [31].

**Endothelin receptor antagonists:** Concurrent use with bosentan (a moderate CYP3A4 inducer) reduces tadalafil exposure by approximately 42 percent. The PAH indication uses 40 mg daily to compensate. Ambrisentan and macitentan do not significantly affect tadalafil pharmacokinetics [38].

# 11. Adverse Events and Safety

## 11.1 Common adverse events

The principal adverse events in placebo-controlled ED trials, at the 10 mg and 20 mg on-demand doses, are:

- Headache (approximately 11 to 15 percent, dose-dependent; reflects cerebral vasodilation)
- Dyspepsia (approximately 4 to 10 percent; reflects esophageal and gastric smooth muscle relaxation)
- Back pain (approximately 3 to 6 percent; attributed to PDE11A inhibition in skeletal muscle)
- Myalgia (approximately 1 to 4 percent; same PDE11A mechanism as back pain)
- Nasal congestion (approximately 3 to 4 percent; reflects nasal mucosal vasodilation)
- Flushing (approximately 2 to 3 percent; reflects cutaneous vasodilation)
- Pain in extremities (approximately 1 to 3 percent)
- Nasopharyngitis (approximately 2 to 4 percent in daily dosing studies)

Back pain and myalgia are characteristically more frequent with tadalafil than with sildenafil or vardenafil, consistent with the lower PDE5/PDE11 selectivity ratio. These events are typically delayed in onset (12 to 24 hours after dosing), bilateral, and self-limiting within 24 to 48 hours [9, 28].

At the 40 mg PAH dose, adverse-event rates are higher: headache (42 percent), myalgia (14 percent), back pain (12 percent), nasal congestion (13 percent), flushing (13 percent), dyspepsia (10 percent) [10].

## 11.2 Rare and serious adverse events

Postmarketing surveillance has identified the following rare but serious safety signals:

- **Nonarteritic anterior ischemic optic neuropathy (NAION):** A small number of cases of NAION (sudden, painless vision loss in one eye) have been reported in temporal association with PDE5 inhibitor use, including tadalafil. Most affected patients had predisposing anatomic (low cup-to-disc ratio, "crowded disc") or vascular (hypertension, diabetes, hyperlipidemia, smoking) risk factors. The causal relationship has not been definitively established; the incidence appears extremely rare (estimated at less than 1 per 100,000 patient-years). Tadalafil is contraindicated in patients with a history of NAION regardless of PDE5 inhibitor association [44].
- **Sudden sensorineural hearing loss:** Cases of sudden decrease or loss of hearing have been reported, sometimes accompanied by tinnitus and vertigo. The mechanism is not established; proposed mechanisms include cGMP-mediated cochlear blood flow alteration. The incidence is extremely rare [45].
- **Priapism:** Prolonged erection (greater than 4 hours) and priapism (greater than 6 hours) have been reported rarely. Risk factors include concurrent use of other vasoactive agents, sickle cell disease, multiple myeloma, and leukemia. Priapism requires emergency urological intervention to prevent penile tissue ischemia [31].
- **Cardiovascular events:** Serious cardiovascular events (myocardial infarction, sudden cardiac death, stroke, chest pain) have been reported in temporal association with tadalafil use. However, controlled clinical trial data have not demonstrated an increased cardiovascular risk compared to placebo, and the background rate of cardiovascular events in the ED population (older men with cardiovascular risk factors) provides a substantial baseline incidence [46].
- **Hypersensitivity reactions:** Rare cases including Stevens-Johnson syndrome and exfoliative dermatitis have been reported postmarketing [31].

## 11.3 Cardiovascular safety profile

Tadalafil produces a mean reduction in sitting systolic blood pressure of approximately 1.6 mmHg and diastolic blood pressure of approximately 0.8 mmHg at therapeutic doses. In clinical pharmacology studies in healthy volunteers, tadalafil 20 mg did not augment the blood pressure-lowering effect of amlodipine 5 mg, metoprolol 50 mg, enalapril 10 to 20 mg, or angiotensin II receptor blockers beyond additive effects [31, 46]. The compound does not prolong the QTc interval at therapeutic or supratherapeutic (up to 100 mg) doses.

## 11.4 Contraindications

- Concurrent organic nitrates (any form, any route)
- Concurrent soluble guanylate cyclase stimulators (riociguat)
- Known hypersensitivity to tadalafil or any excipient
- History of NAION (relative contraindication in prescribing labels)
- Situations where sexual activity is medically inadvisable (recent myocardial infarction, unstable angina, uncontrolled arrhythmia, severe aortic stenosis, uncontrolled hypertension above 170/100 mmHg, New York Heart Association class IV heart failure)

## 12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five PDE5 inhibitor alternatives against tadalafil, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical), and overall validation. The five comparators were selected as the principal PDE5 inhibitors with substantive clinical evidence in erectile dysfunction and, where applicable, in pulmonary hypertension and other indications.

### 12.1 Sildenafil (Viagra, Revatio)

**Mechanism:** Selective PDE5 inhibitor. IC<sub>50</sub> for PDE5 approximately 3 to 5 nanomolar. Selectivity over PDE6 approximately 16-fold; over PDE1 approximately 380-fold; over PDE11 approximately 1000-fold [8, 18].

**Development trajectory:** Developed by Pfizer; originally investigated for angina pectoris, repositioned for ED after the penile erection side effect was recognized in Phase 1 trials. FDA-approved for ED in March 1998 (the first PDE5 inhibitor approved for any indication) and for PAH (as Revatio) in June 2005 [47].

**Novelty:** Low (first-in-class, now a mature compound with extensive generic availability).

**Effect size:** ED: response rates of approximately 60 to 70 percent on IIEF and SEP measures, broadly equivalent to tadalafil at optimal doses. PAH: the SUPER-1 trial demonstrated a 45-meter improvement in 6MWD at 80 mg three times daily (greater absolute improvement than tadalafil at 40 mg daily, though cross-trial comparisons are unreliable) [47].

**Promising potential:** Low for novel indications. High for continued first-line use in ED and PAH. Extensive generic availability. Actively investigated in neuroprotection, heart failure, and other experimental applications.

**Side-effect profile:** Higher incidence of visual disturbances (blue-tinged vision, increased light sensitivity) than tadalafil, attributable to lower PDE5/PDE6 selectivity (16-fold vs. 700-fold). Lower incidence of back pain and myalgia than tadalafil (higher PDE5/PDE11 selectivity). Comparable headache, flushing, and dyspepsia rates. Requires food avoidance (high-fat meals delay absorption) [48].

**Overall validation:** Very high. The most extensively studied PDE5 inhibitor, with more than 25 years of clinical use and the largest clinical evidence base.

**Comparison to tadalafil:** Sildenafil has a shorter half-life (3 to 5 hours vs. 17.5 hours), a shorter window of effect (4 to 8 hours vs. 24 to 36 hours), food-dependent absorption, more visual disturbances, and fewer musculoskeletal adverse events. Tadalafil offers dosing convenience (once-daily option, food-independent) at the cost of higher back pain/myalgia rates. Efficacy in ED is broadly comparable at optimal doses.

## 12.2 Vardenafil (Levitra, Staxyn)

**Mechanism:** Selective PDE5 inhibitor. IC<sub>50</sub> for PDE5 approximately 0.1 to 0.7 nanomolar (the most potent of the marketed PDE5 inhibitors at the enzyme level). Selectivity over PDE6 approximately 21-fold; over PDE1 approximately 1000-fold; over PDE11 approximately 9300-fold [8, 18].

**Development trajectory:** Developed by Bayer and GlaxoSmithKline. FDA-approved for ED in August 2003. An orodispersible tablet formulation (Staxyn) was subsequently approved. Not approved for PAH or BPH [49].

**Novelty:** Low (third-to-market PDE5 inhibitor, pyrimidinone structure related to sildenafil).

**Effect size:** ED: response rates of approximately 65 to 70 percent, comparable to sildenafil and tadalafil at optimal doses. Evidence of rapid onset of action (some men achieve successful intercourse within 10 to 15 minutes) [49, 50].

**Promising potential:** Low for novel indications. Moderate for continued ED use. Limited by single-indication approval and competition from tadalafil and generic sildenafil.

**Side-effect profile:** Lower back pain/myalgia than tadalafil (highest PDE5/PDE11 selectivity of all marketed PDE5 inhibitors). Comparable visual disturbance rates to sildenafil (low PDE5/PDE6 selectivity). Food-dependent absorption (moderate effect). Mild QTc prolongation has been reported at supratherapeutic doses [49].

**Overall validation:** Moderate. Narrower clinical evidence base than sildenafil or tadalafil, limited to ED.

**Comparison to tadalafil:** Vardenafil has a shorter half-life (4 to 5 hours), a shorter window of effect, food-dependent absorption, higher enzyme potency, superior PDE11 selectivity (fewer musculoskeletal adverse events), but inferior PDE6 selectivity (more visual disturbances). Tadalafil has the advantage of a long half-life, once-daily dosing, and multi-indication approval.

## 12.3 Avanafil (Stendra)

**Mechanism:** Selective PDE5 inhibitor. IC<sub>50</sub> for PDE5 approximately 4.4 to 5.2 nanomolar. Distinguished by very high selectivity: over PDE6 approximately 120-fold; over PDE1 greater than 10,000-fold; over PDE11 greater than 19,000-fold. The most selective of the marketed PDE5 inhibitors across all PDE family members [51].

**Development trajectory:** Developed by Vivus and MTPC (Mitsubishi Tanabe Pharma). FDA-approved for ED in April 2012. Not approved for PAH or BPH [51].

**Novelty:** Moderate (newest marketed PDE5 inhibitor, highest selectivity profile).

**Effect size:** ED: response rates of approximately 57 to 65 percent, slightly lower than tadalafil and sildenafil at optimal doses in some comparisons. Rapid onset of action (some patients achieve successful intercourse within 15 minutes) [51, 52].

**Promising potential:** Moderate. The selectivity profile offers a theoretical advantage for patients susceptible to off-target PDE adverse events. Limited by single-indication approval and lower market penetration.

**Side-effect profile:** The most favorable overall adverse-event profile among marketed PDE5 inhibitors. Lower rates of visual disturbances (superior PDE6 selectivity), lower musculoskeletal events (superior PDE11 selectivity), and comparable headache and flushing rates. Food has a moderate effect on absorption [51].

**Overall validation:** Moderate. Smaller clinical evidence base than sildenafil or tadalafil. The selectivity advantage is mechanistically compelling but has not translated into a dominant clinical position.

**Comparison to tadalafil:** Avanafil has a shorter half-life (approximately 5 hours), a shorter therapeutic window, superior selectivity (fewer off-target adverse events), but lower absolute efficacy in some comparisons and a single-indication approval. Tadalafil offers the long-acting, multi-indication profile; avanafil offers the rapid-onset, high-selectivity profile.

## 12.4 Mirodenafil (SK-3530, Mvix)

**Mechanism:** Selective PDE5 inhibitor. IC<sub>50</sub> for PDE5 approximately 0.33 nanomolar. Selectivity over PDE6 approximately 50-fold [53].

**Development trajectory:** Developed by SK Chemicals (Republic of Korea). Approved for ED in the Republic of Korea in 2007. Not approved in the United States, European Union, or Japan. Limited international registration [53].

**Novelty:** Low (regional PDE5 inhibitor without international regulatory footprint).

**Effect size:** ED: in Korean registration trials, response rates comparable to sildenafil at the 100 mg dose. The clinical evidence base outside Korea is limited to a small number of published studies [53, 54].

**Promising potential:** Low outside the Korean market. The compound does not have an active international development program.

**Side-effect profile:** Comparable to sildenafil in Korean clinical trials. Flushing and headache are the principal adverse events. Visual disturbance rates reflect the modest PDE5/PDE6 selectivity [53].

**Overall validation:** Low (regional approval, limited international evidence base).

**Comparison to tadalafil:** Mirodenafil is a short-acting PDE5 inhibitor with regional availability and a substantially smaller evidence base. Tadalafil is superior in every dimension of clinical validation, duration of action, and indication breadth.

## 12.5 Udenafil (Zydena)

**Mechanism:** Selective PDE5 inhibitor. IC50 for PDE5 approximately 8.3 nanomolar. Half-life approximately 11 to 13 hours, intermediate between sildenafil/vardenafil and tadalafil [55].

**Development trajectory:** Developed by Dong-A Pharmaceutical (Republic of Korea). Approved for ED in the Republic of Korea in 2005. Not approved in the United States or European Union. Investigated in a Phase 3 trial (FUEL trial) for adolescent patients with single-ventricle congenital heart disease undergoing Fontan palliation; the trial demonstrated improved exercise capacity and myocardial performance [55, 56].

**Novelty:** Moderate (unique positioning as an intermediate-duration PDE5 inhibitor with pediatric congenital heart disease data).

**Effect size:** ED: response rates comparable to sildenafil in Korean trials. Fontan trial: statistically significant improvement in peak oxygen consumption and ventricular performance in adolescents with single-ventricle physiology [56].

**Promising potential:** Moderate. The Fontan application is a novel and clinically meaningful niche. ED indication is constrained by regional approval.

**Side-effect profile:** Comparable to sildenafil. Flushing, headache, and nasal congestion are the principal adverse events [55].

**Overall validation:** Low to moderate (regional ED approval, emerging pediatric congenital heart disease data).

**Comparison to tadalafil:** Udenafil has an intermediate half-life (11 to 13 hours vs. 17.5 hours), regional availability, and a unique pediatric cardiovascular application. Tadalafil is superior in indication breadth, international availability, and evidence base depth.

## 12.6 Comparator summary

The five comparators occupy distinct positions in the PDE5 inhibitor landscape. **Sildenafil** is the historical first-in-class compound with the largest evidence base and the broadest international availability, representing the benchmark for efficacy and safety. **Vardenafil** offers the highest enzyme potency and best PDE11 selectivity but is limited to a single indication and has a shorter therapeutic window. **Avanafil**

offers the best overall selectivity profile and rapid onset but has lower absolute efficacy in some comparisons and is limited to ED. **Mirodenafil** and **udenafil** are regionally available compounds with limited international evidence bases; udenafil is distinguished by its intermediate half-life and emerging pediatric cardiovascular application.

Tadalafil occupies the unique position of the long-acting, multi-indication PDE5 inhibitor. It is the only compound approved for all three major PDE5-responsive indications (ED, PAH, BPH). Its 17.5-hour half-life enables a once-daily dosing paradigm that decouples medication from sexual activity, a feature that is strongly preferred by many patients and that supports the BPH indication (where continuous dosing is required). The principal trade-off is the higher incidence of back pain and myalgia attributable to the lower PDE5/PDE11 selectivity, a characteristic unique among the marketed PDE5 inhibitors.

The choice among PDE5 inhibitors in clinical practice depends on individual patient factors: tadalafil for patients who prefer long-acting, on-demand flexibility or once-daily dosing, and for patients with concurrent BPH; sildenafil or vardenafil for patients who prefer a shorter pharmacokinetic window or who are intolerant of tadalafil-specific musculoskeletal adverse events; and avanafil for patients who prioritize rapid onset and minimal off-target effects.

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