

RESEARCH MONOGRAPH . COMPOUND PROFILE

Nortadalafil

An unapproved, demethylated structural analogue of tadalafil with retained nanomolar PDE5 inhibitory potency, identified principally as a synthetic adulterant in dietary supplements marketed for sexual enhancement and as a reference standard for forensic and analytical chemistry.

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COMPOUND CLASS	Synthetic phosphodiesterase type 5 (PDE5) inhibitor; N-desmethyl analogue of tadalafil

ABSTRACT

Nortadalafil (demethyl tadalafil, CAS 171596-36-4) is a synthetic analogue of the clinically approved phosphodiesterase type 5 (PDE5) inhibitor tadalafil, distinguished from the parent compound by the absence of the N-methyl substituent on the piperazinedione ring of the hexahydropyrazinopyridoindole scaffold. The compound retains nanomolar inhibitory potency against PDE5 (IC₅₀ approximately 11 to 12 nM against bovine PDE5, compared to approximately 5 nM for tadalafil) and produces cGMP-mediated smooth muscle relaxation with EC₅₀ values of 300 to 600 nM in rat aortic preparations. Despite this pharmacological activity, nortadalafil has never been submitted for regulatory approval in any jurisdiction and has not been the subject of controlled clinical trials in human subjects. The compound first entered the scientific literature through its detection as an undeclared adulterant in herbal and dietary supplements marketed for erectile dysfunction, a context in which it represents one member of a large and expanding family of synthetic PDE5 inhibitor analogues (including aminotadalafil, N-octylnortadalafil, chloropretadalafil, and others) introduced into the unregulated supplement market to evade analytical screening for the approved parent compounds. Analytical characterization of nortadalafil in adulterated products relies on high-performance liquid chromatography with diode-array and mass spectrometric detection, high-resolution mass spectrometry, and nuclear magnetic resonance spectroscopy. The pharmacokinetic profile of nortadalafil diverges substantially from tadalafil: the reported elimination half-life is approximately 5.9 to 6.2 hours after single oral doses of 40 to 120 mg, compared to the 17.5-hour half-life of

tadalafil, a difference attributable to the loss of the N-methyl group and the resulting alteration of hepatic metabolic clearance. No systematic toxicology, no formal pharmacokinetic characterization in healthy volunteers under regulatory oversight, and no controlled efficacy data exist for the compound. Safety concerns are inferred from the PDE5 inhibitor class and include the absolute contraindication of concurrent nitrate administration (risk of severe, potentially fatal hypotension), the interaction with alpha-adrenergic receptor antagonists and potent CYP3A4 inhibitors, and the unknown dose-response and adverse-event profile of a compound consumed without medical supervision at uncharacterized doses in adulterated supplements. This monograph reviews the chemistry, synthesis, and structural relationship of nortadalafil to tadalafil; the molecular pharmacology of PDE5 inhibition and the cGMP-nitric oxide signaling cascade; the limited pharmacokinetic data; the forensic and regulatory context of dietary supplement adulteration; sourcing and quality verification for research applications; handling and reconstitution; stack-interaction considerations; the adverse-event and safety signal inferred from the PDE5 inhibitor class; and a comparative assessment of five PDE5 inhibitor compounds against nortadalafil on five competency standards. The compound is not approved by any regulatory authority. It is available as a research-grade reference standard; investigators should obtain analytical confirmation of identity and purity on every lot.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Preferred name: Nortadalafil.

Synonyms: Demethyl tadalafil, N-desmethyl tadalafil, desmethyl tadalafil, nortadalafil.

Chemical Abstracts Service registry number: 171596-36-4.

PubChem Compound Identifier: CID 9820973.

International Union of Pure and Applied Chemistry name: (6R,12aR)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydropyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione. The compound is the N-desmethyl congener of tadalafil, differing exclusively by the replacement of the N-methyl group at position 2 of the piperazine-dione ring with a hydrogen atom.

Relationship to tadalafil: Nortadalafil is structurally derived from tadalafil (CAS 171489-17-1), the (6R,12aR)-configured PDE5 inhibitor approved under the trade name Cialis (Eli Lilly/ICOS). The sole structural difference is the absence of the methyl group on the nitrogen at position 2 of the 2,5-diketopiperazine (piperazine-dione) ring system. Nortadalafil is not a characterized in vivo metabolite of tadalafil; the principal hepatic metabolic pathway of tadalafil proceeds through CYP3A4-mediated demethylenation of the 1,3-benzodioxol ring to a catechol intermediate, not through N-demethylation of the piperazinedione nitrogen [1, 2].

1.2 Structural class and chemistry

Nortadalafil belongs to the hexahydropyrazinopyridindole structural class, a series of condensed polycyclic heterocycles incorporating an indole ring fused to a partially saturated pyrido ring and bridged by a 2,5-diketopiperazine (piperazine-dione). The class was developed through medicinal chemistry programs at ICOS Corporation (later ICOS/Eli Lilly) beginning in the mid-1990s, directed at selective PDE5 inhibition for the treatment of erectile dysfunction [3, 4]. The 1,3-benzodi-

oxol-5-yl (piperonyl) substituent at position 6 is the pharmacophore responsible for interaction with the catalytic site of PDE5 and is shared between tadalafil and nortadalafil.

Molecular formula: C₂₁H₁₇N₃O₄.

Exact mass: 375.1219 g/mol (monoisotopic).

Molecular weight: 375.38 g/mol.

Physical properties: Off-white to pale yellow crystalline powder. Sparingly soluble in water; soluble in dimethyl sulfoxide (DMSO) and dimethylformamide (DMF); moderately soluble in methanol and ethanol. Melting point data are limited in the published literature; values approximating 290 to 300 degrees Celsius (with decomposition) have been reported by commercial suppliers. The compound is stable under ambient dry conditions and under refrigerated storage.

Stereochemistry: Nortadalafil retains the (6R,12aR) absolute configuration of tadalafil. The two stereocenters at carbons 6 and 12a of the pyridoindole ring system control the spatial relationship between the piperonyl substituent and the indole NH. The (6R,12aR) diastereomer is the pharmacologically active configuration for PDE5 inhibition; the three other possible diastereomers exhibit substantially reduced potency. Investigators acquiring research-grade nortadalafil should confirm stereochemical identity by chiral high-performance liquid chromatography or by comparison of optical rotation to a certified reference standard.

1.3 Synthesis

The most direct laboratory-scale route to nortadalafil is N-demethylation of tadalafil. The methyl group on the 2-nitrogen of the piperazinedione ring can be removed using boron tribromide (BBr₃) in anhydrous dichloromethane at low temperature, or by treatment with other strong Lewis acid demethylating agents under controlled conditions [5]. The product is isolated by aqueous workup, purified by recrystallization (typically from ethanol or ethyl acetate) or by preparative high-performance liquid chromatography, and characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, and melting point.

An alternative total synthesis proceeds through the Pictet-Spengler condensation of D-tryptophan with piperonal to generate the hexahydro-beta-carboline intermediate, followed by cyclization with an unsubstituted glycine-derived dike-

topiperazine equivalent rather than the N-methylglycine (sarcosine) equivalent used in the tadalafil synthesis [3, 6]. This route avoids the need for a demethylation step but requires careful control of the Pictet-Spengler stereochemistry to obtain the desired (6R,12aR) diastereomer.

Industrial-scale synthesis for use as an analytical reference standard or as an adulterant precursor likely follows variants of these two approaches. The compound is manufactured at greater than 98 percent purity by HPLC by multiple commercial suppliers and is available in milligram to gram quantities.

2. Abstract

Nortadalaflil (demethyl tadalafil, CAS 171596-36-4) is a synthetic phosphodiesterase type 5 (PDE5) inhibitor and the N-desmethyl structural analogue of tadalafil, the clinically approved agent marketed as Cialis for the treatment of erectile dysfunction, benign prostatic hyperplasia, and pulmonary arterial hypertension. The compound inhibits PDE5 with an IC₅₀ of approximately 11 to 12 nM, retaining substantial potency relative to the parent tadalafil (IC₅₀ approximately 5 nM) and producing downstream accumulation of cyclic guanosine monophosphate (cGMP) in smooth muscle, with consequent nitric oxide-dependent vasodilation [7, 8].

Nortadalaflil has never been approved for clinical use in any jurisdiction and has not been evaluated in controlled human clinical trials. The compound entered the scientific and regulatory literature principally through its identification as an undeclared adulterant in herbal dietary supplements marketed for sexual enhancement. The first formal report of nortadalaflil in health food products was published by Zou et al. (2006), who isolated and characterized the compound from a commercially available supplement using HPLC, mass spectrometry, and NMR spectroscopy [9]. Subsequent surveillance by regulatory agencies including the United States Food and Drug Administration (FDA), the Health Sciences Authority of Singapore, and the European Medicines Agency has identified nortadalaflil (and its alkylated derivatives, including N-octylnortadalaflil, N-butylnortadalaflil, N-cyclohexylnortadalaflil, N-cyclopentylnortadalaflil, and 2-hydroxypropylnortadalaflil) as recurring adulterants in the global dietary supplement supply chain [10, 11, 12, 13].

The limited pharmacokinetic data available for nortadalaflil indicate an oral elimination half-life of approximately 5.9 to 6.2 hours after single doses of 40 to 120 mg, substantially shorter than the 17.5-hour half-life of tadalafil [8, 14]. This pharmacokinetic difference is clinically significant: the extended duration of action (up to 36 hours) that distinguishes tadalafil from other approved PDE5 inhibitors is not expected to be preserved in nortadalaflil. No oral bioavailability, volume of distribution, or protein binding data specific to nortadalaflil have been published under regulatory oversight.

Safety concerns for nortadalafile are inferred entirely from the PDE5 inhibitor class. The absolute contraindication of concurrent organic nitrate use (the combination can produce severe, potentially fatal hypotension through additive cGMP accumulation) applies to nortadalafile as to all PDE5 inhibitors [15]. Consumers of adulterated supplements containing undeclared nortadalafile are exposed to this risk without awareness and without the opportunity for prescriber-mediated drug interaction assessment. Additional class-effect safety considerations include interactions with alpha-adrenergic antagonists, potent CYP3A4 inhibitors and inducers, and antihypertensive agents.

This monograph documents the chemistry, synthesis, molecular pharmacology, limited pharmacokinetics, forensic and regulatory context, sourcing and quality considerations, reconstitution and handling, stack interactions, adverse-event signal, and a comparative assessment of five PDE5 inhibitor compounds against nortadalafile.

3. Discovery and Development History

3.1 Origin of the tadalafil structural class

The hexahydropyrazinopyridoindole structural class from which nortadalafil is derived was developed at ICOS Corporation in Bothell, Washington, beginning in 1993 as part of a medicinal chemistry program directed at the identification of selective PDE5 inhibitors for the treatment of erectile dysfunction. The program was motivated by the clinical success of sildenafil (Viagra, Pfizer), the first approved PDE5 inhibitor, and sought to identify structurally distinct compounds with improved selectivity and pharmacokinetic properties [3, 4].

The discovery chemistry was led by Daugan and colleagues, who explored the Pictet-Spengler condensation of tryptophan derivatives with aryl aldehydes to produce beta-carboline intermediates, followed by diketopiperazine cyclization to generate the hexahydropyrazinopyridoindole scaffold. Systematic variation of the aryl aldehyde (the C-6 substituent), the amino acid component (the piperazinedione nitrogen substituent), and the stereochemistry led to the identification of tadalafil as the optimal compound: the (6R,12aR)-configured N-methyl derivative with a 1,3-benzodioxol-5-yl substituent [3]. Tadalafil was selected for clinical development on the basis of potent and selective PDE5 inhibition (IC₅₀ approximately 5 nM), a favorable selectivity ratio over PDE6 (greater than 700-fold) and other PDE isoforms, oral bioavailability, and a long plasma elimination half-life (17.5 hours) that supported once-daily dosing and an extended window of therapeutic effect.

3.2 ICOS/Lilly development and regulatory approval of tadalafil

ICOS partnered with Eli Lilly and Company in 1998 to form the Lilly ICOS joint venture for the development and commercialization of tadalafil. The compound advanced through Phase 1, 2, and 3 clinical trials for erectile dysfunction and received FDA approval in November 2003 under the trade name Cialis. Subsequent approvals followed for benign prostatic hyperplasia (2011) and pulmonary arterial hyperten-

sion (marketed as Adcirca, 2009) [4]. Tadalafil became one of the most commercially successful PDE5 inhibitors, generating peak annual revenues exceeding \$2 billion prior to patent expiration and generic entry.

3.3 Emergence of nortadalafil as a dietary supplement adulterant

Nortadalafil was not developed through a formal drug discovery program. The compound first appeared in the scientific literature through its identification as an undeclared adulterant in dietary supplements marketed for sexual enhancement. The earliest published report identifying nortadalafil in health food products is attributed to Zou et al. (2006), who detected and characterized the compound in commercially available supplements using analytical methods including HPLC-UV, electrospray ionization mass spectrometry (ESI-MS), and proton nuclear magnetic resonance spectroscopy [9]. The structural elucidation confirmed that the adulterant was the N-desmethyl analogue of tadalafil, differing by 14 mass units (loss of CH₂) from the parent compound.

The detection of nortadalafil in supplements is understood in the context of a broader phenomenon: the systematic adulteration of herbal sexual enhancement products with synthetic PDE5 inhibitors and their structural analogues. Surveys of the dietary supplement market have consistently identified high rates of adulteration. A systematic analysis of FDA warning letters from 2007 through 2016 identified unapproved pharmaceutical ingredients in 776 dietary supplements, with sexual enhancement products representing the most commonly adulterated category [16]. In targeted analytical surveys, 67 to 81 percent of herbal sexual enhancement products tested positive for at least one PDE5 inhibitor or PDE5 inhibitor analogue [17, 18].

3.4 Proliferation of nortadalafil-derived analogues

Following the initial detection of nortadalafil, manufacturers of adulterated supplements developed a series of N-substituted nortadalafil derivatives designed to evade the analytical screening methods used by regulatory agencies. These include N-octylnortadalafil (CAS 1173706-35-8), N-butylnortadalafil, N-cyclohexylnortadalafil, N-cyclopentylnortadalafil (reported by Kee et al., 2015), 2-hydroxypropylnortadalafil (CAS 1353020-85-5), 2-hydroxyethylnortadalafil, N-3-hydroxypropylnortadalafil, and others [10, 11, 12, 13]. Each derivative modifies the piperazinedione

nitrogen with a different substituent while preserving the core hexahydropyrazinopyridoindole PDE5-inhibitory pharmacophore. The pharmacological activity and safety profiles of these derivatives are essentially unknown; their existence reflects the ongoing regulatory challenge of screening for novel synthetic adulterants in the global supplement supply chain.

4. Mechanism of Action

4.1 Phosphodiesterase type 5 inhibition

Nortadalafil is a selective inhibitor of phosphodiesterase type 5 (PDE5), a member of the cyclic nucleotide phosphodiesterase superfamily that catalyzes the hydrolysis of cyclic guanosine monophosphate (cGMP) to the inactive 5'-GMP. PDE5 is expressed at high density in vascular smooth muscle (particularly in the corpus cavernosum of the penis, in the pulmonary vasculature, and in systemic arterioles), in platelets, in the cerebellar Purkinje cell layer, and at lower density in visceral smooth muscle and in the gastrointestinal tract [19, 20].

Under physiological conditions, sexual stimulation triggers the release of nitric oxide (NO) from non-adrenergic, non-cholinergic nerve terminals and from vascular endothelial cells in the corpus cavernosum. Nitric oxide activates soluble guanylate cyclase, increasing intracellular cGMP concentrations. cGMP activates protein kinase G (PKG), which phosphorylates downstream effectors including myosin light chain phosphatase and calcium-activated potassium channels, producing smooth muscle relaxation, vasodilation, and penile erection. PDE5 terminates the cGMP signal by hydrolysis; inhibition of PDE5 therefore prolongs and amplifies the NO-cGMP-PKG signaling cascade, enhancing the erectile response to sexual stimulation [19].

Nortadalafil inhibits bovine PDE5 with IC₅₀ values of approximately 11.0 to 12.0 nM, approximately 2-fold less potent than tadalafil (IC₅₀ approximately 5 nM) at the same enzyme preparation [7, 8]. This potency is within the pharmacologically active range and comparable to or exceeding the potency of sildenafil (IC₅₀ approximately 3.5 to 6.6 nM) and vardenafil (IC₅₀ approximately 0.7 to 0.9 nM) at PDE5 [20]. The compound produces cGMP-dependent relaxation of rat aortic smooth muscle with EC₅₀ values of approximately 300 to 600 nM, confirming functional PDE5 inhibitory activity in intact vascular tissue [7].

4.2 PDE isoform selectivity

The PDE5 inhibitor class is differentiated in part by selectivity against the other ten human PDE families (PDE1 through PDE4, PDE6 through PDE11). Selectivity data specific to nortadalafil have not been published in peer-reviewed literature. By analogy to the closely related parent compound tadalafil, nortadalafil is expected to exhibit high selectivity for PDE5 over PDE1, PDE2, PDE3, PDE4, PDE7, PDE8, PDE9, and PDE10 (selectivity ratios greater than 1000-fold for tadalafil). Tadalafil is approximately 700-fold selective for PDE5 over PDE6 (the retinal phosphodiesterase responsible for the visual disturbance adverse effect observed with sildenafil) and approximately 5- to 14-fold selective for PDE5 over PDE11A4, an orphan phosphodiesterase expressed in skeletal muscle, prostate, liver, kidney, and testis whose physiological function remains incompletely characterized [20, 21]. Whether the removal of the N-methyl group alters the PDE11 selectivity ratio for nortadalafil is unknown.

4.3 Structural basis of PDE5 inhibition

Crystallographic studies of tadalafil bound to the catalytic domain of PDE5 (PDB: 1UDT) have demonstrated that the indole moiety occupies the hydrophobic clamp formed by Phe820, Val782, and Leu804; the piperonyl (1,3-benzodioxol) group projects into the metal-binding pocket adjacent to the catalytic zinc and magnesium ions; and the diketopiperazine ring makes hydrogen bond contacts with Gln817 and with a conserved water molecule in the binding site [22]. The N-methyl group of tadalafil contributes van der Waals contacts with the protein surface but does not participate in direct hydrogen bonding to the enzyme. The removal of this methyl group in nortadalafil therefore eliminates a modest hydrophobic contact, which is consistent with the approximately 2-fold reduction in IC₅₀ potency observed experimentally and predicts that the overall binding mode is preserved.

4.4 Downstream physiological consequences

The principal physiological consequence of PDE5 inhibition is vasodilation, mediated through the NO-cGMP-PKG pathway described above. In the corpus cavernosum, this produces the therapeutic effect in erectile dysfunction. In the pulmonary vasculature, PDE5 inhibition reduces pulmonary arterial pressure (the basis for the pulmonary arterial hypertension indication of tadalafil). In the systemic vasculature, PDE5 inhibition produces modest reductions in systemic blood pres-

sure (typically 1 to 5 mmHg systolic and 1 to 3 mmHg diastolic at therapeutic doses of approved PDE5 inhibitors) that are generally not clinically significant in normotensive individuals but become hazardous in the context of concurrent nitrate use or in patients with borderline hypotension [15].

Additional physiological effects of PDE5 inhibition include relaxation of lower urinary tract smooth muscle (the basis for the benign prostatic hyperplasia indication of tadalafil), antiplatelet activity through cGMP-dependent inhibition of platelet aggregation, and emerging evidence for anti-inflammatory, anti-fibrotic, and neuroprotective effects in preclinical models [23]. Whether nortadalafil shares these downstream effects in proportion to its PDE5 inhibitory potency is plausible but has not been experimentally verified.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Formal oral bioavailability studies of nortadalafil under regulatory oversight have not been published. The limited pharmacokinetic data derive from studies of single oral doses in the range of 40 to 120 mg (substantially higher than the approved tadalafil dose range of 2.5 to 20 mg), conducted outside the framework of regulatory clinical trials [8]. These studies report measurable plasma concentrations following oral administration, confirming gastrointestinal absorption, but do not provide absolute bioavailability estimates relative to an intravenous reference dose.

By analogy to tadalafil (oral bioavailability approximately 36 percent in fasted subjects, with food having no clinically significant effect on absorption), nortadalafil is expected to be orally bioavailable, though the specific extent may differ owing to the altered lipophilicity and hydrogen bonding capacity resulting from the absence of the N-methyl group.

5.2 Distribution

Volume of distribution data specific to nortadalafil have not been published. Tadalafil has a mean steady-state volume of distribution of approximately 63 liters, indicating distribution into tissues beyond the plasma compartment. Plasma protein binding of tadalafil is approximately 94 percent, predominantly to albumin. Nortadalafil, lacking the N-methyl group, may exhibit modestly reduced lipophilicity and correspondingly altered tissue distribution and protein binding, but no experimental data are available.

5.3 Metabolism

The hepatic metabolism of nortadalafil has not been characterized by in vitro microsomal or recombinant CYP enzyme studies. By analogy to tadalafil, metabolism is expected to be mediated predominantly by CYP3A4, with the principal metabolic pathway involving demethylenation of the 1,3-benzodioxol ring to a catechol inter-

mediate, followed by methylation (catechol-O-methyltransferase) and glucuronidation [1, 2]. The catechol metabolite is reported to be pharmacologically inactive at PDE5 [14]. Minor contributions from CYP3A5 and CYP3A7 have been characterized for tadalafil and are expected to apply to nortadalafil.

The absence of the N-methyl group on the piperazinedione nitrogen eliminates one potential site of metabolic transformation but does not alter the principal CYP3A4-mediated demethylenation pathway. The shorter elimination half-life of nortadalafil (5.9 to 6.2 hours) relative to tadalafil (17.5 hours) suggests either more rapid hepatic clearance, reduced absorption, or altered distribution; the molecular basis for this pharmacokinetic difference has not been formally characterized [8, 14].

5.4 Elimination

The plasma elimination half-life of nortadalafil is approximately 5.9 to 6.2 hours after single oral doses of 40 to 120 mg [8]. This is substantially shorter than the 17.5-hour half-life of tadalafil and comparable to the half-lives of sildenafil (approximately 4 hours) and vardenafil (approximately 4 to 6 hours). The implication is that the extended duration of therapeutic effect (up to 36 hours) that distinguishes tadalafil from other approved PDE5 inhibitors is not expected to be preserved with nortadalafil.

Elimination routes for nortadalafil have not been characterized. Tadalafil is eliminated predominantly as metabolites: approximately 61 percent in feces and approximately 36 percent in urine, with less than 0.1 percent excreted unchanged [14]. A similar metabolic elimination pattern is expected for nortadalafil.

5.5 Routes of administration

Nortadalafil has been detected in dietary supplements formulated as oral capsules, tablets, and powdered preparations. The compound is intended for oral administration in both the supplement adulterant context and in research applications. No parenteral, sublingual, or other routes of administration have been characterized.

5.6 Special populations

No pharmacokinetic data in special populations (renal impairment, hepatic impairment, elderly, pediatric, CYP polymorphism) exist for nortadalafil. Investigators should note that tadalafil exposure is increased in subjects with hepatic impairment (Child-Pugh class A and B) and that CYP3A4 genetic polymorphisms and concurrent strong CYP3A4 inhibitor exposure alter tadalafil clearance; analogous effects on nortadalafil pharmacokinetics are expected but unquantified.

6. Clinical Evidence Base

6.1 Absence of formal clinical trials

Nortadalafile has not been evaluated in any controlled clinical trial registered in public databases (ClinicalTrials.gov, EU Clinical Trials Register, WHO International Clinical Trials Registry Platform). No efficacy data, no dose-response data, and no formal safety data from human clinical studies exist.

6.2 Forensic and epidemiological evidence

The principal human exposure data for nortadalafile come from forensic case reports and regulatory surveillance of dietary supplement adulteration. The FDA has issued multiple public notifications and warning letters regarding dietary supplements found to contain nortadalafile and its derivatives [16, 24]. The Health Sciences Authority of Singapore has published analytical reports characterizing nortadalafile in supplements sold in Southeast Asian markets [9, 10, 11].

Adverse event reports associated with adulterated supplements containing PDE5 inhibitor analogues (including nortadalafile) include symptomatic hypotension, syncope, priapism, visual disturbance, headache, and myocardial infarction in the setting of concurrent nitrate use [17, 25]. Attribution of specific adverse events to nortadalafile (as opposed to other co-adulterants or to the parent compounds sildenafil and tadalafil) is generally not possible from these reports.

6.3 In vitro pharmacology as surrogate for clinical activity

The IC₅₀ of nortadalafile against PDE5 (11 to 12 nM) and its functional activity in rat aortic smooth muscle preparations (EC₅₀ 300 to 600 nM) confirm that the compound possesses pharmacological activity consistent with the PDE5 inhibitor class [7, 8]. The approximately 2-fold reduction in potency relative to tadalafil, combined with the approximately 3-fold shorter elimination half-life, predicts that nortadalafile at equivalent oral doses would produce a less potent and shorter-duration vasodilatory effect than tadalafil. However, no clinical dose-response comparison has been conducted.

6.4 Research applications

Nortadalafil serves as a reference standard in forensic and analytical chemistry for the detection and quantification of tadalafil-related adulterants in dietary supplements, herbal preparations, and illicit pharmaceutical products. The compound is also used as a tool compound in PDE5 structure-activity relationship studies and in the development of analytical screening methods for novel PDE5 inhibitor analogues [10, 11, 12, 13].

7. Reported Research Dose Ranges

7.1 Approved doses

Nortadalaflil is not approved in any jurisdiction. No regulatory agency has established an approved dose, dosage form, or dosing regimen.

7.2 Doses detected in adulterated supplements

Analytical surveys of adulterated dietary supplements have detected nortadalaflil at doses ranging from less than 1 mg to greater than 50 mg per dosage unit, with substantial variability between products and between lots of the same product [17, 18]. These doses are not standardized, are not accompanied by pharmacokinetic characterization, and represent uncontrolled exposure to an unapproved pharmaceutical agent.

7.3 Pharmacokinetic study doses

The limited pharmacokinetic data available for nortadalaflil derive from studies using single oral doses of 40 to 120 mg [8]. These doses are substantially higher than the approved therapeutic doses of tadalafil (2.5 to 20 mg) and reflect the research or characterization context rather than any proposed therapeutic dose range.

7.4 Research applications

For in vitro PDE5 inhibition assays, nortadalaflil is typically used at concentrations of 0.1 nM to 10 micromolar. For tissue bath preparations (isolated vascular smooth muscle), concentrations of 1 nM to 10 micromolar are standard. Investigators should select concentrations based on the IC₅₀ and EC₅₀ values described in Section 4 and should include the parent compound tadalafil as a positive control.

8. Sourcing and Quality Verification

Research-grade nortadalafil is supplied by multiple chemical and pharmaceutical research suppliers, including MedChemExpress, Sigma-Aldrich, Cayman Chemical, BOC Sciences, Santa Cruz Biotechnology, LGC Standards, Smolecule, BenchChem, BioCrick, APExBIO, TargetMol, GlpBio, InvivoChem, and Creative Diagnostics. The compound is available as a certified reference standard (for analytical and forensic applications) and as a research-grade preparation (for in vitro and in vivo pharmacology) at purity greater than 98 percent by HPLC. Supply is typically in milligram quantities (1 mg to 100 mg); gram-scale quantities are available on request from some suppliers.

Pricing varies by supplier, purity grade, and quantity, typically in the range of \$50 to \$300 per 10 mg of certified reference standard material.

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

- High-performance liquid chromatography with ultraviolet and/or mass spectrometric detection, confirming area-percent purity greater than 98 percent
- High-resolution mass spectrometry confirmation of molecular weight (376.1292 for the protonated molecular ion $[M+H]^+$, corresponding to $C_{21}H_{18}N_3O_4^+$)
- Nuclear magnetic resonance spectroscopy (proton and carbon-13) for structural confirmation, with particular attention to the absence of the N-methyl singlet (approximately δ 3.0 ppm in tadalafil) that distinguishes nortadalafil from tadalafil
- Chiral HPLC or optical rotation confirmation of stereochemical identity ((6R,12aR) configuration)
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, others) provide independent confirmation of vendor certificates of analysis. Given the forensic context of nortadalafil (its primary application is as a reference standard for adulterant detection), analytical rigor in identity and purity confirmation is particularly

important; co-elution or mass spectrometric overlap with other tadalafil analogues (aminotadalafil, N-alkylnortadalafil derivatives) is a documented analytical challenge [10, 12].

9. Reconstitution and Handling

Nortadalafile is typically supplied as a lyophilized or crystalline powder. The compound is sparingly soluble in water. For research applications, stock solutions are prepared as follows:

DMSO stock solutions: Nortadalafile dissolves readily in DMSO at concentrations up to 10 mg/mL (approximately 26.6 mM). DMSO stock solutions are stable at minus 20 degrees Celsius for at least 6 months when protected from moisture and light. Aliquoting into single-use volumes is recommended to minimize freeze-thaw cycles.

Ethanol stock solutions: The compound is moderately soluble in ethanol. Stock solutions at 1 to 5 mg/mL are achievable with brief sonication. Ethanol solutions should be prepared fresh or stored at minus 20 degrees Celsius for no longer than 1 month.

Aqueous preparations: For tissue bath experiments or cell culture assays, DMSO stock solutions are diluted into aqueous buffers to the desired final concentration. The final DMSO concentration should not exceed 0.1 percent (v/v) to avoid solvent-related effects on smooth muscle contractility or cell viability. If higher aqueous solubility is required, the use of cyclodextrin complexation (hydroxypropyl-beta-cyclodextrin) or co-solvent systems (polyethylene glycol 400) may be considered.

Storage of solid material: Refrigerated storage (2 to 8 degrees Celsius) in a desiccated, light-protected container is recommended. The compound is stable at room temperature under dry conditions but prolonged exposure to light, heat, or moisture may promote degradation of the methylenedioxy bridge or the diketopiperazine ring.

Handling precautions: Nortadalafile is a pharmacologically active PDE5 inhibitor. Standard laboratory personal protective equipment (gloves, laboratory coat, eye protection) should be used when handling the compound. Avoid inhalation of powder or aerosol. The compound should be treated as a pharmacologically active agent and handled accordingly in waste disposal (chemical waste, not drain disposal).

10. Stack Interaction Considerations

Nortadalaflil interacts with several drug and compound classes through its PDE5 inhibitory mechanism and through its anticipated CYP3A4-mediated metabolism. Investigators conducting research with nortadalaflil, particularly in combination studies or in contexts where research participants may have concurrent medication exposure, should consider the following interactions:

Organic nitrates and nitric oxide donors (absolute contraindication): Concurrent administration of any PDE5 inhibitor with organic nitrates (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, amyl nitrite) or with nitric oxide donors produces severe, potentially fatal hypotension through additive cGMP accumulation in vascular smooth muscle [15]. This interaction is the most clinically significant drug interaction in the PDE5 inhibitor class and constitutes an absolute contraindication. The interaction applies to nortadalaflil as to all PDE5 inhibitors. Given the shorter half-life of nortadalaflil (approximately 6 hours), the minimum recommended separation from nitrate administration may be shorter than the 48-hour interval recommended for tadalafil, but no formal study has been conducted and a conservative approach is warranted.

Alpha-adrenergic receptor antagonists: PDE5 inhibitors produce additive hypotension when co-administered with alpha-1 adrenergic antagonists (prazosin, terazosin, doxazosin, tamsulosin, alfuzosin, silodosin). The magnitude of the interaction varies by alpha-blocker selectivity and dose. Tadalafil labeling recommends initiation at the lowest dose with clinical monitoring in patients on alpha-blocker therapy [14]. The same precaution applies to nortadalaflil.

CYP3A4 inhibitors: Strong CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, nefazodone, grapefruit juice) substantially increase tadalafil exposure (2- to 4-fold increases in AUC have been reported) [1, 14]. An analogous increase in nortadalaflil exposure is expected with concurrent CYP3A4 inhibitor use, though the magnitude has not been characterized.

CYP3A4 inducers: Strong CYP3A4 inducers (rifampin, phenytoin, carbamazepine, St. John's wort) reduce tadalafil exposure. Concurrent use would be expected to reduce nortadalaflil exposure and may compromise pharmacological activity in research applications.

Other PDE5 inhibitors: Concurrent use of nortadalafil with approved PDE5 inhibitors (sildenafil, vardenafil, tadalafil, avanafil) produces additive PDE5 inhibition and additive vasodilation, increasing the risk of symptomatic hypotension. The combination is not recommended and is pharmacologically redundant.

Antihypertensive agents: PDE5 inhibitors produce modest additive blood pressure reduction when co-administered with antihypertensive agents (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, beta-blockers, diuretics). The effect is typically small (1 to 5 mmHg additional systolic reduction) and generally not clinically significant, but may become relevant in patients with low baseline blood pressure or volume depletion.

Riociguat: The soluble guanylate cyclase stimulator riociguat (Adempas) is contraindicated with all PDE5 inhibitors due to the risk of severe symptomatic hypotension through dual enhancement of the cGMP pathway [14]. This contraindication applies to nortadalafil.

Alcohol: Ethanol produces additive vasodilation and may potentiate the hypotensive effects of PDE5 inhibitors. The interaction is generally modest at moderate alcohol consumption but may be clinically significant at higher intake.

11. Adverse Events and Safety

11.1 Absence of formal safety data

No formal safety assessment of nortadalafil from controlled clinical trials exists. All safety information is inferred from the PDE5 inhibitor class, from forensic case reports involving adulterated supplements, and from the pharmacological profile of the compound.

11.2 Anticipated class-effect adverse events

Based on the PDE5 inhibitor class, the following adverse events are expected at pharmacologically active doses of nortadalafil:

- Headache (10 to 15 percent with approved PDE5 inhibitors, the most common class-effect adverse event, resulting from cGMP-mediated meningeal vasodilation)
- Flushing (5 to 10 percent, resulting from cutaneous vasodilation)
- Dyspepsia (5 to 10 percent, resulting from PDE5 inhibition in gastrointestinal smooth muscle)
- Nasal congestion (2 to 5 percent, resulting from nasal mucosal vasodilation)
- Back pain and myalgia (2 to 6 percent; associated particularly with tadalafil and attributed to PDE11 cross-reactivity in skeletal muscle) [20, 21]
- Dizziness (1 to 3 percent, resulting from transient blood pressure reduction)
- Visual disturbance (rare with tadalafil owing to its favorable PDE5/PDE6 selectivity; more common with sildenafil. The selectivity profile of nortadalafil for PDE6 is unknown)

11.3 Serious adverse events

Serious adverse events associated with the PDE5 inhibitor class include:

- Severe hypotension in the setting of concurrent organic nitrate use or concurrent alpha-blocker therapy, potentially leading to syncope, myocardial infarction, or death [15]

- Priapism (sustained, painful erection exceeding 4 hours), reported rarely with all approved PDE5 inhibitors and constituting a urological emergency if untreated
- Non-arteritic anterior ischemic optic neuropathy (NAION), a rare but serious cause of sudden vision loss reported in temporal association with PDE5 inhibitor use; a causal relationship has not been established but patients with preexisting risk factors (small cup-to-disc ratio, diabetes, hypertension) may be at increased risk [26]
- Sudden sensorineural hearing loss, reported rarely in temporal association with PDE5 inhibitor use [27]

11.4 Unknown risks specific to nortadalafil

Several safety-relevant unknowns apply specifically to nortadalafil:

- The PDE isoform selectivity profile has not been characterized; cross-reactivity with PDE6 (visual effects), PDE11 (myalgia), or other PDE families cannot be excluded
- The dose-response relationship for adverse events is unknown; doses detected in adulterated supplements (up to 50 mg or more per unit) may substantially exceed the therapeutic window
- Chronic toxicity, reproductive toxicity, genotoxicity, and carcinogenicity data do not exist
- Drug interaction magnitudes have not been quantified; the predicted CYP3A4 interactions are based entirely on analogy to tadalafil
- The shorter half-life (approximately 6 hours versus 17.5 hours for tadalafil) may reduce the duration of adverse events relative to tadalafil but does not reduce the peak-effect magnitude at equivalent doses

11.5 Public health significance

The principal public health concern regarding nortadalafil is its presence as an undeclared adulterant in dietary supplements sold without medical supervision. Consumers of these products are exposed to a pharmacologically active PDE5 inhibitor without awareness of the drug interaction risks (particularly the absolute contraindication with nitrates), without dose standardization, and without the opportunity for prescriber-mediated risk assessment. Regulatory agencies have re-

sponded with public notifications, product recalls, and import alerts, but the speed of novel analogue introduction (described in Section 3.4) continues to outpace analytical screening capacity [16, 24].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five PDE5 inhibitor compounds against nortadalafil, evaluated on five competency standards: novelty, effect size (pharmacological potency), promising potential (regulatory and clinical trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal approved and investigational PDE5 inhibitors with substantive clinical or pharmacological relevance to the nortadalafil profile.

12.1 Tadalafil

Mechanism: Selective PDE5 inhibitor. IC₅₀ approximately 5 nM. The parent compound from which nortadalafil is derived.

Regulatory status: Approved by FDA (2003) and by regulatory agencies worldwide for erectile dysfunction, benign prostatic hyperplasia, and pulmonary arterial hypertension. Marketed as Cialis (erectile dysfunction, BPH) and Adcirca (pulmonary arterial hypertension). Generic versions widely available following patent expiration.

Novelty: Low relative to nortadalafil. Tadalafil is the established parent compound; nortadalafil represents a minor structural modification (N-demethylation) without any novel pharmacological property.

Effect size: Superior to nortadalafil. The IC₅₀ of tadalafil (5 nM) is approximately 2-fold more potent than nortadalafil (11 to 12 nM). The elimination half-life of tadalafil (17.5 hours) supports a 36-hour therapeutic window not achievable with nortadalafil (half-life approximately 6 hours). Tadalafil has demonstrated efficacy in large Phase 3 clinical trials with thousands of subjects across multiple indications [4, 14].

Promising potential: Established. Tadalafil is a fully approved, commercially successful pharmaceutical with well-characterized efficacy, safety, and pharmacokinetics.

Side-effect profile: Well characterized through clinical trials and extensive post-marketing surveillance. The principal adverse events are headache, dyspepsia, back pain, myalgia, flushing, and nasal congestion. Serious adverse events are rare and class-related.

Overall validation: Very high. Tadalafil is the gold standard against which nortadalafil and all tadalafil analogues are evaluated.

Comparison to nortadalafil: Nortadalafil is pharmacologically inferior to tadalafil by every measured parameter: lower potency, shorter duration of action, no clinical data, no regulatory approval, and unknown safety profile. The only context in which nortadalafil is preferred over tadalafil is as an analytical reference standard for adulterant detection.

12.2 Sildenafil

Mechanism: Selective PDE5 inhibitor. IC₅₀ approximately 3.5 to 6.6 nM. The first approved PDE5 inhibitor (Pfizer, 1998), marketed as Viagra (erectile dysfunction) and Revatio (pulmonary arterial hypertension).

Novelty: Low. Sildenafil is structurally distinct from the tadalafil/nortadalafil hexahydropyrazinopyridoindole class, employing a pyrazolopyrimidinone scaffold.

Effect size: PDE5 inhibitory potency is comparable to or slightly superior to nortadalafil. The elimination half-life (approximately 4 hours) is comparable to nortadalafil. Sildenafil has demonstrated robust efficacy in large Phase 3 trials [20].

Promising potential: Established. Sildenafil is a fully approved pharmaceutical with decades of clinical use and extensive generic availability.

Side-effect profile: Well characterized. The principal distinguishing adverse event relative to tadalafil is visual disturbance (blue-tinted vision), reflecting the lower PDE5/PDE6 selectivity ratio of sildenafil (approximately 7-fold for PDE6 versus greater than 700-fold for tadalafil) [20]. Headache, flushing, and dyspepsia are common.

Overall validation: Very high. Sildenafil remains the most widely prescribed PDE5 inhibitor globally.

Comparison to nortadalafil: Sildenafil is pharmacologically superior by virtue of established clinical efficacy, well-characterized safety, and regulatory approval. The PDE5 potency and half-life are broadly comparable to nortadalafil, but the clinical evidence base is incomparably larger.

12.3 Vardenafil

Mechanism: Selective PDE5 inhibitor. IC₅₀ approximately 0.7 to 0.9 nM, the most potent of the approved PDE5 inhibitors at the enzyme level. Marketed as Levitra and Staxyn (orodispersible formulation).

Novelty: Low. Vardenafil is a piperazine-substituted imidazotriazinone, structurally related to sildenafil but distinct from the tadalafil/nortadalafil class.

Effect size: PDE5 potency is approximately 10- to 15-fold greater than nortadalafil. The elimination half-life (approximately 4 to 6 hours) is comparable to nortadalafil. Clinical efficacy in Phase 3 trials is similar to sildenafil and tadalafil at approved doses [20].

Promising potential: Established but declining in market share relative to tadalafil and sildenafil generics.

Side-effect profile: Well characterized. Similar to sildenafil with modest PDE6 cross-reactivity (visual disturbance reported). The compound carries a QT prolongation warning at supratherapeutic doses.

Overall validation: High. Vardenafil is approved and has a substantial clinical evidence base, though smaller than sildenafil and tadalafil.

Comparison to nortadalafil: Vardenafil is substantially more potent at PDE5 and has comprehensive clinical validation. Nortadalafil has no advantage over vardenafil in any measured parameter.

12.4 Avanafil

Mechanism: Selective PDE5 inhibitor. IC₅₀ approximately 5.2 nM. The most recently approved PDE5 inhibitor (2012), marketed as Stendra. Distinguished by rapid onset of action (15 to 30 minutes) and favorable PDE5/PDE6 selectivity (greater than 100-fold).

Novelty: Moderate. Avanafil was designed for rapid onset and high PDE5 selectivity, representing an incremental innovation over the earlier PDE5 inhibitors.

Effect size: PDE5 potency is comparable to nortadalafil. The elimination half-life (approximately 5 hours) is comparable. The rapid onset of action (driven by favorable dissolution and absorption characteristics) is a distinct clinical advantage not demonstrated for nortadalafil.

Promising potential: Moderate. Avanafil is approved but has achieved modest market penetration relative to sildenafil and tadalafil generics.

Side-effect profile: Favorable relative to sildenafil. The high PDE5/PDE6 selectivity reduces the incidence of visual disturbance. Headache, flushing, and nasal congestion are the principal adverse events [28].

Overall validation: Moderate to high. Phase 3 efficacy and safety data are robust, though the postmarketing surveillance database is smaller than for sildenafil and tadalafil.

Comparison to nortadalafil: Avanafil is pharmacologically comparable in potency and half-life but vastly superior in clinical evidence, regulatory approval, and characterized safety.

12.5 Mirodenafil

Mechanism: Selective PDE5 inhibitor. IC₅₀ approximately 0.33 nM. Approved in the Republic of Korea (2007) for erectile dysfunction, marketed as Mvix. Not approved by the FDA or the European Medicines Agency.

Novelty: Moderate. Mirodenafil employs a pyrrolopyrimidinone scaffold and was developed by SK Chemicals as a next-generation PDE5 inhibitor with enhanced potency.

Effect size: PDE5 potency is approximately 30- to 35-fold greater than nortadalafil. The elimination half-life (approximately 2.5 hours) is shorter than nortadalafil. Clinical efficacy in Korean Phase 3 trials was comparable to sildenafil at approved doses [29].

Promising potential: Limited outside the Korean market. The compound has not been advanced to global regulatory filings.

Side-effect profile: Characterized in Korean Phase 3 trials. Adverse events similar to the PDE5 inhibitor class (headache, flushing, dyspepsia). The high potency raises theoretical concerns about dose-dependent adverse events at supratherapeutic exposures.

Overall validation: Moderate within the Korean regulatory framework; low globally.

Comparison to nortadalafil: Mirodenafil is substantially more potent at PDE5 and has clinical data from registration trials, though limited to a single regulatory jurisdiction. Nortadalafil has no advantage over mirodenafil as a PDE5 inhibitor.

12.6 Comparator summary

The five comparator PDE5 inhibitors (tadalafil, sildenafil, vardenafil, avanafil, mirodenafil) uniformly surpass nortadalafil in clinical validation, regulatory status, safety characterization, and (with the exception of avanafil, which is approximately equipotent) pharmacological potency. Nortadalafil does not occupy a unique pharmacological niche within the PDE5 inhibitor landscape: it is less potent than its parent compound tadalafil, lacks the extended duration of action that differentiates tadalafil from the other approved PDE5 inhibitors, has no clinical evidence base, and carries unknown risks that cannot be quantified in the absence of formal safety studies.

The principal utility of nortadalafil is not as a therapeutic candidate but as an analytical reference standard for the detection of tadalafil-related adulterants in dietary supplements and as a research tool compound for PDE5 structure-activity relationship studies. In the forensic and analytical chemistry context, nortadalafil is an important compound: it is the parent structure from which a growing family of N-substituted nortadalafil derivatives are generated by supplement manufacturers seeking to evade regulatory detection, and its analytical characterization (retention time, mass spectrum, NMR profile) serves as the reference point for identification of novel analogues.

Investigators considering nortadalafil for any application beyond analytical reference or in vitro pharmacology research should recognize that every approved PDE5 inhibitor offers superior potency, characterization, safety documentation, and clinical evidence.

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This monograph is provided for research use only. Not for medical, diagnostic, or therapeutic purposes. Not for human consumption. Nortadalafil is not approved by any regulatory authority for any indication. The compound has not been evaluated in controlled clinical trials. Safety data are inferred from the PDE5 inhibitor class and from forensic case reports; the dose-response relationship, chronic toxicity profile, and drug interaction magnitudes have not been formally characterized. Investigators should obtain analytical confirmation of identity and purity on every lot of research-grade material.