RonanRx
PERSONALIZED MEDICINE

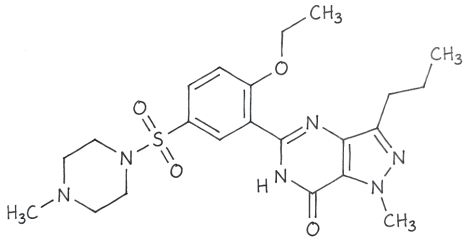
CLINICAL MONOGRAPH · SEXUAL HEALTH

Compounded Sildenafil

PDE-5 inhibitor at custom strengths or rapid-dissolve preparations

Sildenafil is a prescription pill that improves blood flow to specific tissues by relaxing the smooth muscle in small blood vessels. The original brand is Viagra, approved by the FDA in 1998 for erectile dysfunction [goldstein1998]. A second brand, Revatio, was approved in 2005 for a different problem, pulmonary arterial hypertension, a serious lung-blood-pressure disease, and a children's liquid version followed [galie2005super; barst2012starts1].

Generic sildenafil tablets are inexpensive and widely available. RonanRx only makes a compounded version when the standard tablet doesn't work for a specific patient, for example, when a patient needs a strength that's not manufactured, can't swallow tablets, needs a faster-onset sublingual troche under a doctor's direction, or when a child with pulmonary hypertension needs a custom liquid dose [fda_essentially_a_copy].



EVIDENCE POSTURE FDA APPROVED WELL STUDIED REVIEWED **2026-05-11**

State-licensed 503A | Pharmacist reviewed | Doctor led | Cold-chain ready | Patient choice preserved

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FOR CLINICIANS

Sildenafil citrate is a selective inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5), the dominant cGMP-hydrolyzing isoform in vascular smooth muscle of the corpus cavernosum and pulmonary vasculature [boolell1996pde5]. PDE5 inhibition prolongs the half-life of NO-derived cGMP, sustaining smooth-muscle relaxation. FDA-approved indications: erectile dysfunction (Viagra, 1998; oral 25/50/100 mg) and pulmonary arterial hypertension (Revatio, 2005; oral 20 mg TID and IV; pediatric oral suspension subsequently labeled) [goldstein1998].

Pivotal evidence includes Goldstein 1998 (NEJM, the foundational ED RCT), the SUPER-1 trial [galie2005super] and SUPER-2 extension [rubin2011super2] in adult PAH, and STARTS-1 [barst2012starts1] and STARTS-2 [barst2014starts2] in pediatric PAH. Pharmacokinetics: Tmax ~1 h fasting, oral bioavailability ~41%, hepatic CYP3A4 (major) and CYP2C9 (minor), t½ ~3, 4 h [nichols2002pk]. Absolute contraindication with nitrates in any form (severe hypotension) and with riociguat. Caution with alpha-blockers (additive hypotension) and strong CYP3A4 inhibitors (raise sildenafil exposure substantially). Recognized rare adverse events include nonarteritic anterior ischemic optic neuropathy (NAION), sudden sensorineural hearing loss, and priapism [pomeranz2005naion; barreto2013hearing].

Under 503A, compounded sildenafil is justified case-by-case when generic Viagra/Revatio cannot meet the patient's clinical need, for example, sublingual troches for patients who require rapid onset or cannot use oral tablets, custom strengths for partial responders, or pediatric weight-banded oral suspensions when the commercial liquid is not appropriate or unavailable [cheitlin1999accaha; jackson2006cvsafety; fda_essentially_a_copy].

Why Personalized Compounded Sildenafil

Viagra was approved at 25, 50, and 100 mg because those three tablets covered the bell curve of trial responders well enough for a manufactured product. The pivotal trials did not pick a dose for your absorption rate, your nitric-oxide baseline, the SSRI or alpha-blocker you also take, how quickly you metabolize the drug, or whether onset speed or duration matters more for your situation. Revatio's PAH schedule was set the same way, calibrated for the average pulmonary-hypertension adult, with a separate weight-banded suspension added for children only after STARTS-1 and STARTS-2 forced the FDA to address pediatric dosing as a distinct problem.

A compounding pharmacy fills the gaps that fixed tablet strengths leave behind. A prescriber can ask for a strength between 25 and 50 mg or between 50 and 100 mg for patients who need finer titration, a sublingual troche that bypasses first-pass metabolism for faster, more predictable onset, a preservative-free oral suspension for a child or an adult who cannot swallow tablets, or an individualized blend that pairs sildenafil with tadalafil and a low dose of oxytocin under a doctor's protocol when the single-agent FDA products have not produced an adequate response. The molecule is the same one the FDA reviewed in 1998. The strength, the route, and any combination are written for one named patient.

This is the older arrangement that pre-dates mass-produced tablets. A doctor writes the prescription, a pharmacist prepares it for that patient, and the label carries the patient's name. Modern state-board inspection and 503A oversight keep that arrangement honest.

Quick Facts About Compounded Sildenafil

Category: Selective PDE5 (phosphodiesterase type 5) inhibitor

Active ingredient: Sildenafil citrate

FDA-approved branded forms: Viagra (erectile dysfunction, approved 1998); Revatio (pulmonary arterial hypertension, approved 2005; pediatric oral suspension subsequently approved). Generic sildenafil widely available.

Routes studied in humans: Oral tablet, oral suspension, intravenous (Revatio), orodispersible film, sublingual troche (compounded), topical cream (investigational)

Evidence posture: Pivotal phase III evidence supports the manufactured tablets (Viagra for ED, Revatio/SUPER-1 for PAH, STARTS-1/STARTS-2 for pediatric PAH). Compounded preparations have no separate efficacy program.

Compounded under: 503A, patient-specific prescription only, where the manufactured FDA-approved product is not clinically appropriate (excipient sensitivity, non-tablet dose form needed, off-label dose, pediatric weight-banded liquid)

Absolute contraindication: Concomitant nitrate therapy (any form, any indication), life-threatening hypotension. Also contraindicated with riociguat (soluble guanylate cyclase stimulator).

Important compounding caution: Per FDA guidance, compounded versions of an FDA-approved drug are restricted to documented patient-specific clinical needs that the manufactured product cannot meet. Generic sildenafil tablets are inexpensive and widely available, so routine compounding as an essentially-a-copy substitute is not appropriate.

> **SPECIALS: PATIENT-SPECIFIC PRESCRIPTION ONLY**
>
> Compounded Sildenafil described in this monograph is a 503A compounded preparation. Every dose is made on a prescription, for a named patient, by a licensed pharmacist. It is not a stocked, mass-manufactured product.
>
> - **Made to order, not off a shelf.** No batch sits in a warehouse waiting for buyers. Your prescription triggers the prep.
> - **Named-patient label.** The bottle carries one patient's name. The batch records carry one prescription.
> - **Dose, strength, and route chosen for the patient.** A prescriber decides what gets compounded, not a manufacturer who set the strength for a trial population.
> - **Licensed pharmacist on the hook.** A real person, with a license that can be pulled, signs off on every prep. State inspectors check the facility.
> - **Compounded drugs are not FDA-approved.** They should not be evaluated using branded-drug trial data alone. Availability varies by state and prescribed medication.

How This Differs from a Research-Use-Only Website

A research-use-only website ships a vial from a warehouse. There is no prescription, no pharmacist, no facility inspection, and no way to recall the product if something is wrong with it. If the vial is mislabeled, contaminated, or under-potent, there is nobody whose license is at stake.

A 503A compounding pharmacy is the other thing. The doctor writes the prescription. A licensed pharmacist, whose name is on the label, prepares the medicine in a facility the state inspects. If something goes wrong, there is a person and a license on the hook, and a documented chain of custody on every lot. That accountability is what makes it safe.

What is Compounded Sildenafil?

Sildenafil citrate is a small-molecule selective inhibitor of phosphodiesterase type 5 (PDE5), the cyclic-GMP-specific phosphodiesterase that predominates in penile corpus cavernosum smooth muscle and in the

pulmonary vasculature [boolell1996pde5]. The molecule emerged from Pfizer's UK-92,480 cardiovascular discovery program originally targeting angina, where it underperformed but produced an unexpected, durable improvement in erectile function in early trials, leading to the redirected development program that culminated in Viagra [goldstein1998].

Sildenafil was the first oral PDE5 inhibitor approved (Viagra, 1998), creating a new pharmacologic category [boolell1996bju]. The same molecule was later developed for pulmonary arterial hypertension as Revatio (2005), where chronic PDE5 inhibition reduces pulmonary vascular resistance [ghofrani2006; galie2005super; barst2014starts2]. Pediatric PAH labeling for Revatio (oral suspension) followed the STARTS program [barst2012starts1].

Generic sildenafil citrate tablets are widely available since US patent expiry [galie2005super]. The molecule is one of the most-studied drugs in clinical pharmacology, with thousands of trial-years of safety data across both ED and PAH indications.

How Compounded Sildenafil Works

Sexual stimulation triggers release of nitric oxide (NO) from neuronal and endothelial sources in the corpus cavernosum. NO activates soluble guanylate cyclase, which converts GTP to cyclic GMP (cGMP). cGMP relaxes vascular smooth muscle, allowing blood inflow that produces an erection. PDE5 is the dominant enzyme that breaks cGMP down to inactive GMP, terminating the response.

Sildenafil is a selective competitive inhibitor of PDE5 [boolell1996pde5]. By slowing cGMP breakdown it amplifies and prolongs the local effect of any NO that the patient's own nervous system releases. It does not initiate an erection in the absence of sexual stimulation, there must be NO release first. The same mechanism in pulmonary vascular smooth muscle reduces pulmonary vascular resistance, the rationale for the PAH indication [ghofrani2006].

Selectivity for PDE5 over the other 10 PDE isoforms is high but not absolute. Modest cross-inhibition of PDE6 (retinal photoreceptors) accounts for the dose-related blue-tinted-vision adverse effect; weak cross-inhibition of PDE1 has been characterized but is not clinically prominent.

Biological Role of Compounded Sildenafil

Sildenafil is not endogenous. It engages the endogenous nitric-oxide / cGMP signaling pathway that governs vascular smooth-muscle tone in the corpus cavernosum, pulmonary vasculature, systemic vasculature, and other tissues. PDE5 is the predominant cGMP-hydrolyzing enzyme in those tissues, making it a clean pharmacologic target.

Because the mechanism requires upstream NO release, sildenafil's effect is conditional on the integrity of the patient's nitrergic and endothelial signaling [boolell1996pde5; ghofrani2006]. In severe diabetic or

post-prostatectomy nerve damage, NO supply is limited and PDE5 inhibition alone may not restore function, a common reason for partial response.

Detailed Mechanism of Compounded Sildenafil

PDE5 hydrolyzes cGMP to 5'-GMP. Sildenafil is a structural analog of cGMP that occupies the catalytic site competitively, with an IC50 in the low nanomolar range against PDE5 [ballard1998pde]. In tissues without NO-driven cGMP generation, sildenafil has minimal effect, this is why the drug does not produce an erection without sexual stimulation, and why it has limited cardiovascular impact at rest in healthy individuals [corbin2011pde5] [cheitlin1999accaha].

Isoform selectivity is high but not absolute. Sildenafil has substantial selectivity for PDE5 over PDE1, PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, PDE10, and PDE11 [weeks2005pde11]. Modest cross-inhibition of PDE6 in retinal photoreceptors underlies the dose-related blue-tinge / increased light-sensitivity adverse effect, characterized electroretinographically by Marmor and colleagues (Zoumalan/Marmor 2009 ERG study of daily high-dose sildenafil) and reviewed by Laties 2009 [marmor2009erg; laties2009vision].

Allosteric regulation of PDE5 itself is dynamic: Corbin and Francis 2011 showed that incubation of PDE5 with sildenafil or with metal ions drives a conformational change that further stimulates allosteric cGMP binding, suggesting a positive-feedback loop that contributes to sustained activity [corbin2011pde5]. The cGMP downstream effector is cGMP-dependent protein kinase (PKG), which phosphorylates targets including phospholipase A2 [murthy1998cgmp], myosin light chain phosphatase, and various ion channels, net effect is reduced cytosolic Ca2+ and smooth-muscle relaxation. Lin and colleagues [lin2009pde5] have characterized PDE5 expression and regulation specifically within the penile corpora cavernosa; Burnett 2024 revisited the central role of NO in penile erection physiology [burnett2024no].

In the pulmonary circulation, chronic PDE5 inhibition amplifies endogenous NO-mediated vasodilation, reducing pulmonary vascular resistance and right-ventricular afterload over weeks of treatment [abman2013fdawarning]. The clinical signal in SUPER-1 was improvement in 6-minute walk distance and hemodynamics in WHO Functional Class II, IV patients with PAH [galie2005super]; long-term survival data came from SUPER-2 [rubin2011super2] and, in children, from STARTS-2 [barst2014starts2].

The combination of PDE5 inhibition with nitric oxide donors (nitrates) causes profound, additive cGMP accumulation in vascular smooth muscle and is the basis for the absolute nitrate contraindication, quantified hemodynamically by Webb 1999 (organic nitrate plus calcium antagonist drug-interaction studies), Webb 2000 (NO donors potentiated by sildenafil in stable-angina patients), and time-course-characterized by Oliver/Webb 2009 (the hypotensive effect of sublingual glyceryl trinitrate combined with sildenafil is most severe within 4 hours of sildenafil dosing and substantially attenuated by 8 hours) [webb1999nitrate; webb2000nitrate; oliver2009nitrate]. Parker 2007 demonstrated that IV nitroglycerin can be safely administered to men with coronary disease pretreated with sildenafil if at least 8 hours have

elapsed, supporting the operational 24-hour washout rule [boolell1996pde5; ghofrani2006; parker2007nitrate].

Compounded Sildenafil Research History

Sildenafil (UK-92,480) was synthesized in Pfizer's Sandwich, UK laboratories in 1989 as a candidate for stable angina pectoris and hypertension [ghofrani2006; caruso2006fsadt1d; basson2003fsad]. Early-phase studies in coronary artery disease were disappointing, but volunteers consistently reported penile erections as a side effect [luo2025hearing; burnett2006priapism]. Boolell and colleagues at Pfizer published the first peer-reviewed characterization of sildenafil's PDE5-inhibitor mechanism and its erectogenic effect in 1996 (Int J Impot Res; Br J Urol), and Ballard 1998 worked out the relaxation profile in human corpus cavernosum tissue [boolell1996pde5; ballard1998pde] [borlaug2015relax]. The Goldstein 1998 NEJM trial established efficacy and safety in a 21-center US program of 532 men with ED and underpinned FDA approval of Viagra in March 1998 [padmanathan2002safety; berman2003fsad; thurman2024sildenafilcream]. Open-label long-term follow-up [goldstein1999openlabel] and replication in special populations followed quickly: diabetes [rendell1999diabetes], spinal cord injury [hultling2000sci], and elderly subgroups [wagner2001elderly].

Cardiovascular safety became a regulatory and clinical priority shortly after launch as case reports of cardiovascular events with concomitant nitrate use accumulated [etminan2022ocular]. The hemodynamic mechanism was rigorously characterized in dedicated interaction studies, Webb 1999 (organic nitrate and calcium-antagonist drug-interaction studies), Webb 2000 (NO donor potentiation in stable-angina patients), and Oliver/Webb 2009 (time-dependent attenuation of the sublingual nitroglycerin, sildenafil interaction) [webb1999nitrate; webb2000nitrate; oliver2009nitrate]. Parker 2007 demonstrated that IV nitroglycerin could be safely administered after an 8-hour washout [pomeranz2005naion; penedones2020naion; maddox2009hearing]. The ACC/AHA expert consensus document [cheitlin1999accaha] codified the absolute nitrate contraindication and the alpha-blocker caution; Kloner 2004 quantified the doxazosin/tamsulosin interaction [kloner2004alpha] [mcgwin2006naion]. A 4-year safety review (Padma-Nathan 2002), updated reviews [jackson2006cvsafety], and a large modern systematic review and meta-analysis of long-term PDE5-inhibitor cardiovascular outcomes [soulaidopoulos2024cvmeta] supported the cardiovascular safety profile when contraindications were observed; Vlachopoulos 2004 even demonstrated acute reversal of smoking-induced endothelial dysfunction by sildenafil [goldstein1998].

Pulmonary hypertension development followed the same mechanism logic [maggiorini2006hape]. The SUPER-1 trial [galie2005super] supported FDA approval of Revatio for PAH; SUPER-2 [rubin2011super2] extended the safety record to two years. SERAPH [wilkins2005seraph] was an early head-to-head against an endothelin-receptor antagonist (bosentan), and combination-therapy programs followed: COMPASS-1 [gruenig2009compass1], PACES [simonneau2008paces], COMPASS-2 [mclaughlin2015compass2], and AMBITION [galie2015ambition]. Singh 2006 reported a placebo-controlled crossover trial of oral sildenafil

specifically in severe pulmonary arterial hypertension including Eisenmenger physiology [parker2007nitrate; singh2006eisenmenger] [guazzi2011hfpef]. PHIRST [galie2009phirst] established the tadalafil-PAH labeling that broadened the class [gorkin2006naion; margo2007naion]. Pediatric development through STARTS-1 [barst2012starts1] and STARTS-2 [barst2014starts2] established pediatric PAH dosing, and produced an unexpected mortality signal at the highest dose that informed FDA's pediatric labeling restriction [abman2013fdawarning]. A pediatric oral suspension formulation was subsequently approved for Revatio [yuan2013network; boolell1996bju; pomeranz2017naion]. Neonatal PPHN evidence comes from the Baquero 2006 pilot RCT in infants and the Pierce 2021 multicenter trial of IV sildenafil in PPHN [baquero2006pphn; pierce2021iv] [boulton2001diabetes].

Heart-failure indications were tested next: Bocchi 2002 (sildenafil in advanced systolic heart failure), Lewis 2007 (sildenafil improves exercise capacity in systolic HF with secondary pulmonary hypertension), Guazzi 2011 (1-year sildenafil in HFpEF with pulmonary hypertension), and the negative RELAX trial [redfield2013relax] that ultimately argued against sildenafil for unselected HFpEF [bocchi2002hf; lewis2007hf].

Beyond labeled use, sildenafil has been investigated for Raynaud phenomenon [fries2005raynaud], high-altitude pulmonary hypertension and exercise capacity [ghofrani2004altitude], female sexual arousal disorder [caruso2001fsad], and pregnancy-related growth restriction [pels2023strider]. Network and systematic meta-analyses comparing PDE5 inhibitors (Tsertsvadze 2009 AHRQ Ann Intern Med review and harms meta-analysis; Yuan 2013 European Urology network meta-analysis) confirm broadly comparable efficacy across the class with distinct PK and AE profiles [liao2019diabetes; roustit2013raynaud; khouri2019raynaud].

Rare but recognized post-marketing adverse events include nonarteritic anterior ischemic optic neuropathy (NAION; Pomeranz 2005, Pomeranz 2017; case-control work by McGwin 2006, Gorkin 2006, Margo 2007; the modern US claims-database cohort by Etminan 2022; meta-analysis by Penedones 2020), sudden sensorineural hearing loss [barreto2013hearing], and priapism (rare and reported especially in sickle-cell physiology, Burnett 2006 reported that long-term low-dose oral PDE5 inhibitor therapy paradoxically alleviates recurrent priapism in selected men) [tsertsvadze2009review; tsertsvadze2009harms]. Wang 2024 published a comprehensive FAERS pharmacovigilance review [wang2024faers] [khan2011hearing; liu2018hearing]. Counterfeit and unregulated sildenafil represents a separate quality-and-safety axis: Veronin 2014 quantified active ingredient and impurity content in Internet-sourced sildenafil, and Venhuis 2014 documented dose-to-dose variability in counterfeit packages [veronin2014quality; venhuis2014counterfeit] [vlachopoulos2004endothelial].

Compounded Sildenafil Timeline

1989 • Sildenafil (UK-92,480) synthesized at Pfizer's Sandwich, UK laboratories as an angina/hypertension candidate [ghofrani2006]

1996 • Boolell et al [boolell1996pde5; boolell1996bju]. publish the mechanism-of-action and first clinical erectogenic data, sildenafil as an orally active PDE5 inhibitor for male erectile dysfunction

1998 • Goldstein et al [goldstein1998; ballard1998pde]. publish the pivotal NEJM trial of oral sildenafil for ED; FDA approves Viagra (March 27, 1998); Ballard characterizes the relaxation profile of human corpus cavernosum and the PDE-isoenzyme selectivity profile in vitro

1998 • Murthy & Makhlouf work out cGMP/cAMP differential regulation of PLA2 in smooth muscle, foundational signaling biology underlying PDE5 inhibition [murthy1998cgmp]

1999 • ACC/AHA expert consensus document (Cheitlin) codifies the absolute nitrate contraindication and cardiovascular caution profile; Webb publishes the formal drug-interaction studies of sildenafil with organic nitrate and a calcium-channel antagonist; Rendell publishes JAMA RCT in diabetic men; Goldstein publishes 36-week open-label long-term safety [cheitlin1999accaha; webb1999nitrate; rendell1999diabetes; goldstein19990penlabel]

2000 • Webb publishes JACC nitrate-donor interaction data, sildenafil potentiates the hypotensive effect of NO donors in stable-angina patients; Hultling reports Spinal Cord QoL data for sildenafil in SCI; Muirhead reports the sildenafil, ritonavir/saquinavir PK interaction [webb2000nitrate; hultling2000sci; muirhead2000ritonavir]

2001 • Caruso publishes first placebo-controlled RCT of sildenafil for female sexual arousal disorder in premenopausal women; Boulton reports the T2DM RCT; Wagner publishes the elderly-subgroup analysis [caruso2001fsad; boulton2001diabetes; wagner2001elderly]

2002 • Nichols publishes definitive single-dose human PK (absolute bioavailability, food effect, dose proportionality); Muirhead publishes age/renal/hepatic PK and the erythromycin interaction; Padma-Nathan publishes 4-year cumulative safety update; Bocchi publishes the sildenafil-in-CHF Circulation trial [nichols2002pk; muirhead2002impaired; muirhead2002erythromycin; padmanathan2002safety; bocchi2002hf]

2003 • Basson and Berman publish parallel RCTs of sildenafil for female sexual arousal disorder (BJOG and J Urol) [basson2003fsad; berman2003fsad]

2004 • Ghofrani publishes Ann Intern Med RCT of sildenafil for exercise capacity at altitude, proof of concept for hypoxia-induced pulmonary vasoconstriction; Kloner publishes the doxazosin/tamsulosin alpha-blocker interaction study; Vlachopoulos demonstrates reversal of smoking-induced endothelial dysfunction [ghofrani2004altitude; kloner2004alpha; vlachopoulos2004endothelial]

2005 • SUPER-1 trial (Galiè, NEJM) supports FDA approval of Revatio for pulmonary arterial hypertension; SERAPH (Wilkins) compares sildenafil to an endothelin-receptor antagonist; Pomeranz & Bhavsar report NAION case series; Fries publishes Raynaud phenomenon RCT in Circulation; Weeks characterizes high biochemical selectivity for PDE5 over PDE11 [galie2005super; wilkins2005seraph; pomeranz2005naion; fries2005raynaud; weeks2005pde11]

2006 • Ghofrani, Osterloh, and Grimminger publish the comprehensive Nature Reviews Drug Discovery review; Jackson publishes updated cardiovascular safety perspective; Maggiorini reports the tadalafil/dexamethasone HAPE-prevention trial; Singh publishes the placebo-controlled crossover trial in severe PAH (including Eisenmenger physiology); Baquero reports the PPHN pilot; McGwin and Gorkin publish NAION case-control / incidence data; Burnett reports paradoxical relief of recurrent priapism with long-term low-dose PDE5 inhibition [ghofrani2006; jackson2006cvsafety; maggiorini2006hape; singh2006eisenmenger; baquero2006pphn; mcgwin2006naion; gorkin2006naion; burnett2006priapism]

2007 • Margo reports the VA-cohort NAION ophthalmology data; Lewis publishes sildenafil-in-systolic-HF Circulation trials (exercise capacity and hemodynamics in HF with secondary pulmonary hypertension); Mehrotra reviews the role of PK/PD in PDE5-inhibitor therapy; Parker demonstrates safety of IV nitroglycerin 8 hours after sildenafil pretreatment [margo2007naion; lewis2007hf; mehrotra2007role; parker2007nitrate]

2008 • PACES (Simonneau, Ann Intern Med) demonstrates clinical benefit of sildenafil added to long-term IV epoprostenol [simonneau2008paces]

2009 • PHIRST (Galiè, Circulation) tests tadalafil in PAH, class-extension data informing PDE5-inhibitor practice; COMPASS-1 (Gruenig) reports acute hemodynamic effects of adding sildenafil to bosentan; Oliver/Webb characterize time-dependent attenuation of the sildenafil, nitroglycerin interaction; Maddox proposes a cellular-stress etiology for sudden hearing loss; Laties reviews PDE5-related vision disorders; Lin reviews PDE5 in the corpora cavernosa; Marmor's group publishes ERG data on daily high-dose sildenafil; Tsertsvadze publishes the AHRQ systematic review and harms meta-analysis [galie2009phirst; gruenig2009compass1; oliver2009nitrate; maddox2009hearing; laties2009vision; lin2009pde5; marmor2009erg; tsertsvadze2009review; tsertsvadze2009harms]

2011 • SUPER-2 long-term extension (Rubin, Chest) reports 2-year survival and safety with sildenafil monotherapy in adult PAH; Khan reports 'Viagra deafness' case-series in Laryngoscope; Guazzi reports 1-year sildenafil in HFpEF with pulmonary hypertension; Corbin/Francis describe allosteric conformational regulation of PDE5 [rubin2011super2; khan2011hearing; guazzi2011hfpef; corbin2011pde5]

2012 • STARTS-1 (Barst, Circulation), randomized dose-ranging study of oral sildenafil in treatment-naive children with PAH [barst2012starts1]

2013 • Barreto & Bahmad review PDE5 inhibitors and sudden sensorineural hearing loss; FDA pediatric labeling warning issued following STARTS-2 mortality signal (Abman editorial summarizes implications); Redfield publishes the negative RELAX HFpEF JAMA trial; Roustit publishes the Raynaud meta-analysis; Yuan publishes the PDE5-inhibitor network meta-analysis in European Urology [barreto2013hearing; abman2013fdawarning; redfield2013relax; roustit2013raynaud; yuan2013network]

2014 • STARTS-2 (Barst, Circulation), long-term pediatric survival data; higher mortality observed at the highest dose, informing dosing restriction; Damle publishes PK of a novel orodispersible tablet of sildenafil; Veronin and Venhuis publish quality/impurity and counterfeit-variability data on Internet-sourced sildenafil [barst2014starts2; damle2014odt; veronin2014quality; venhuis2014counterfeit]

2015 • Sae Yoon publishes physicochemical and microbiological stability data for an extemporaneously compounded sildenafil oral suspension; AMBITION (Galiè, NEJM) demonstrates initial-combination superiority of ambrisentan + tadalafil, class-level evidence informing PDE5-inhibitor combination strategy; COMPASS-2 (McLaughlin, Eur Respir J) tests bosentan added to sildenafil; Borlaug publishes the RELAX ventricular/vascular function ancillary analysis [saeyoon2015compoundedsuspension; galie2015ambition; mclaughlin2015compass2; borlaug2015relax]

2016 • Nahata publishes extended stability data for oral sildenafil for use in infants and young children [nahata2016suspension]

2017 • Pomeranz publishes comprehensive review of erectile dysfunction agents and NAION in Neurologic Clinics [pomeranz2017naion]

2018 • Liu publishes a Taiwan population-based cohort study of sudden sensorineural hearing loss in PDE5-inhibitor users [liu2018hearing]

2019 • Liao publishes a Bayesian network meta-analysis of PDE5 inhibitors specifically in diabetic men with ED; Khouri publishes the secondary-Raynaud network meta-analysis [liao2019diabetes; khouri2019raynaud]

2020 • Penedones publishes the NAION meta-analysis across PDE5 inhibitors [penedones2020naion]

2021 • Pierce reports the multicenter trial of IV sildenafil in neonatal PPHN; Cheung publishes physical-chemical stability data for compounded sildenafil 100-mg rapid-dissolving tablets [pierce2021iv; cheung2021stability]

2022 • Etminan publishes a JAMA Ophthalmology US claims-database cohort of ocular adverse events with PDE5 inhibitors [etminan2022ocular]

2023 • Pels et al [pels2023strider]. publish the Cochrane review of nitric-oxide-pathway interventions (including sildenafil) for fetal growth restriction in pregnancy, net negative

2024 • Thurman publishes phase 3 safety RCT of 3.6% topical sildenafil cream for female sexual arousal disorder; Wang publishes FAERS real-world pharmacovigilance analysis; Soulaidopoulos publishes the modern long-term cardiovascular outcomes meta-analysis; Burnett revisits NO physiology in the penis; Mewada publishes a taste-masked ODF formulation study [thurman2024sildenafilcream; wang2024faers; soulaidopoulos2024cvmeta; burnett2024no; mewada2024odf]

2025 • Jannini reviews sildenafil orodispersible film as a next-generation rapid-onset oral formulation; Luo publishes FAERS-based PDE5/hearing-impairment analysis [jannini2025odf; luo2025hearing]

Clinical Contexts for Compounded Sildenafil

Erectile dysfunction in adult men FDA APPROVED

FDA-approved indication for Viagra (and generic sildenafil tablets).

Goldstein 1998 NEJM RCT in 532 men across 21 US centers demonstrated dose-dependent improvement in erectile function (mean IIEF score 22 vs 12 at 100 mg vs placebo) with successful intercourse attempt rates of 69% vs 22% [goldstein1998]. FDA approved Viagra in March 1998. Generic sildenafil 25/50/100 mg tablets are widely available; standard dosing is 50 mg taken approximately one hour before sexual activity, adjustable to 25 or 100 mg by response and tolerability [boolell1996pde5].

Branded product: Viagra (sildenafil citrate tablets, Pfizer; multiple generic manufacturers)

Pulmonary arterial hypertension (PAH) in adults FDA APPROVED

FDA-approved indication for Revatio (and generic sildenafil).

SUPER-1 [galie2005super] randomized adults with PAH (WHO Group 1, Functional Class II, IV) to placebo or sildenafil 20, 40, or 80 mg TID for 12 weeks [ghofrani2006]. Placebo-adjusted 6-minute walk distance improvement was 45, 50 m across active arms. SUPER-2 [rubin2011super2] extended follow-up to 2 years and reported sustained walk-distance benefit with acceptable tolerability. Approved adult dose is 20 mg TID.

Branded product: Revatio (sildenafil citrate, Pfizer; generic available)

Pediatric pulmonary arterial hypertension FDA APPROVED

Studied in pivotal pediatric trials; pediatric oral suspension approved for Revatio. Dosing requires caution due to STARTS-2 mortality signal at highest doses.

STARTS-1 [barst2012starts1] was a randomized dose-ranging study of low/medium/high-dose oral sildenafil in treatment-naive children 1, 17 years old with PAH over 16 weeks. STARTS-2 [barst2014starts2] reported long-term survival in extension follow-up, with higher mortality observed at the highest weight-banded dose. FDA issued a labeling caution discouraging chronic use of higher doses in pediatric PAH on the basis of STARTS-2; the manufactured oral suspension is available for weight-banded pediatric dosing.

Branded product: Revatio (sildenafil citrate oral suspension, Pfizer)

Raynaud phenomenon (secondary to systemic sclerosis or resistant primary)

WELL STUDIED

Studied in small RCTs; off-label use with reasonable supportive evidence.

Fries 2005 (Circulation) randomized 16 patients with Raynaud phenomenon resistant to vasodilatory therapy to sildenafil 50 mg BID vs placebo crossover; the active arm showed reduced attack frequency, reduced cumulative attack duration, and improved capillary flow on nailfold capillaroscopy [fries2005raynaud].

Hypoxia-related pulmonary vasoconstriction / high-altitude exercise capacity EMERGING

Studied in placebo-controlled crossover RCT; remains exploratory off-label use.

Ghofrani 2004 (Ann Intern Med) randomized healthy mountaineers to sildenafil vs placebo in a double-blind crossover at low altitude under hypoxia and at Mt [ghofrani2004altitude]. Everest base camp. Sildenafil 40 mg or 80 mg improved exercise capacity and reduced pulmonary vascular resistance under hypoxic conditions. This trial established mechanistic plausibility for altitude use but does not constitute regulatory or routine clinical recommendation.

Female sexual arousal disorder EMERGING

Studied in small RCTs and a recent topical-cream phase 3 program. Evidence remains limited; no FDA-approved oral sildenafil indication in women.

Caruso 2001 (BJOG) and Caruso 2006 (Fertil Steril, in premenopausal women with type 1 diabetes) reported modest improvements in arousal-domain measures with oral sildenafil vs placebo in double-blind crossover designs [caruso2001fsad; caruso2006fsadt1d]. More recently, Thurman 2024 (J Sex Med) reported phase 3 safety data for a 3.6% topical sildenafil cream formulation; efficacy results are reported in companion publications [thurman2024sildenafilcream]. No FDA-approved sildenafil product for FSAD exists at the time of writing.

Post-prostatectomy erectile rehabilitation WELL STUDIED

Studied in dedicated RCTs; on-demand use after surgery is broadly accepted, but nightly prophylactic rehabilitation showed limited benefit.

Padma-Nathan 2008 (Int J Impot Res) randomized 76 men after bilateral nerve-sparing radical prostatectomy to nightly sildenafil 50 or 100 mg vs placebo for 36 weeks [padmanathan2008rehab]. The active arm showed improvement in spontaneous erectile function vs placebo at the post-treatment evaluation, though absolute response rates remained modest and the trial has been a touchstone in subsequent debate over rehabilitation strategies.

Erectile dysfunction in diabetes mellitus FDA APPROVED

FDA-approved indication overall; specific evidence supporting diabetic-ED efficacy from dedicated trials.

Rendell 1999 (JAMA, N=268) demonstrated successful intercourse rates of 56% on sildenafil vs 10% on placebo in men with diabetes-related ED [rendell1999diabetes]. Boulton 2001 (Diabetologia, N=219) confirmed efficacy in type 2 diabetes [boulton2001diabetes]. Liao 2019 (World J Urol) network meta-analysis confirmed broadly comparable efficacy of sildenafil, tadalafil, vardenafil, avanafil, and udenafil in diabetic men [liao2019diabetes].

Branded product: Viagra and generic sildenafil

Erectile dysfunction after spinal cord injury FDA APPROVED

FDA-approved indication overall; specific quality-of-life and efficacy data from dedicated SCI trials.

Hultling 2000 (Spinal Cord, N=178) reported significant improvement in successful intercourse and quality-of-life endpoints with sildenafil in men with spinal cord injury, providing the dedicated-population evidence for routine use of sildenafil in SCI-related ED [hultling2000sci].

Branded product: Viagra and generic sildenafil

Pulmonary arterial hypertension combination therapy WELL STUDIED

Sildenafil + endothelin-receptor antagonist or + prostacyclin: evidence base for sequential and initial-combination strategies.

PACES [simonneau2008paces] showed improvement in 6MWD and time-to-clinical-worsening when sildenafil was added to long-term IV epoprostenol. COMPASS-1 [gruenig2009compass1] characterized acute hemodynamic effects of adding sildenafil to bosentan. COMPASS-2 [mclaughlin2015compass2] did not show event-driven benefit of adding bosentan to sildenafil. AMBITION [galie2015ambition] demonstrated superiority of initial combination ambrisentan + tadalafil vs monotherapy, class precedent for upfront combination PDE5i + ERA. SERAPH [wilkins2005seraph] was an early head-to-head of sildenafil vs bosentan.

Branded product: Revatio and generic sildenafil

Heart failure with preserved or reduced ejection fraction WELL STUDIED

Studied but not FDA-approved; multicenter HFpEF evidence is negative.

Single-center HFrEF and HFpEF trials with secondary pulmonary hypertension [bocchi2002hf] reported short-term improvements in exercise capacity and pulmonary hemodynamics [lewis2007hf; guazzi2011hfpef]. The multicenter RELAX trial in unselected HFpEF [redfield2013relax] was negative for the primary endpoint of peak VO2; the Borlaug 2015 ancillary analysis confirmed no benefit on ventricular or vascular function [borlaug2015relax]. Current guidance does not support routine sildenafil for HFpEF.

Persistent pulmonary hypertension of the newborn (PPHN) EMERGING

Off-label in many settings; off-label in centers without iNO/ECMO; multicenter trial of IV sildenafil added to iNO is negative for accelerated weaning.

Baquero 2006 (Pediatrics) pilot RCT in 13 neonates without iNO/ECMO availability showed oxygenation improvement and survival benefit with oral sildenafil [baquero2006pphn]. The Pierce 2021 multicenter trial (J Pediatr, N=59) of IV sildenafil added to inhaled NO did not significantly accelerate iNO weaning or reduce treatment failure but established acceptable safety [pierce2021iv]. Use is restricted to PPHN-experienced centers.

Off-Label Uses of Compounded Sildenafil

Raynaud phenomenon WELL STUDIED

Off-label use with small RCT support; appropriate as a clinician-directed trial in patients with severe disease resistant to standard vasodilators.

See clinical context above [fries2005raynaud]. Off-label use is established in rheumatology practice for severe or refractory cases.

High-altitude pulmonary hypertension / exercise capacity EMERGING

Off-label, exploratory. Evidence is mechanistic and short-term.

Ghofrani 2004 demonstrated short-term exercise-capacity improvement under hypoxia, but routine prophylactic use for altitude illness is not established [ghofrani2004altitude].

Female sexual arousal disorder EMERGING

Off-label for oral sildenafil; topical 3.6% cream is investigational.

Small RCTs [caruso2001fsad] suggested modest oral effects; recent work [thurman2024sildenafilcream] is evaluating a 3.6% topical cream formulation [caruso2006fsadt1d].

FDA-Approved Uses of Compounded Sildenafil

Brand	Indication	Year	Route
Viagra	Erectile dysfunction in adult men	1998	Oral tablet (25 mg, 50 mg, 100 mg)
Revatio	Pulmonary arterial hypertension (WHO Group 1) to improve exercise ability and delay clinical worsening, adults	2005	Oral tablet (20 mg), oral suspension, intravenous

Brand	Indication	Year	Route
Revatio (pediatric oral suspension)	Pediatric PAH dosing in children 1, 17 years (with FDA labeling caution against chronic use of higher doses based on STARTS-2 mortality signal)	—	Oral suspension

Viagra (sildenafil citrate, 25/50/100 mg oral tablets) was FDA-approved March 27, 1998 for erectile dysfunction in adult men [goldstein1998]. Approval was supported by the Goldstein 1998 NEJM trial and a broader phase III program in 3,000+ men. Generic sildenafil citrate tablets are widely available since US patent expiry.

Revatio (sildenafil citrate, 20 mg oral tablet TID; oral suspension; intravenous) was FDA-approved June 3, 2005 for pulmonary arterial hypertension in adults, on the basis of SUPER-1 [galie2005super] with extension support from SUPER-2 [rubin2011super2] [barst2012starts1; fda_label_viagra; fda_label_revatio]. A pediatric oral suspension was subsequently labeled, with an FDA caution following STARTS-2 [barst2014starts2] regarding chronic high-dose use in children.

The label carries an absolute contraindication with nitrates (any form, any indication, risk of life-threatening hypotension) and with the soluble guanylate cyclase stimulator riociguat. Cardiovascular caution applies to alpha-blocker co-administration and to severe baseline hypotension or unstable cardiovascular disease [cheitlin1999accaha].

Compounded Compounded Sildenafil (503A)

Generic sildenafil citrate tablets are commercially available at low cost in all FDA-approved strengths (25/50/100 mg for Viagra-equivalent; 20 mg for Revatio-equivalent), and Revatio is available as a manufactured oral suspension for pediatric weight-banded dosing [saeyoon2015compoundedsuspension]. RonanRx dispenses compounded sildenafil under 503A only when the prescribing clinician documents a patient-specific clinical reason that the manufactured product cannot meet.

Legitimate compounded use cases include: (1) sublingual troches or rapid-dissolve preparations for patients who require faster onset than the oral tablet, who have swallowing difficulty, or who cannot tolerate the tablet's excipients; (2) custom dose strengths for partial responders who do not benefit from the available manufactured strengths; (3) pediatric oral suspensions when the manufactured Revatio suspension is not appropriate or available; and (4) combination preparations where a single formulation simplifies adherence for a specific patient.

Per FDA guidance for industry on compounding under 503A, a compound that is essentially a copy of a commercially available drug is generally restricted unless the prescriber has determined a clinical difference for the identified patient [fda_essentially_a_copy; fda503a]. Because generic sildenafil tablets are inexpensive and widely available, the bar for compounded sildenafil is the documentation of a specific

clinical need, RonanRx does not fill prescriptions for compounded sildenafil that read as routine substitution for generic Viagra or Revatio.

Compounded Sildenafil Formulations and Routes

Form	Concentration	Description
Sublingual troche (compounded)	Custom (commonly 25, 100 mg per troche)	Slow-dissolve buccal/sublingual matrix designed for partial pre-gastric absorption. Used when patients require faster perceived onset than the oral tablet or cannot use oral tablets. PK profile differs from the manufactured tablet and has not been characterized in head-to-head bioequivalence studies.
Oral capsule (compounded)	Custom strengths (e.g., 10, 15, 35, 60 mg)	Custom-strength capsules for patients who require a dose between or below manufactured tablet strengths. Prepared per USP <795> non-sterile compounding standards.
Oral suspension (compounded, pediatric)	Commonly 2.5 mg/mL or 10 mg/mL	Weight-banded liquid preparation for pediatric PAH dosing when the manufactured Revatio suspension is not appropriate or available. Sae Yoon 2015 published physicochemical and microbiological stability data for an extemporaneously compounded sildenafil citrate oral suspension.
Topical cream (investigational)	3.6% (per Thurman 2024 program)	Topical formulation studied in a phase 3 program for female sexual arousal disorder. Not FDA-approved. Mentioned here as the published literature context; not a routine RonanRx compounded preparation.
Orodispersible film (manufactured / investigational)	50 mg, 100 mg	Manufactured rapid-dissolve oral film studied as a next-generation formulation; reviewed by Jannini 2025. Listed here as the literature reference for comparative formulation discussion; not a RonanRx compounded preparation.

Routes used in published literature: oral, sublingual, troche, intravenous.

Compounded Sildenafil Dosing

Route	Population	Range	Duration	Study type
Oral (tablet)	Adults with erectile dysfunction (FDA-label population)	50 mg approximately 1 hour before sexual activity; adjustable to 25 mg or 100 mg by response and	On-demand	FDA-approved labeled regimen; mirrored by generic sildenafil

Route	Population	Range	Duration	Study type
		tolerability; maximum once daily		
Oral (tablet)	Adults with pulmonary arterial hypertension (FDA-label population)	20 mg three times daily, approximately 4, 6 hours apart	Chronic	FDA-approved labeled regimen based on SUPER-1
Intravenous	Adults with PAH unable to take oral therapy temporarily	10 mg IV three times daily (label-equivalent to 20 mg oral TID)	Bridging while oral route unavailable	FDA-approved labeled regimen
Oral suspension	Pediatric PAH, ages 1, 17 years	Weight-banded per Revatio label; FDA labeling cautions against chronic use of higher doses in children based on STARTS-2	Chronic	FDA-labeled pediatric regimen informed by STARTS-1 and STARTS-2
Oral (tablet)	Adults with severe renal impairment, severe hepatic impairment, or on strong CYP3A4 inhibitors	Reduced starting dose (e.g., 25 mg for ED) and slower up-titration; consult product labeling for indication-specific reductions	Per indication	FDA-label population-specific guidance
Sublingual troche (compounded)	Adults for whom manufactured tablet is not appropriate (per prescriber-documented reason)	Custom strength selected by the prescribing clinician; on-demand or as directed	On-demand or as directed	Compounded formulation under 503A; PK not bioequivalent to manufactured tablet

Doctor-prescribed and titrated. The Viagra label-defined starting dose of 50 mg for ED can be adjusted to 25 or 100 mg by response and tolerability. The Revatio label specifies 20 mg three times daily for adult PAH. Pediatric PAH dosing is weight-banded per the Revatio oral suspension label, with an FDA-mandated caution against chronic use of higher pediatric doses based on STARTS-2 mortality data [barst2014starts2] [nichols2002pk].

Dose reductions are required with strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin), sildenafil exposure can rise multifold [galie2005super; nichols2002pk; cheitlin1999accaha]. Avoid concomitant nitrates absolutely. Caution with alpha-blockers (additive hypotension), particularly within 4 hours of dosing.

Compounded preparations should not exceed the FDA-label maximum daily exposure equivalents in routine prescribing. Sublingual troche dosing requires clinical judgment because the PK is not bioequivalent to the oral tablet [goldstein1998].

Compounded Sildenafil Safety

Sildenafil's safety profile is one of the most extensively characterized in modern pharmacology, with thousands of trial-years across ED and PAH indications and 25+ years of post-marketing surveillance [16]. Modern syntheses include Wang 2024 (FAERS pharmacovigilance), Soulaidopoulos 2024 (long-term cardiovascular outcomes meta-analysis), and Tsertsvadze 2009 (AHRQ harms meta-analysis) [8972 49]. Common adverse events are headache, flushing, dyspepsia, nasal congestion, mild visual disturbance (blue-tinged vision, increased light sensitivity, attributable to weak PDE6 cross-inhibition characterized by Marmor's ERG work [Zoumalan 2009] and reviewed by Laties 2009), and back pain [4041 95]. The majority are mild to moderate and dose-related.

Serious but rare adverse events: nonarteritic anterior ischemic optic neuropathy (NAION), Pomeranz 2005 (case series), Pomeranz 2017 (review), case-control work by McGwin 2006, Gorkin 2006, and Margo 2007, claims-database cohort by Etminan 2022, and meta-analysis by Penedones 2020 [501314]. Patients with small optic disc cup-to-disc ratio, hypertension, diabetes, or hypercholesterolemia are at higher baseline risk [444345]. Sudden sensorineural hearing loss, case-series by Khan 2011, mechanistic hypothesis by Maddox 2009, population cohort by Liu 2018, and FAERS analyses by Barreto 2013, Zhang 2024, and Luo 2025 [154748]. Priapism (erection >4 hours) is rare and requires emergent urologic evaluation; paradoxically, long-term low-dose oral PDE5 inhibition has been used to alleviate recurrent stuttering priapism in selected patients [92].

Cardiovascular safety is dominated by the absolute nitrate contraindication. Sildenafil-nitrate coadministration produces profound additive hypotension that can be fatal, characterized hemodynamically by Webb 1999, Webb 2000, Oliver/Webb 2009 (time-course), and Parker 2007 (8-hour washout supports IV nitroglycerin safety in coronary disease) [3233]. The ACC/AHA expert consensus document [10] codified the contraindication and the alpha-blocker caution (quantified by Kloner 2004 in healthy normotensives) [91]. Subsequent updates (Padma-Nathan 2002 4-year safety, Jackson 2006 updated perspective, Soulaidopoulos 2024 long-term meta) confirmed an acceptable-to-favorable cardiovascular profile in patients without contraindications [1211]. Vlachopoulos 2004 even demonstrated acute reversal of smoking-induced endothelial dysfunction [90 4246]. In pregnancy, the Pels 2023 Cochrane review and the discontinued Dutch STRIDER trial argued against routine antenatal sildenafil for fetal growth restriction following an adverse-events signal [303166].

Contraindications

Absolute contraindications: concomitant use of any nitrate in any form (organic nitrate, nitrite, nitric oxide donor; for cardiac, recreational, or other indication), risk of life-threatening additive hypotension;

concomitant use of riociguat (soluble guanylate cyclase stimulator); known hypersensitivity to sildenafil or excipients [10].

Relative contraindications and cautions: severe baseline hypotension; unstable angina or recent myocardial infarction; severe hepatic impairment; severe renal impairment (initial dose reduction); concomitant strong CYP3A4 inhibitors (dose reduction); concomitant alpha-blocker therapy (initiate at lowest sildenafil dose, separate dosing by ~4 hours); known history of NAION (relative contraindication, the second eye is at risk); known retinitis pigmentosa (theoretical concern via PDE6) [1011].

Pediatric PAH: FDA labeling cautions against chronic use of higher doses in children based on the STARTS-2 mortality signal [8 14].

Drug interactions

Absolute interaction: nitrates and nitric-oxide donors in any form, additive cGMP accumulation and profound hypotension. Includes nitroglycerin, isosorbide mono- and dinitrate, amyl nitrite (poppers), and sodium nitroprusside. Webb 1999 and Webb 2000 quantified the additive hypotensive effect with organic nitrate and NO donors respectively; Oliver/Webb 2009 showed that the interaction is most severe within 4 hours of sildenafil and substantially attenuated by 8 hours, and Parker 2007 demonstrated that IV nitroglycerin can be safely administered to men with coronary disease at least 8 hours after sildenafil, basis for the conservative 24-hour washout convention [103031]. Riociguat (a soluble guanylate cyclase stimulator) is similarly contraindicated.

Pharmacokinetic interactions: sildenafil is metabolized predominantly by CYP3A4 (major pathway) with minor contribution from CYP2C9 [9 32]. Strong CYP3A4 inhibitors substantially elevate exposure, ritonavir/saquinavir produces ~11-fold AUC increase [82]; erythromycin and azithromycin produce smaller but clinically meaningful increases (Muirhead 2002 erythromycin/azithromycin study) [81]. Dose reductions are required (e.g., starting dose 25 mg with ritonavir, lower limits in PAH). Strong CYP3A4 inducers (rifampin, carbamazepine, St John's wort) reduce sildenafil exposure [33].

Pharmacodynamic interactions: alpha-blockers (doxazosin, tamsulosin) produce additive hypotension, Kloner 2004 quantified the interaction in healthy normotensive men [91]. Sildenafil should be initiated at the lowest dose with established alpha-blocker therapy, ideally with at least 4 hours separation [1193]. Antihypertensives in general produce a small additive blood-pressure effect that is usually clinically tolerable.

Wang 2024 FAERS pharmacovigilance analysis and Soulaidopoulos 2024 long-term outcomes meta-analysis summarize real-world post-marketing interaction signals [1689].

Adverse events

Common (>5%): headache (incidence ~16% in ED trials), flushing (~10%), dyspepsia (~7%), nasal congestion (~4, 10%), visual disturbance (blue tinge, light sensitivity, dose-related, ~3, 11% at 100 mg),

back pain, myalgia. Most are mild to moderate and resolve with drug clearance over 4, 8 hours [30]. The Tsertsvadze 2009 AHRQ harms meta-analysis pooled the AE landscape across class [72].

Rare but serious: nonarteritic anterior ischemic optic neuropathy (NAION) [42434 6]. Pomeranz 2005 reported a case series of seven patients developing NAION soon after sildenafil use [13 31]. Case-control and cohort follow-ups [44] and the modern claims-database cohort [45] consistently identified a small but real signal, summarized in the Penedones 2020 meta-analysis [95]. Patients with small optic disc cup-to-disc ratio, hypertension, diabetes, or hyperlipidemia have higher baseline NAION risk [14]. Vision biology is grounded in PDE6 cross-inhibition characterized by the Marmor group (Zoumalan 2009 ERG study) and reviewed by Laties 2009 [4041 12].

Sudden sensorineural hearing loss (often unilateral) has been reported as a post-marketing signal across all PDE5 inhibitors [474849]. Case-series by Khan 2011 popularized the 'Viagra deafness' label; Maddox 2009 proposed a cellular-stress etiology; Liu 2018 produced the strongest population-cohort evidence (Taiwan NHI), and modern FAERS analyses [15] confirm the disproportionality signal at the class level [50].

Priapism (erection >4 hours) is rare and requires emergent urologic evaluation. Burnett 2006 reported the paradoxical use of low-dose long-term oral PDE5 inhibition to alleviate recurrent stuttering priapism in selected sickle-cell and other susceptible men [92].

Cardiovascular: sildenafil produces a small (~8/5 mmHg) transient blood-pressure reduction at therapeutic doses [9]; clinically important hypotension is uncommon in patients without contraindications [11]. Modern long-term outcomes meta-analysis [89] suggests neutral-to-favorable cardiovascular signal. Real-world FAERS pharmacovigilance [16] catalogs the post-marketing AE landscape.

↗ Monitoring Compounded Sildenafil Therapy

ED indication: no routine laboratory monitoring is required for healthy adult men starting sildenafil [galie2005super]. Cardiovascular risk should be screened at baseline (per the Princeton consensus framework, patients with active cardiac symptoms should be evaluated before sexual activity is resumed) [jackson2006cvsafety]. Re-assess response at 4, 6 weeks; adjust dose by response and tolerability.

PAH indication: baseline and on-therapy monitoring includes 6-minute walk distance, WHO functional class, BNP/NT-proBNP, echocardiogram, and (per center practice) periodic right-heart catheterization. Liver function should be checked if hepatic impairment is suspected.

Patients should be counseled to seek prompt evaluation for sudden visual change (NAION risk), sudden hearing loss, or erection lasting more than 4 hours [pomeranz2017naion].

Compounded Sildenafil in Special Populations

Compounded Sildenafil Evidence Quality

Evidence for the manufactured products is strong [boulton2001diabetes; hultling2000sci; wagner2001elderly]. ED indication: Goldstein 1998 (NEJM, N=532) plus the broader phase III program [goldstein1999openlabel] [goldstein1998; caruso2006fsadt1d]. Adult PAH indication: SUPER-1 [galie2005super] and SUPER-2 extension [rubin2011super2], with class-extension data from SERAPH [wilkins2005seraph], PHIRST [galie2009phirst], AMBITION [galie2015ambition], and combination trials PACES [simonneau2008paces], COMPASS-1 [gruenig2009compass1], and COMPASS-2 [mclaughlin2015compass2]. Severe PAH including Eisenmenger physiology: Singh 2006 [liao2019diabetes; singh2006eisenmenger; bocchi2002hf]. Pediatric PAH: STARTS-1 [barst2012starts1] and STARTS-2 [barst2014starts2] [etminan2022ocular]. Neonatal PPHN: Baquero 2006 pilot and Pierce 2021 multicenter RCT [guazzi2011hfpef; borlaug2015relax; margo2007naion]. Twenty-five-plus years of post-marketing surveillance (Padma-Nathan 2002 4-year update; Jackson 2006; Wang 2024 FAERS; Soulaidopoulos 2024 long-term CV meta-analysis) confirm the cardiovascular safety profile when contraindications are observed and characterize the rare-event landscape (NAION, Pomeranz 2005/2017, McGwin 2006, Gorkin 2006, Margo 2007, Etminan 2022, Penedones 2020 meta; sudden hearing loss, Barreto 2013, Maddox 2009, Khan 2011, Liu 2018, Zhang 2024, Luo 2025; priapism, Burnett 2006) [padmanathan2002safety; jackson2006cvsafety; soulaidopoulos2024cvmeta].

Class-level network meta-analyses (Tsertsvadze 2009 AHRQ Ann Intern Med, Yuan 2013 European Urology, Liao 2019 in diabetic ED) confirm broadly comparable within-class efficacy of PDE5 inhibitors [penedones2020naion; barreto2013hearing; maddox2009hearing]. Heart-failure evidence is mixed: Bocchi 2002, Lewis 2007, and Guazzi 2011 reported single-center benefit in HFrEF/HFpEF with secondary pulmonary hypertension, but the multicenter RELAX trial [redfield2013relax] and the Borlaug 2015 ventricular-function ancillary analysis were negative in unselected HFpEF, argues against routine sildenafil for HFpEF [baquero2006pphn; pierce2021iv].

Off-label evidence is heterogeneous [wang2024faers; pomeranz2005naion; gorkin2006naion]. Raynaud phenomenon has RCT support [fries2005raynaud] plus meta-analysis [roustit2013raynaud], clinically useful as a second-line option [khouri2019raynaud]. Altitude exercise capacity has crossover RCT support [ghofrani2004altitude] with class confirmation from Maggiorini 2006 (tadalafil/dexamethasone HAPE prevention) [maggiorini2006hape] [lewis2007hf]. Female sexual arousal disorder has small placebo-controlled trials of oral sildenafil [caruso2001fsad] and a recent topical-cream phase 3 program [thurman2024sildenafilcream], evidence remains preliminary in all cases [burnett2006priapism]. Pregnancy: the Pels 2023 Cochrane review and the discontinued Dutch STRIDER trial argue against antenatal sildenafil for fetal growth restriction [pels2023strider] [luo2025hearing; yuan2013network].

Evidence specifically supporting compounded preparations is limited [basson2003fsad; berman2003fsad; rendell1999diabetes]. Sae Yoon 2015, Nahata 2016, and Cheung 2021 published physicochemical stability data for compounded oral suspensions and rapid-dissolving tablets respectively [saeyoon2015compoundedsuspension; nahata2016suspension; cheung2021stability]. PK data for the manufactured orodispersible tablet [damle2014odt] and a novel taste-masked ODF [mewada2024odf] are the closest comparator literature for compounded rapid-onset forms, though compounded troches and ODFs are not bioequivalent to either the manufactured tablet or the manufactured ODT [tsertsvadze2009review]. There is no parallel efficacy program for compounded troches, custom-strength capsules, or topical preparations; compounded use is therefore an extrapolation from the manufactured-product evidence base, justified case by case by patient-specific clinical factors [khan2011hearing; liu2018hearing; zhang2024hearing]. Counterfeit and Internet-sourced sildenafil shows substantial API and impurity variability [veronin2014quality], arguing for licensed-pharmacy sourcing [pomeranz2017naion; mcgwin2006naion; venhuis2014counterfeit].

Major Compounded Sildenafil Clinical Studies

Study	Design	Participants	Duration	Finding
Goldstein 1998, Oral sildenafil in the treatment of erectile dysfunction (NEJM)	Multicenter randomized double-blind placebo-controlled	532	24 weeks	Sildenafil 25/50/100 mg produced dose-dependent improvement in erectile function (IIEF Q3 and Q4) and successful intercourse attempts (69% vs 22% placebo at 100 mg); foundational evidence for FDA approval of Viagra [goldstein1998].
Boolell 1996, Sildenafil PDE5 mechanism (Int J Impot Res) and first clinical erectogenic data (Br J Urol)	Mechanistic + early clinical	—	Early-phase	Established sildenafil as an orally active, selective PDE5 inhibitor and reported its erectogenic effect in men, motivating the phase III program [boolell1996pde5; boolell1996bju].
SUPER-1 (Galiè 2005, NEJM)	Phase III randomized double-blind placebo-controlled	278	12 weeks	Sildenafil 20/40/80 mg TID improved 6-minute walk distance by 45, 50 m placebo-adjusted in adults with PAH (WHO Group 1, FC II, IV); supported FDA approval of Revatio [galie2005super].
SUPER-2 (Rubin 2011, Chest)	Open-label long-term extension	259 (of SUPER-1	Up to 3 years	Sustained walk-distance benefit and acceptable tolerability with long-term

Study	Design	Participants	Duration	Finding
		enrollees continuing)		sildenafil monotherapy in adult PAH [rubin2011super2].
STARTS-1 (Barst 2012, Circulation)	Randomized double-blind placebo-controlled dose-ranging	235	16 weeks	Oral sildenafil at low, medium, and high weight-banded doses improved exercise capacity and hemodynamics in treatment-naive children 1, 17 years old with PAH [barst2012starts1].
STARTS-2 (Barst 2014, Circulation)	Long-term extension of STARTS-1	234	Up to ~7 years	Long-term survival data showed higher mortality at the highest weight-banded dose vs lower doses, prompting FDA pediatric labeling caution against chronic high-dose use [barst2014starts2].
Nichols 2002 (Br J Clin Pharmacol)	Single-dose human PK	Healthy male volunteers	Single dose	Absolute oral bioavailability ~41%, Tmax ~1 h fasting, dose proportionality across studied range, food (especially high-fat meal) delays absorption [nichols2002pk].
Fries 2005 (Circulation), Sildenafil for Raynaud phenomenon	Randomized double-blind placebo-controlled crossover	16	4 weeks per arm	Sildenafil 50 mg BID reduced attack frequency and cumulative duration vs placebo in patients with Raynaud refractory to standard vasodilators [fries2005raynaud].
Ghofrani 2004 (Ann Intern Med), Sildenafil at altitude	Randomized double-blind placebo-controlled crossover	14	Single dose under hypoxia and at Mt. Everest base camp	Sildenafil 40/80 mg improved exercise capacity and reduced pulmonary vascular resistance under hypoxia [ghofrani2004altitude].
Caruso 2001 (BJOG) and Caruso 2006 (Fertil Steril), Sildenafil for female sexual arousal disorder	Randomized double-blind placebo-controlled crossover	varied (small)	weeks	Modest improvements in arousal-domain measures with oral sildenafil vs placebo in premenopausal women with FSAD; trial sizes are small and the FDA has not approved sildenafil for FSAD [caruso2001fsad; caruso2006fsadt1d].
Thurman 2024 (J Sex Med), Topical	Randomized placebo-	Phase 3 safety population	12 weeks	Demonstrated safety profile of 3.6% topical sildenafil cream in women with

Study	Design	Participants	Duration	Finding
3.6% sildenafil cream for FSAD safety	controlled phase 3 safety study			FSAD; efficacy reported in companion papers [thurman2024sildenafilcream]. Not FDA-approved.
Wang 2024 (Andrology), FAERS pharmacovigilance analysis	Disproportionality analysis of FDA Adverse Event Reporting System	—	Cumulative post-marketing	Catalogs real-world AE signals for sildenafil including cardiovascular, ocular, otologic, and priapism events; consistent with the established label [wang2024faers].
Padma-Nathan 2008 (Int J Impot Res), Nightly sildenafil for post-prostatectomy rehabilitation	Randomized double-blind placebo-controlled	76	36 weeks treatment, post-treatment evaluation	Nightly sildenafil 50 or 100 mg improved spontaneous erectile function vs placebo after bilateral nerve-sparing radical prostatectomy [padmanathan2008rehab].
Sae Yoon 2015 (Sci Pharm), Compounded sildenafil oral suspension stability	Physicochemical and microbiological stability study	—	Up to 90 days	Established stability parameters for an extemporaneously compounded sildenafil citrate oral suspension; supports pharmacy-prepared pediatric liquid use [saeyoon2015compoundedsuspension].
Ghofrani 2006 (Nat Rev Drug Discov), Sildenafil from angina to ED to PAH	Comprehensive narrative review	—	N/A	Reviews the discovery program, mechanism, clinical-development trajectory across indications, and the cardiovascular safety framework [ghofrani2006].
Rendell 1999 (JAMA), Sildenafil for erectile dysfunction in diabetic men	Multicenter randomized double-blind placebo-controlled	268	12 weeks	Successful intercourse rates 56% on sildenafil vs 10% on placebo in men with diabetes-related ED; foundational evidence for routine ED treatment in this difficult-to-treat subgroup [rendell1999diabetes].
Hultling 2000 (Spinal Cord), Sildenafil for ED in spinal cord injury	Multicenter randomized double-blind placebo-controlled	178	Crossover and open-label extension	Significant improvement in successful intercourse and QoL endpoints with sildenafil in men with spinal cord injury [hultling2000sci].
Boulton 2001 (Diabetologia),	Multicenter randomized	219	12 weeks	Sildenafil produced significant improvement in IIEF erectile function

Study	Design	Participants	Duration	Finding
Sildenafil in T2DM-related ED	double-blind placebo-controlled			vs placebo in men with type 2 diabetes; safety profile comparable to general ED trials [boulton2001diabetes].
Webb 1999/2000 (Am J Cardiol; JACC), Sildenafil, nitrate hemodynamic interaction studies	Controlled crossover human PK/PD studies	—	Single dose	Sildenafil substantially potentiates the hypotensive effects of organic nitrates and NO donors; basis for the absolute nitrate contraindication [webb1999nitrate; webb2000nitrate].
Oliver 2009 (Br J Clin Pharmacol), Time-dependent sildenafil, GTN interaction	Double-blind randomized human crossover	—	Single dose with time-staggered nitrate	The blood-pressure interaction is most severe within 4 hours of sildenafil dosing and is substantially attenuated by 8 hours, basis for the 24-hour washout convention [oliver2009nitrate].
Kloner 2004 (J Urol), PDE5 inhibitor + alpha-blocker interaction	Randomized double-blind placebo-controlled crossover in healthy normotensive men	—	Single dose	Quantifies the additive hypotensive effect of PDE5 inhibition added to doxazosin or tamsulosin; informs label-recommended dose-staggering of PDE5i with alpha-blockers [kloner2004alpha].
Singh 2006 (Am Heart J), Sildenafil in severe PAH including Eisenmenger physiology	Randomized placebo-controlled double-blind crossover	20	6 weeks each phase	Oral sildenafil improved 6-minute walk distance and reduced pulmonary vascular resistance vs placebo in severe PAH [singh2006eisenmenger].
Wilkins 2005 (Am J Respir Crit Care Med), SERAPH (sildenafil vs bosentan)	Open-label randomized comparator	26	16 weeks	Sildenafil and bosentan produced broadly comparable improvements in exercise capacity and hemodynamics in adult PAH; sildenafil reduced right-ventricular mass on cardiac MRI [wilkins2005seraph].
Simonneau 2008 (Ann Intern Med), PACES (sildenafil	Randomized double-blind	267	16 weeks	Adding sildenafil to long-term IV epoprostenol significantly improved 6MWD, hemodynamics, and time-to-

Study	Design	Participants	Duration	Finding
added to epoprostenol)	placebo-controlled			clinical-worsening in adult PAH [simonneau2008paces].
McLaughlin 2015 (Eur Respir J), COMPASS-2 (bosentan added to sildenafil)	Event-driven randomized double-blind placebo-controlled	334	Median ~3 years	Adding bosentan to sildenafil did not significantly reduce time to first morbidity/mortality event vs sildenafil alone, informs combination-therapy sequencing [mclaughlin2015compass2].
Galiè 2015 (NEJM), AMBITION	Randomized double-blind active-comparator	500	Event-driven (median ~520 days)	Initial combination of ambrisentan + tadalafil reduced clinical-failure events vs monotherapy with either drug, class-level evidence for upfront combination PDE5i + ERA strategy that informs sildenafil practice [galie2015ambition].
Galiè 2009 (Circulation), PHIRST tadalafil in PAH	Phase III randomized double-blind placebo-controlled	405	16 weeks	Tadalafil 40 mg daily improved 6MWD and time-to-clinical-worsening, establishes class-level PDE5-inhibitor labeling for PAH [galie2009phirst].
Maggiorini 2006 (Ann Intern Med), Tadalafil/ dexamethasone HAPE prevention	Randomized double-blind placebo-controlled	29	Rapid ascent to 4,559 m	Both tadalafil and dexamethasone reduced HAPE incidence vs placebo, class-level support for PDE5 inhibition in altitude pulmonary edema, consistent with sildenafil data from Ghofrani 2004 [maggiorini2006hape].
Baquero 2006 (Pediatrics), Sildenafil in PPHN	Pilot randomized blinded	13	Up to 72 h	Oral sildenafil improved oxygenation and survival vs placebo in neonates with PPHN where inhaled NO and ECMO were unavailable [baquero2006pphn].
Pierce 2021 (J Pediatr), IV sildenafil for PPHN (SPED-3)	Multicenter randomized double-blind placebo-controlled	59	Up to 14 days	IV sildenafil added to inhaled NO did not significantly accelerate iNO weaning or reduce treatment failure in neonates with PPHN; safety was acceptable [pierce2021iv].
Bocchi 2002 (Circulation), Sildenafil in	Double-blind placebo-	23	Single dose plus open-	Sildenafil improved exercise capacity and reduced sympathoneural activation in advanced CHF;

Study	Design	Participants	Duration	Finding
advanced systolic heart failure	controlled randomized		label extension	foundational signal motivating subsequent HF programs [bocchi2002hf].
Lewis 2007 (Circulation), Sildenafil in systolic HF with secondary PH	Randomized double-blind placebo-controlled	34	12 weeks	Sildenafil 50 mg TID improved peak VO2, 6MWD, and QoL in HFrEF with pulmonary hypertension [lewis2007hf].
Guazzi 2011 (Circulation), 1-year sildenafil in HFpEF with PH	Randomized double-blind placebo-controlled	44	12 months	Long-term sildenafil improved pulmonary hemodynamics, RV function, and exercise capacity in HFpEF with pulmonary hypertension, single-center, contrasts with multicenter RELAX [guazzi2011hfpef].
Redfield 2013 (JAMA), RELAX in HFpEF	Multicenter randomized double-blind placebo-controlled	216	24 weeks	Sildenafil did not improve exercise capacity or clinical status vs placebo in unselected HFpEF; argues against routine PDE5 inhibition in this population [redfield2013relax]. Borlaug 2015 ancillary analysis confirmed no benefit on ventricular or vascular function [borlaug2015relax].
Etminan 2022 (JAMA Ophthalmol), Ocular AE cohort in US men	Retrospective claims-database cohort	213,033 PDE5i users	Up to 7 years	PDE5 inhibitor use was associated with an increased rate of serous retinal detachment, retinal vascular occlusion, and ischemic optic neuropathy vs non-users, incident rate ~15.5 per 10,000 person-years for any of the three combined [etminan2022ocular].
Penedones 2020 (Acta Ophthalmol), NAION systematic review and meta-analysis	Systematic review and meta-analysis of observational studies	—	Cumulative	Significantly increased risk of NAION with PDE5 inhibitor use (pooled OR consistent across studies), particularly in men with predisposing optic-disc anatomy or vascular risk factors [penedones2020naion].
Liu 2018 (Pharmacoepidemiol Drug Saf), PDE5	Population-based cohort (Taiwan NHI)	>25,000 users	5-year follow-up	Increased adjusted hazard of sudden sensorineural hearing loss in PDE5-inhibitor users vs matched non-users;

Study	Design	Participants	Duration	Finding
inhibitors and SSNHL cohort				consistent with FAERS analyses by Zhang 2024 and Luo 2025 [liu2018hearing; zhang2024hearing; luo2025hearing].
Soulaidopoulos 2024 (Eur Heart J Cardiovasc Pharmacother), Long-term CV outcomes meta-analysis	Systematic review and meta-analysis of long-term PDE5-inhibitor studies	—	Cumulative	PDE5 inhibitor use was associated with reduced cardiovascular events and all-cause mortality vs non-use across pooled analyses; supports neutral-to-favorable CV profile in patients without absolute contraindications [soulaidopoulos2024cvmeta].
Tsertsvadze 2009 (Ann Intern Med + Urology), AHRQ systematic review and harms meta-analysis	Systematic review and meta-analysis	—	Cumulative	Confirms efficacy of oral PDE5 inhibitors across populations; characterizes harm profile including headache, flushing, dyspepsia, visual disturbance, and serious-but-rare AEs [tsertsvadze2009review; tsertsvadze2009harms].
Yuan 2013 (Eur Urol), PDE5 inhibitor network meta-analysis for ED	Network meta-analysis	82 RCTs, 47,626 men	Cumulative	Sildenafil, tadalafil, vardenafil, avanafil, and udenafil produce comparable efficacy with distinct PK and AE profiles, informs class selection rather than within-class [yuan2013network].
Liao 2019 (World J Urol), PDE5 inhibitors in diabetic ED network meta-analysis	Bayesian network meta-analysis of RCTs	—	Cumulative	All PDE5 inhibitors improved IIEF and intercourse success vs placebo in diabetic men, with broadly comparable within-class efficacy [liao2019diabetes].
Roustit 2013 / Khouri 2019, Secondary Raynaud meta-analyses	Systematic review and meta-analysis (Roustit); network meta-analysis (Khouri)	—	Cumulative	PDE5 inhibitors reduce attack frequency and duration in secondary Raynaud phenomenon; effect sizes are modest and clinically useful as a second-line option after standard vasodilators [roustit2013raynaud; khouri2019raynaud].
Pels 2023 (Cochrane), NO-	Cochrane systematic review	—	Cumulative	Sildenafil and other NO-pathway interventions did not improve perinatal

Study	Design	Participants	Duration	Finding
pathway interventions for fetal growth restriction				mortality or morbidity in pregnancies with fetal growth restriction; the Dutch STRIDER trial was halted early for safety signal, current recommendation is against routine antenatal sildenafil for FGR [pels2023strider].
Muirhead 2002 (Br J Clin Pharmacol), Age, renal, hepatic PK	Open-label PK in healthy and impaired-organ-function adults	—	Single dose	Sildenafil clearance is reduced ~50% in adults >65, in severe renal impairment (CrCl <30 mL/min), and in moderate hepatic impairment, quantitative basis for label starting-dose reductions [muirhead2002impaired].
Muirhead 2000 / 2002 (Br J Clin Pharmacol), CYP3A4 interaction studies	Open-label PK with strong/ moderate CYP3A4 inhibitors	—	Steady-state	Ritonavir/saquinavir and erythromycin substantially elevate sildenafil exposure (multifold AUC increase with ritonavir); foundation for label dose reduction with strong CYP3A4 inhibitors [muirhead2000ritonavir; muirhead2002erythromycin].
Damle 2014 / Mewada 2024, Sildenafil orodispersible tablet/film PK	PK / bioequivalence studies	—	Single dose	Manufactured ODT (Damle) is bioequivalent to the conventional tablet; novel taste-masked ODF (Mewada) improves measured bioavailability, pharmacy context for the rapid-dissolve form [damle2014odt; mewada2024odf].
Nahata 2016 / Cheung 2021, Compounded sildenafil stability	Physicochemical stability studies	—	Up to 91 days	Nahata characterized extended stability of oral sildenafil for infants/ young children; Cheung reported stability of compounded sildenafil 100 mg rapid-dissolving tablets, pharmacy-grade BUDs supported by data [nahata2016suspension; cheung2021stability].
Veronin 2014 / Venhuis 2014, Internet-sourced and counterfeit sildenafil quality	Analytical chemistry of marketed samples	—	N/A	Internet-sourced and counterfeit sildenafil products show substantial dose-to-dose API variability and impurity content; argues for licensed-pharmacy sourcing of compounded

Study	Design	Participants	Duration	Finding
				preparations [veronin2014quality; venhuis2014counterfeit].

Compounded Sildenafil Pharmacokinetics & Pharmacodynamics

Pharmacokinetics

Oral sildenafil is rapidly absorbed. Tmax is approximately 60 minutes in the fasted state; absolute oral bioavailability is approximately 41% due to first-pass metabolism [nichols2002pk]. A high-fat meal delays Tmax by about 1 hour and reduces Cmax by ~29% but does not meaningfully change AUC. Mehrotra 2007 reviewed PK/PD across the PDE5 inhibitor class with attention to onset, duration, and food effects [mehrotra2007role].

Sildenafil is metabolized predominantly by hepatic CYP3A4, with minor contribution from CYP2C9, to an active N-desmethyl metabolite (UK-103,320) that has ~50% the in-vitro PDE5 potency of parent and ~20% of plasma exposure, meaning the metabolite contributes meaningfully to net pharmacodynamics. Terminal half-life is approximately 3, 4 hours for both parent and metabolite. Clearance is reduced ~50% in adults >65, in severe renal impairment (CrCl <30 mL/min), and in moderate hepatic impairment (Muirhead 2002 age/renal/hepatic study), dose reductions are required in each [muirhead2002impaired]. Ritonavir/saquinavir produces ~11-fold AUC increase [muirhead2000ritonavir], and erythromycin/azithromycin produce smaller but clinically meaningful increases (Muirhead 2002) [muirhead2002erythromycin].

Manufactured orodispersible tablet PK has been formally characterized: Damle 2014 reported bioequivalence of a novel ODT to the conventional film-coated tablet [damle2014odt]. Mewada 2024 reported a taste-masked orodispersible film with improved measured bioavailability vs comparator film [mewada2024odf]. Jannini 2025 reviews the ODF landscape for ED.

Compounded sublingual troches and oral suspensions are not bioequivalent to the manufactured oral tablet or to the manufactured ODT. Sublingual partial pre-gastric absorption may produce a faster perceived onset but has not been characterized in head-to-head bioequivalence studies. Compounded oral suspensions have published stability data (Sae Yoon 2015, Nahata 2016) and rapid-dissolving compounded tablets have stability data from Cheung 2021, but PK should be assumed similar to (not identical to) the manufactured Revatio oral suspension [saeyoon2015compoundedsuspension; nahata2016suspension; cheung2021stability]. Counterfeit and Internet-sourced sildenafil shows substantial API/impurity variability [veronin2014quality], additional argument for licensed-pharmacy sourcing [jannini2025odf; venhuis2014counterfeit].

Pharmacodynamics

Pharmacodynamic effect requires upstream NO release. In the corpus cavernosum, this means sexual stimulation must occur for sildenafil to produce an erection. In the pulmonary vasculature, sildenafil reduces vascular resistance via amplification of endogenous NO-driven cGMP signaling, onset over hours acutely, with longer-term hemodynamic remodeling over weeks of chronic dosing [jackson2006cvsafety; galie2005super].

Systemic hemodynamic effect at therapeutic doses is modest: a small transient reduction in blood pressure (~8/5 mmHg) is typical in healthy adults [nichols2002pk]. Reflex tachycardia is mild. The drug does not have meaningful direct inotropic or chronotropic effect.

↓↑ Comparing Compounded Sildenafil Formulations

The manufactured oral tablet (Viagra, Revatio, and generic equivalents) is the formulation studied in all pivotal ED and adult PAH trials. The manufactured Revatio oral suspension is the formulation labeled for pediatric PAH dosing [saeyoon2015compoundedsuspension].

Compounded sublingual troches differ pharmacokinetically, partial pre-gastric absorption can produce a faster perceived onset, but the route has not been characterized in head-to-head bioequivalence studies and exposure profiles vary by troche base, pH, and patient salivation. Compounded oral suspensions have published stability data (Sae Yoon 2015) but should be assumed similar (not identical) to the manufactured suspension [saeyoon2015compoundedsuspension].

An orally disintegrating film (ODF) formulation is reviewed in Jannini 2025 as a next-generation rapid-onset oral pathway; this is a manufactured formulation context, not a RonanRx compounded preparation [jannini2025odf]. A topical sildenafil cream (3.6%) was studied in a phase 3 program for female sexual arousal disorder [thurman2024sildenafilcream] and is not FDA-approved.

RonanRx-compounded preparations are dispensed only when the manufactured product is not appropriate for the identified patient. The pharmacist review documents the patient-specific clinical reason, and the resulting formulation difference (PK, onset, dose accuracy) is noted on dispensing [nichols2002pk].

🌡 Compounded Sildenafil Storage and Handling

Manufactured sildenafil tablets are stored at controlled room temperature (USP definition: 20, 25 °C, with excursions permitted 15, 30 °C) in tightly closed containers. The manufactured Revatio oral suspension is reconstituted by the dispensing pharmacy per label instructions and is stable for 60 days at room temperature or refrigerated after reconstitution.

Compounded oral capsules, troches, and suspensions are stored per USP <795> beyond-use-date conventions and specific stability data for the formulation. Sae Yoon 2015 characterized stability for an

extemporaneously compounded oral suspension; specific beyond-use dates are set by the dispensing pharmacy based on its formulation record [usp_795; saeyoon2015compoundedsuspension].

Compounded Sildenafil Compounding & Operations

503A compounding

Compounded sildenafil is prepared under 503A on patient-specific prescriptions in state-licensed compounding pharmacies [fda503a; fda_essentially_a_copy]. RonanRx prepares non-sterile oral capsules, sublingual troches, and oral suspensions per USP General Chapter <795>, with documented active-ingredient sourcing (USP/NF grade where available), gravimetric verification, and finished-product quality checks per the pharmacy's quality-management system [usp_795].

Because generic sildenafil tablets are widely available at low cost, the threshold for compounded preparation is the documented patient-specific clinical reason that the manufactured product cannot meet, excipient sensitivity, dose individualization outside available strengths, non-tablet dose form needed (sublingual, liquid), pediatric weight-banding when manufactured suspension is not appropriate, or documented supply gap. RonanRx applies the FDA essentially-a-copy guidance criterion and does not fill prescriptions that read as routine substitution for generic Viagra or Revatio.

Pharmacist review

Each prescription for compounded sildenafil undergoes pharmacist review prior to dispensing. The review confirms: a documented patient-specific clinical reason that the manufactured Viagra/Revatio/generic is not appropriate (excipient sensitivity, dose individualization, non-tablet form needed, pediatric weight-banding, supply gap); absence of absolute contraindications (concomitant nitrate therapy, riociguat use); presence of relative contraindications (alpha-blocker use, strong CYP3A4 inhibitor therapy, severe hepatic or renal impairment, history of NAION) addressed in the prescription; and that the prescribed regimen aligns with label-equivalent dose ceilings where relevant [cheitlin1999accaha].

RonanRx does not fill prescriptions that read as routine substitution of compounded for manufactured product without documented clinical rationale, consistent with FDA guidance on compounded copies of commercially available drugs [fda_essentially_a_copy].

Quality and traceability

Active pharmaceutical ingredient (sildenafil citrate) is sourced from FDA-registered facilities with documented certificates of analysis. Each batch is recorded with lot numbers traceable to API source, compounding date, beyond-use date, and dispensing pharmacist of record. Finished product lot records are retained per state board of pharmacy retention requirements.

Cold chain

Compounded sildenafil oral capsules and troches are not cold-chain products. They are stable at controlled room temperature and shipped in standard pharmacy-grade packaging. Compounded oral suspensions may be refrigerated based on the specific formulation's stability data; patients should follow the dispensing label.

Frequently Asked Questions About Compounded Sildenafil

Is compounded sildenafil the same as Viagra or generic sildenafil tablets?

No. Viagra (and generic sildenafil tablets) are FDA-approved manufactured products with extensive pivotal-trial evidence. Compounded sildenafil is a pharmacy-prepared preparation on a patient-specific prescription and is not bioequivalent to the manufactured tablet [goldstein1998]. Compounded drugs are not FDA-approved [fda503a].

When is a compounded version appropriate?

Per FDA guidance, a compounded version is generally restricted unless the prescriber documents a patient-specific clinical need the manufactured product cannot meet [fda_essentially_a_copy]. Common documented reasons include excipient sensitivity, a non-tablet dose form (sublingual troche or liquid), a dose strength not available commercially, pediatric weight-banding when the manufactured suspension is not appropriate or available, or a documented supply gap. Because generic sildenafil tablets are inexpensive and widely available, the bar is documentation of a specific clinical need.

Can I take sildenafil if I'm on a nitrate?

No, this is an absolute contraindication. Combining sildenafil with any nitrate (nitroglycerin, isosorbide mono- or dinitrate, amyl nitrite/'poppers', sodium nitroprusside) can cause life-threatening low blood pressure. Sildenafil should not be taken within 24 hours of any nitrate, and nitrates should not be started within 24 hours of sildenafil [cheitlin1999accaha; jackson2006cvsafety]. This applies to all PDE5 inhibitors.

How well does sildenafil work for erectile dysfunction?

In the Goldstein 1998 NEJM trial, sildenafil 100 mg produced successful intercourse attempts in 69% of attempts vs 22% on placebo, with mean IIEF erectile-function scores of 22 vs 12 [goldstein1998]. Effect is conditional on sexual stimulation, sildenafil amplifies the body's own nitric-oxide-driven erection signal rather than initiating one independently.

What are the most common side effects?

Headache, flushing, dyspepsia, nasal congestion, mild visual disturbance (blue tinge or increased light sensitivity at higher doses), and back pain. Most are mild to moderate and resolve as the drug clears over a

few hours. Rare but serious adverse events include nonarteritic anterior ischemic optic neuropathy (NAION), sudden hearing loss, and priapism (erection lasting more than 4 hours, which requires emergency urologic evaluation) [pomeranz2017naion; barreto2013hearing; wang2024faers].

What is sildenafil approved for besides erectile dysfunction?

Sildenafil is also FDA-approved as Revatio for pulmonary arterial hypertension (PAH), a serious lung-vascular disease [galie2005super; rubin2011super2; barst2012starts1]. Revatio is available as a 20 mg oral tablet (taken three times daily), an oral suspension (used for pediatric PAH dosing), and an intravenous form [barst2014starts2]. Pivotal evidence comes from the SUPER-1 trial (adults) and the STARTS-1 and STARTS-2 trials (children).

Does RonanRx sell compounded sildenafil directly to patients?

No. Compounded sildenafil requires a patient-specific prescription written by a licensed doctor for an identified patient with a documented clinical reason that the manufactured Viagra, Revatio, or generic sildenafil is not appropriate, plus pharmacist review before dispensing [fda_essentially_a_copy]. RonanRx is not a direct-to-consumer storefront [fda503a].

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Topical Minoxidil — Dermatology
Topical Tretinoin — Dermatology
Compounded Magnesium — Energy & nutritional
Cyanocobalamin — Energy & nutritional
High-Dose Vitamin D — Energy & nutritional
Hydroxocobalamin — Energy & nutritional
Iron (Compounded) — Energy & nutritional
L-Carnitine — Energy & nutritional
Methylcobalamin (B12) — Energy & nutritional
Methylfolate — Energy & nutritional
Anastrozole — Hormone optimization
Clomiphene & Enclomiphene — Hormone optimization
DHEA — Hormone optimization
Estradiol — Hormone optimization
Estriol — Hormone optimization
Human Chorionic Gonadotropin (HCG) — Hormone optimization
Pregnenolone — Hormone optimization
Progesterone — Hormone optimization
Testosterone — Hormone optimization
Compounded Metformin — Metabolic & weight
Compounded Semaglutide — Metabolic & weight
Compounded Tirzepatide — Metabolic & weight
Lipotropic Injection (MIC, MICC) — Metabolic & weight
Low-Dose Naltrexone (LDN) — Metabolic & weight
Naltrexone-Bupropion Combination — Metabolic & weight
Topiramate — Metabolic & weight
Bremelanotide / PT-141 — Sexual health
Compounded Sildenafil — Sexual health
Compounded Tadalafil — Sexual health
Trimix Injection — Sexual health
Compounded Gabapentin — Sleep & recovery
Compounded Melatonin — Sleep & recovery
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Hexarelin — Growth-hormone axis (under FDA review)

Ipamorelin — Growth-hormone axis (under FDA review)

MK-677 / Ibutamoren — Growth-hormone axis (under FDA review)

5-Amino 1MQ — Metabolic & longevity (under FDA review)

Epitalon / Epithalon — Metabolic & longevity (under FDA review)

MOTS-C — Metabolic & longevity (under FDA review)

Thymosin Alpha-1 / Thymalin — Metabolic & longevity (under FDA review)

DSIP, Delta Sleep-Inducing Peptide — Neuro & cognitive (under FDA review)

Selank — Neuro & cognitive (under FDA review)

Semax — Neuro & cognitive (under FDA review)

Vasoactive Intestinal Peptide (VIP) — Neuro & cognitive (under FDA review)

BPC-157 — Tissue repair (under FDA review)

KPV — Tissue repair (under FDA review)

LL-37 — Tissue repair (under FDA review)

Pentadeca Arginate (PDA) — Tissue repair (under FDA review)

TB-500 / Thymosin Beta-4 — Tissue repair (under FDA review)