

RESEARCH MONOGRAPH . COMPOUND PROFILE

Mirodenafil

A second-generation pyrrolopyrimidinone PDE5 inhibitor developed by SK Chemicals in South Korea for erectile dysfunction, distinguished from first-generation agents by approximately 10-fold higher PDE5 affinity, superior isoenzyme selectivity, and an emerging multimodal research profile in Alzheimer's disease through cGMP/PKG/CREB signaling, autophagy enhancement, and neuroinflammatory modulation.

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ABSTRACT

Mirodenafil (SK3530) is a potent, selective, and reversible inhibitor of cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 (PDE5) belonging to the pyrrolopyrimidinone structural class. Developed by SK Chemicals Life Science (Seongnam, South Korea) and approved in 2007 by the Korea Ministry of Food and Drug Safety for the treatment of erectile dysfunction, mirodenafil is marketed as Mvix in 50 mg and 100 mg oral tablet formulations and as a 50 mg orally dissolving film. The compound inhibits PDE5 with an IC₅₀ of 0.34 nmol/L, approximately 10-fold more potent than sildenafil (IC₅₀ 3.5 nmol/L), and exhibits selectivity ratios of approximately 48,235-fold over PDE1, 254,000-fold over PDE3, and greater than 10,000-fold over PDE11. The PDE6 selectivity ratio is approximately 30-fold, intermediate between sildenafil and tadalafil but clinically associated with a low incidence of visual disturbance at therapeutic doses. Pharmacokinetically, mirodenafil is rapidly absorbed after oral administration with a time to maximum plasma concentration of 0.67 to 1.5 hours, an elimination half-life of 1.32 to 3.0 hours, oral bioavailability of 24 to 43 percent for the parent compound, and approximately 97 percent plasma protein binding. Metabolism is predominantly hepatic through CYP3A4-mediated N-dealkylation to the active metabolite SK-3541, which retains approximately one-tenth of the PDE5 inhibitory activity of the parent compound. Clinical efficacy in erectile dysfunction has been demonstrated in multiple randomized, double-blind, placebo-controlled trials totaling more than 700 patients across general, diabetic, and hypertensive populations, with improvements in the International Index of

Erectile Function erectile function domain score of 7 to 12 points over placebo. Adverse events are predominantly mild to moderate, with flushing (3.3 to 24.1 percent) and headache (1.8 to 14.8 percent) as the most common; no visual disturbances or myalgia have been reported in published trials. Beyond erectile dysfunction, mirodenafil (designated AR1001 by licensee AriBio) has entered clinical development for Alzheimer's disease on the basis of preclinical evidence demonstrating multimodal neuroprotective activity: activation of the cGMP/PKG/CREB signaling pathway, enhancement of autophagy-lysosome clearance of amyloid-beta and phosphorylated tau, suppression of neuroinflammation, and improvement of mitochondrial function. A Phase 2 randomized placebo-controlled trial in 210 patients with mild to moderate Alzheimer's disease reported that AR1001 30 mg daily as monotherapy produced a statistically significant 4.019-point improvement on the ADAS-Cog 13 at 26 weeks ($p = 0.012$) with concurrent reductions in plasma phosphorylated tau-181 and tau-217 biomarkers. The global Phase 3 POLARIS-AD trial, enrolling approximately 1,150 participants with early Alzheimer's disease across 200 sites under FDA, EMA, and MHRA authorization, is currently underway with a primary endpoint of change in Clinical Dementia Rating Sum of Boxes at 52 weeks. This monograph reviews the chemistry, pharmacology, pharmacokinetics, clinical evidence, sourcing, handling, stack interactions, safety profile, and comparative positioning of mirodenafil against five PDE5 inhibitor alternatives.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Mirodenafil.

Marketed names: Mvix (SK Chemicals Life Science; South Korea).

Development codes: SK3530 (SK Chemicals), SK-3530 (alternative notation). The compound has been designated AR1001 by AriBio for Alzheimer's disease clinical development; the active pharmaceutical ingredient in AR1001 is mirodenafil dihydrochloride [1, 2].

Chemical Abstracts Service registry numbers: 862189-95-5 (free base), 862189-96-6 (dihydrochloride salt). The dihydrochloride salt is the pharmaceutical-grade formulation used in commercial tablets and in clinical trial material.

International Union of Pure and Applied Chemistry name: 5-Ethyl-2-[5-[4-(2-hydroxyethyl)piperazin-1-yl]sulfonyl-2-propoxyphenyl]-7-propyl-3,5-dihydro-4H-pyrrolo[3,2-d]pyrimidin-4-one.

1.2 Structural class and chemistry

Mirodenafil is a pyrrolopyrimidinone compound, sharing the core heterocyclic scaffold with sildenafil but differing in the replacement of the pyrazolopyrimidine ring system with a dihydropyrrole ring and in the N- and O-side chain substitution pattern [3, 4]. The structural class places it among the second-generation PDE5 inhibitors, a group designed to improve upon the potency, selectivity, and pharmacokinetic profile of the first-generation agents (sildenafil, tadalafil, vardenafil).

Molecular formula: C₂₆H₃₇N₅O₅S (free base); C₂₆H₃₉Cl₂N₅O₅S (dihydrochloride).

Molecular weight: 531.67 g/mol (free base); 604.59 g/mol (dihydrochloride salt).

Physical properties: White to off-white crystalline powder. Soluble in water as the dihydrochloride salt; soluble in dimethyl sulfoxide and methanol. The free base is sparingly soluble in aqueous media.

Stereochemistry: Mirodenafil does not contain classical stereocenters in the standard pharmaceutical form. The pyrrolopyrimidinone core is achiral, and the piperazine and phenyl ring substituents do not introduce asymmetric carbon centers. The compound is supplied as a single chemical entity without enantiomeric considerations.

1.3 Synthesis

The published medicinal chemistry of mirodenafil derives from structure-activity relationship optimization around the pyrrolopyrimidinone scaffold at SK Chemicals. The synthesis proceeds through construction of the 7H-pyrrolo[2,3-d]pyrimidine core, alkylation at the 5- and 7-positions with ethyl and propyl groups respectively, introduction of the 2-propoxyphenyl moiety bearing the sulfonyl linker, and coupling of the 4-(2-hydroxyethyl)piperazine group through sulfonamide bond formation [3, 5]. The dihydrochloride salt is prepared by treatment of the free base with hydrochloric acid in appropriate solvent and recrystallization. The compound is manufactured to pharmaceutical-grade purity (greater than 99 percent by HPLC) for the marketed Mvix formulation. The orally dissolving film (ODF) formulation, developed in December 2011, uses a polymer-based matrix to deliver 50 mg of mirodenafil dihydrochloride with rapid buccal dissolution [6].

2. Abstract

Mirodenafil (SK3530) is a potent and selective inhibitor of phosphodiesterase type 5 (PDE5), the enzyme responsible for hydrolysis of cyclic guanosine monophosphate (cGMP) in smooth muscle cells of the corpus cavernosum, the pulmonary vasculature, and other tissues. The compound was developed by SK Chemicals Life Science as a second-generation PDE5 inhibitor with improved potency and selectivity over first-generation agents and was approved in South Korea in 2007 for the treatment of erectile dysfunction under the trade name Mvix [1, 3].

The primary mechanism of action is inhibition of PDE5 with an IC₅₀ of 0.34 nmol/L, producing sustained elevation of intracellular cGMP in response to nitric oxide (NO) release during sexual stimulation. This cGMP elevation activates protein kinase G (PKG), which phosphorylates downstream targets including myosin light chain phosphatase, resulting in smooth muscle relaxation, increased arterial blood flow to the corpus cavernosum, and penile erection [4, 7]. The PDE5 inhibitory potency is approximately 10-fold greater than that of sildenafil and is accompanied by superior selectivity over PDE1 (48,235-fold), PDE3 (254,000-fold), and PDE11 (greater than 10,000-fold), with a PDE6 selectivity ratio of approximately 30-fold [4].

Clinical efficacy in erectile dysfunction has been established through multiple Phase 3 randomized, double-blind, placebo-controlled trials. In the pivotal trial (Paick et al. 2008, n = 223), mirodenafil 100 mg on demand produced improvements in the IIEF erectile function domain score of 10.7 points over baseline compared to 2.3 points with placebo, with 62.2 percent of patients recovering normal erectile function (IIEF-EF score 26 or greater) [8]. Subsequent trials confirmed efficacy in diabetic men (Park et al. 2010, n = 108; 9.3-point improvement vs. 1.4 placebo) [9], hypertensive men (Paick et al. 2010, n = 107; 9.35-point improvement vs. 2.66 placebo) [10], and with once-daily 50 mg dosing for concurrent lower urinary tract symptoms (Chung et al. 2013, n = 134) [11]. A meta-analysis of three pivotal trials (Kim et al. 2014, n = 374) confirmed the overall efficacy and tolerability of mirodenafil across the dose range [12].

Pharmacokinetics are characterized by rapid absorption (T_{max} 0.67 to 1.5 hours), short elimination half-life (1.32 to 3.0 hours), moderate oral bioavailability (24 to 43 percent for parent compound), and high plasma protein binding (approximate

mately 97 percent). Metabolism is predominantly hepatic through CYP3A4-mediated N-dealkylation to the active metabolite SK-3541, with minor contribution from CYP2C8 [13, 14]. Excretion is primarily fecal, with less than 2 percent of the administered dose recovered unchanged in urine [4].

The most significant expansion of the mirodenafil research profile is the Alzheimer's disease program conducted by AriBio under the designation AR1001. Preclinical studies demonstrated that mirodenafil crosses the blood-brain barrier and exerts multimodal neuroprotective effects: activation of the cGMP/PKG/CREB signaling cascade, enhancement of autophagy-lysosome clearance of amyloid-beta and phosphorylated tau, suppression of GSK-3beta signaling, reduction of neuroinflammatory markers, and improvement of mitochondrial function in transgenic Alzheimer's disease mouse models [15]. A Phase 2 randomized placebo-controlled trial (NCT03625622) in 210 patients with mild to moderate Alzheimer's disease reported that AR1001 30 mg daily as monotherapy produced a statistically significant 4.019-point improvement on the ADAS-Cog 13 scale at 26 weeks ($p = 0.012$) with concurrent reductions in plasma phosphorylated tau-181 and tau-217 biomarkers, although the compound did not meet its primary endpoint across the full intention-to-treat population [16, 17]. The global Phase 3 POLARIS-AD trial (NCT05531526) is currently enrolling approximately 1,150 participants with early Alzheimer's disease across 200 sites under FDA, EMA, and MHRA authorization, with a primary endpoint of change in Clinical Dementia Rating Sum of Boxes (CDR-SB) at 52 weeks [18].

The compound is well tolerated at registered doses. The principal adverse events are flushing (3.3 to 24.1 percent), headache (1.8 to 14.8 percent), and dyspepsia (0 to 4.4 percent), with overall treatment-emergent adverse event rates of 24.3 to 37.0 percent across published trials [4]. No visual disturbances, myalgia, or back pain have been reported in the mirodenafil clinical literature, distinguishing it from sildenafil and tadalafil on these specific parameters.

3. Discovery and Development History

3.1 Origin

Mirodenafil was developed at SK Chemicals Life Science (now a subsidiary of SK Discovery) in Seongnam, South Korea, as part of a medicinal chemistry program to identify second-generation PDE5 inhibitors with improved pharmacological profiles relative to sildenafil. The program explored structural modifications to the pyrazolopyrimidine core of sildenafil, replacing the pyrazole ring with a dihydropyrrole and modifying the N- and O-side chains to produce the pyrrolopyrimidinone scaffold. SK3530 was selected from this series as the lead candidate on the basis of approximately 10-fold higher PDE5 affinity, substantially improved PDE1 and PDE3 selectivity, oral bioavailability in preclinical species, and a favorable toxicological profile in standard safety pharmacology studies [3, 4].

3.2 Erectile dysfunction registration

SK Chemicals advanced mirodenafil through Phase 1 pharmacokinetic studies in healthy Korean volunteers, through Phase 2 dose-finding studies, and through the pivotal Phase 3 randomized double-blind placebo-controlled trial in men with erectile dysfunction. The compound received approval from the Korea Ministry of Food and Drug Safety (MFDS, then KFDA) in 2007 and was launched as Mvix in 50 mg and 100 mg tablet formulations [1]. The 50 mg orally dissolving film (ODF) formulation was introduced in December 2011, providing a more convenient route for patients who preferred not to swallow tablets [6]. The compound has not been approved by the United States Food and Drug Administration, the European Medicines Agency, or any regulatory authority outside South Korea.

3.3 Expansion to lower urinary tract symptoms

Following the precedent set by tadalafil 5 mg daily for concurrent erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia, investigators evaluated mirodenafil 50 mg daily in this population. Lee et al. (2011) conducted an 8-week open-label study (n = 121) demonstrating significant improvements in both IPSS (from 15.60 to 9.01) and IIEF-5 scores (from 7.78 to

15.22) [19]. Combination therapy with alpha-1 adrenergic receptor blockers was evaluated in a multicenter open-label prospective study (n = 80) that confirmed safety with regard to blood pressure and demonstrated additive improvements in voiding symptoms and sexual function [20].

3.4 AriBio licensing and Alzheimer's disease repositioning

In 2011, SK Chemicals licensed the global rights for mirodenafil in non-erectile dysfunction indications to AriBio (formerly AriBio, Inc.), a Korean-American biotechnology company focused on neurodegenerative diseases. AriBio redesignated mirodenafil dihydrochloride as AR1001 and initiated a preclinical program evaluating the compound in transgenic Alzheimer's disease mouse models. The preclinical results, published in 2022 by Park et al. in *Alzheimer's Research and Therapy*, demonstrated multimodal activity including reduction of amyloid-beta and phosphorylated tau burden, enhancement of autophagy, suppression of neuroinflammation, and cognitive improvement [15]. These data supported the initiation of the Phase 2 clinical trial (NCT03625622) and, subsequently, the global Phase 3 POLARIS-AD trial (NCT05531526), which received FDA authorization in the United States, EMA clinical trial authorization in seven European countries, and MHRA authorization in the United Kingdom [18, 21].

4. Mechanism of Action

Mirodenafil is a competitive, reversible inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5). Its pharmacological effects derive primarily from the inhibition of cGMP hydrolysis in smooth muscle cells, neurons, and other PDE5-expressing tissues, with the consequent sustained elevation of intracellular cGMP driving downstream protein kinase G (PKG) activation and tissue-specific functional responses.

4.1 PDE5 inhibition and the NO/cGMP/PKG pathway

PDE5 is a homodimeric enzyme expressed at high density in the smooth muscle of the corpus cavernosum, the pulmonary vasculature, the bladder detrusor, the prostate, and the vascular smooth muscle of systemic arteries, and at moderate density in the hippocampus, cortex, cerebellum, and other central nervous system regions [7]. The enzyme contains a catalytic domain that hydrolyzes the 3',5'-cyclic phosphodiester bond of cGMP to produce 5'-GMP, thereby terminating the cGMP second-messenger signal.

Mirodenafil binds the catalytic site of PDE5 with an IC₅₀ of 0.34 nmol/L, occupying the cGMP-binding pocket in a competitive and reversible manner [4]. The binding affinity represents an approximately 10-fold improvement over sildenafil (IC₅₀ 3.5 nmol/L), placing mirodenafil among the most potent PDE5 inhibitors characterized to date. The structural basis for the enhanced affinity is the favorable interaction between the pyrrolopyrimidinone core and the glutamine-817 residue in the PDE5 catalytic pocket, combined with the piperazinylsulfonyl side chain interactions with the hydrophobic clamp region [3].

The functional consequence of PDE5 inhibition is the sustained elevation of cGMP in target tissues following nitric oxide (NO) release. In the corpus cavernosum, sexual stimulation triggers non-adrenergic non-cholinergic (NANC) neural release of NO and endothelial NO synthase activation, which activates soluble guanylate cyclase to produce cGMP. The accumulated cGMP activates PKG, which phosphorylates multiple targets including myosin light chain phosphatase (promoting dephosphorylation of myosin light chains and smooth muscle relaxation), the IP₃ receptor-associated cGMP kinase substrate (reducing intracellular calcium

release), and phospholamban (enhancing calcium reuptake into the sarcoplasmic reticulum). The net effect is smooth muscle relaxation, arterial dilation, and increased blood flow to the corpus cavernosum, producing penile erection [7].

4.2 Isoenzyme selectivity

The selectivity profile of mirodenafil across the 11 mammalian PDE isoenzyme families is a defining pharmacological characteristic. Published selectivity ratios (IC₅₀ for the given PDE divided by IC₅₀ for PDE5) include: PDE1, 48,235-fold; PDE3, 254,000-fold; PDE6, approximately 30-fold; PDE11, greater than 10,000-fold [4]. The high PDE1 selectivity (compared to sildenafil at 80-fold) reduces the potential for calcium/calmodulin-dependent signaling disruption. The high PDE3 selectivity (compared to sildenafil at 4,629-fold) reduces the potential for cardiac inotropic and chronotropic effects. The PDE6 selectivity of approximately 30-fold is lower than that of tadalafil (greater than 700-fold) but is clinically associated with an absence of reported visual disturbances in all published mirodenafil trials, suggesting that the therapeutic window at approved doses is sufficient to avoid retinal PDE6 inhibition. The high PDE11 selectivity distinguishes mirodenafil from tadalafil, which has a PDE11 selectivity ratio of only approximately 5-fold and has been associated with myalgia and back pain in a subset of patients [4, 22].

4.3 Central nervous system mechanisms

The Alzheimer's disease research program has characterized several CNS-relevant mechanisms of mirodenafil that extend beyond the canonical smooth muscle relaxation pathway.

cGMP/PKG/CREB signaling. PDE5 is expressed in hippocampal and cortical neurons, where cGMP/PKG signaling activates cAMP response element-binding protein (CREB) through phosphorylation at serine-133. CREB is a transcription factor that drives expression of brain-derived neurotrophic factor (BDNF), synaptic plasticity genes, and anti-apoptotic factors. Mirodenafil has been shown to enhance CREB phosphorylation and BDNF expression in transgenic Alzheimer's disease mouse models [15].

Autophagy enhancement. Mirodenafil activates the autophagosomal pathway, promoting clearance of aggregated amyloid-beta and phosphorylated tau through enhanced lysosomal processing. The mechanism involves PKG-dependent activa-

tion of TFEB (transcription factor EB), the master regulator of lysosomal biogenesis and autophagy gene expression [15].

GSK-3beta suppression. Glycogen synthase kinase 3-beta (GSK-3beta) is a principal tau kinase responsible for the hyperphosphorylation of tau protein that produces neurofibrillary tangles. Mirodenafil downregulates GSK-3beta activity through PKG-mediated inhibitory phosphorylation at serine-9, resulting in reduced tau phosphorylation at disease-relevant epitopes [15].

Neuroinflammatory modulation. Mirodenafil suppresses microglial activation and reduces proinflammatory cytokine release (tumor necrosis factor-alpha, interleukin-1-beta, interleukin-6) in activated microglia, consistent with the known anti-inflammatory effects of cGMP/PKG signaling in immune cells [15].

Wnt/beta-catenin signaling restoration. Mirodenafil modulates transcription factors including glucocorticoid receptor (GR) and Dickkopf-1 (Dkk1) to restore Wnt/beta-catenin signaling, a pathway that is disrupted in Alzheimer's disease and that supports synaptic integrity and neuronal survival [15].

Mitochondrial function. Preclinical data indicate that mirodenafil improves mitochondrial membrane potential and reduces oxidative stress markers in neurons exposed to amyloid-beta oligomers, consistent with the known mitochondrial protective effects of PKG signaling [15].

4.4 Composite pharmacology

At the registered erectile dysfunction dose of 100 mg, peak plasma concentrations of mirodenafil substantially exceed the PDE5 IC50 (0.34 nmol/L), producing near-complete PDE5 inhibition in the corpus cavernosum. At the Alzheimer's disease dose of 30 mg daily (AR1001), the steady-state plasma and CNS concentrations are sufficient to engage the cGMP/PKG/CREB pathway in hippocampal and cortical tissues, as demonstrated by the biomarker effects observed in the Phase 2 clinical trial [16].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Mirodenafil is rapidly absorbed from the gastrointestinal tract after oral administration. Time to maximum plasma concentration (T_{max}) ranges from 0.67 to 1.5 hours across published pharmacokinetic studies in healthy Korean and Mexican volunteers [4, 23]. Maximum plasma concentration (C_{max}) and area under the curve (AUC) increase in an approximately dose-proportional manner across the 25 to 200 mg dose range. Food intake reduces the rate and extent of absorption; the compound is recommended to be taken in the fasted state for optimal onset of action in the erectile dysfunction indication [4].

5.2 Distribution

Plasma protein binding is approximately 97 percent, predominantly to albumin. The volume of distribution has not been precisely reported in published human studies but is estimated from the pharmacokinetic profile to be moderate, consistent with tissue distribution beyond the central compartment. The compound crosses the blood-brain barrier, as demonstrated by central nervous system pharmacological effects in preclinical models and by the cognitive effects observed in the AR1001 Alzheimer's disease clinical trial [15, 16].

5.3 Metabolism

Mirodenafil is metabolized predominantly in the liver by cytochrome P450 enzymes. The principal metabolic transformation is N-dealkylation of the 2-hydroxyethyl group on the piperazine ring, producing the active metabolite SK-3541 (also designated N-dehydroxyethyl mirodenafil). CYP3A4 was identified as the major enzyme responsible for this N-dealkylation, with CYP2C8 as a minor contributor [13, 14].

SK-3541 retains approximately one-tenth of the PDE5 inhibitory activity of the parent compound. The metabolite contributes to the overall pharmacodynamic effect, particularly as its elimination half-life may exceed that of the parent compound, extending the duration of PDE5 inhibition beyond what would be predicted from mirodenafil plasma concentrations alone [4].

Mirodenafil also inhibits CYP3A4, CYP2C19, and CYP2D6 activities in human liver microsomes with IC₅₀ values of 15.6, 38.2, and 77.0 micromolar, respectively [14]. These IC₅₀ values are well above the peak plasma concentrations achieved at clinical doses, suggesting that clinically significant inhibition of these enzymes by mirodenafil itself is unlikely at therapeutic concentrations.

5.4 Elimination

Elimination half-life of the parent compound ranges from 1.32 to 3.0 hours across published studies [4, 23]. This is shorter than the elimination half-lives of sildenafil (3 to 5 hours), vardenafil (4 to 5 hours), and substantially shorter than tadalafil (17.5 hours). The short half-life supports on-demand dosing for erectile dysfunction but may limit the duration of effect for indications requiring sustained PDE5 inhibition.

Oral bioavailability of the parent compound is 24.1 to 43.4 percent, reflecting substantial first-pass hepatic metabolism [4]. Excretion is primarily fecal; less than 2 percent of the administered dose is recovered unchanged in urine. The fecal route of elimination reflects the hepatic metabolic pathway and biliary excretion of metabolites.

5.5 Drug-drug interaction studies

The effects of CYP3A4 modulators on mirodenafil pharmacokinetics have been characterized in a crossover study in healthy Korean male volunteers [24]. Co-administration with ketoconazole (a potent CYP3A4 inhibitor) substantially increased mirodenafil AUC and C_{max}, confirming the CYP3A4 dependence of metabolism. Co-administration with rifampicin (a potent CYP3A4 inducer) reduced mirodenafil AUC by approximately 97 percent (0.03-fold) and increased the metabolic ratio by 2.9-fold, indicating near-complete first-pass metabolism under enzyme induction conditions [24]. These findings establish that concomitant use of strong CYP3A4 inhibitors or inducers requires dose adjustment.

5.6 Routes of administration

Two oral formulations are marketed: conventional film-coated tablets (50 mg and 100 mg mirodenafil dihydrochloride) and an orally dissolving film (50 mg). Both formulations are designed for oral administration. No parenteral formulation has been developed or registered.

5.7 Special populations

Pharmacokinetic studies in Mexican healthy volunteers confirmed the general pharmacokinetic profile observed in Korean subjects, with T_{max} and half-life values within the same range, supporting extrapolation across ethnic groups [23]. Formal studies in hepatic impairment, renal impairment, and elderly populations have not been published in peer-reviewed form as of the monograph revision date.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

Mirodenafil inhibits PDE5 with an IC₅₀ of 0.34 nmol/L in purified enzyme assays [4]. The compound relaxes pre-contracted rabbit corpus cavernosum smooth muscle strips in a concentration-dependent manner, with potency approximately 10-fold greater than sildenafil in the same assay system [3]. In vitro selectivity profiling against all 11 mammalian PDE isoenzyme families has been performed, establishing the selectivity ratios described in Section 4.2.

6.2 Erectile dysfunction animal models

The penile erection efficacy of mirodenafil has been characterized in rabbit models of normal erectile function and in models of erectile dysfunction associated with spinal cord injury. In the spinal cord injury model (surgical transection at the L2 to L4 lumbar vertebra and ischemic-reperfusion injury), oral mirodenafil induced penile erections at doses of 0.3, 1, and 3 mg/kg, while sildenafil required 3 mg/kg for an equivalent erectile response. The onset of erectile activity was faster with mirodenafil than with sildenafil in these models [25].

In a rat model of cavernosal nerve injury (bilateral cavernosal nerve crush), mirodenafil treatment preserved intracavernosal pressure responses to cavernosal nerve electrical stimulation and reduced fibrotic changes in the corpus cavernosum, suggesting a protective effect against post-nerve injury erectile dysfunction [26].

6.3 Alzheimer's disease preclinical models

The most extensive preclinical characterization of mirodenafil outside erectile dysfunction has been conducted in transgenic Alzheimer's disease mouse models. Park et al. (2022) evaluated mirodenafil in 5xFAD transgenic mice (which express five familial Alzheimer's disease mutations and develop aggressive amyloid pathology) and reported the following findings [15]:

Reduction of amyloid-beta plaque burden in the cortex and hippocampus following chronic oral administration. Reduction of phosphorylated tau at multiple disease-relevant epitopes (AT8, AT180, PHF-1). Reversal of spatial memory deficits in the Morris water maze and novel object recognition paradigms. Enhancement of long-term potentiation (LTP) in hippocampal slices. Activation of the cGMP/PKG/CREB signaling cascade with increased phospho-CREB and BDNF expression. Enhancement of autophagy flux as measured by LC3-II conversion and p62 degradation. Suppression of microglial activation markers (Iba1, CD68) and reduction of proinflammatory cytokine levels. Improvement of mitochondrial membrane potential and reduction of reactive oxygen species production.

These multimodal effects, operating through both the canonical cGMP/PKG pathway and downstream transcriptional and autophagy mechanisms, provided the scientific basis for the AR1001 clinical development program.

7. Clinical Evidence Base

7.1 Pivotal erectile dysfunction trial

Paick et al. (2008) conducted the pivotal Phase 3, multicenter, randomized, double-blind, placebo-controlled trial of mirodenafil in Korean men with erectile dysfunction of at least 6 months' duration (n = 223) [8]. Patients were randomized to placebo, mirodenafil 50 mg, or mirodenafil 100 mg taken on demand approximately 1 hour before anticipated sexual activity for 12 weeks. The primary endpoint was change from baseline in the IIEF erectile function domain score.

Results: the 50 mg and 100 mg groups showed IIEF-EF domain improvements of 7.6 and 10.7 points, respectively, compared to 2.3 points in the placebo group ($p < 0.001$ for both comparisons). The Sexual Encounter Profile question 2 (SEP2; vaginal penetration success) response rates improved by 27.72 to 38.98 percentage points over baseline. SEP3 (successful intercourse completion) response rates improved by 44.20 to 67.33 percentage points. Recovery to normal erectile function (IIEF-EF score of 26 or greater) was achieved by 46.6 percent (50 mg) and 62.2 percent (100 mg) of patients [8].

7.2 Diabetic erectile dysfunction

Park et al. (2010) evaluated mirodenafil 100 mg on demand for 12 weeks in a multicenter, randomized, double-blind, placebo-controlled trial in Korean men with diabetes mellitus and erectile dysfunction (n = 108) [9]. The IIEF-EF domain improvement was 9.3 points with mirodenafil versus 1.4 points with placebo ($p < 0.001$). SEP2 improvement was 36.1 percent versus 8.9 percent; SEP3 improvement was 61.8 percent versus 17.8 percent. Return to normal erectile function was achieved by 32.7 percent of patients. The authors concluded that mirodenafil is an effective and well-tolerated agent for the treatment of diabetic men with erectile dysfunction [9].

7.3 Hypertensive erectile dysfunction

Paick et al. (2010) conducted a similar 12-week randomized double-blind placebo-controlled trial in men with hypertension and erectile dysfunction (n = 107) [10]. Mirodenafil 100 mg on demand produced an IIEF-EF domain improvement of 9.35 points versus 2.66 points with placebo ($p < 0.001$). SEP2 improvement was 30.2 percent versus 6.5 percent; SEP3 improvement was 55.3 percent versus 16.5 percent [10].

7.4 Once-daily dosing and lower urinary tract symptoms

Chung et al. (2013) evaluated once-daily administration of mirodenafil 50 mg for 12 weeks in men with erectile dysfunction in a multicenter, double-blind, placebo-controlled trial (n = 134) [11]. The IIEF-5 score improved to 14.82 with mirodenafil versus 10.33 with placebo ($p < 0.001$). SEP2 improved by 43.0 percent versus 17.0 percent; SEP3 improved by 29.0 percent versus 4.5 percent. The once-daily regimen demonstrated sustained efficacy consistent with the contribution of the active metabolite SK-3541 to the overall pharmacodynamic effect [11].

Lee et al. (2011) conducted an 8-week open-label study of mirodenafil 50 mg daily in 121 men with concurrent erectile dysfunction and lower urinary tract symptoms associated with benign prostatic hyperplasia [19]. IPSS decreased from 15.60 at baseline to 9.01 at week 8, and IIEF-5 increased from 7.78 to 15.22. The quality of life index improved significantly. These results supported the dual indication potential of mirodenafil for concurrent erectile dysfunction and LUTS/BPH.

7.5 Orally dissolving film formulation

A Phase IV, multicenter, double-blind, randomized, placebo-controlled, parallel-group study evaluated the mirodenafil 50 mg ODF formulation in Korean men with erectile dysfunction [6]. The ODF formulation demonstrated efficacy and tolerability comparable to the tablet formulation, with the convenience advantage of buccal dissolution without the need for water.

7.6 Meta-analysis

Kim et al. (2014) conducted a meta-analysis of three multicenter, randomized, double-blind, placebo-controlled clinical trials of mirodenafil, comprising 374 patients [12]. The pooled analysis confirmed that mirodenafil at 50 and 100 mg significantly improved erectile function compared to placebo, with an overall IIEF-EF domain improvement of 7.32 points. In a comparative meta-analytic context (Du et al. 2014), the IIEF-EF improvement with mirodenafil (7.32 points) was comparable to that of sildenafil (6.00), tadalafil (7.49), vardenafil (7.11), and udenafil (5.66) [4, 12].

7.7 Alzheimer's disease Phase 2 trial

The Phase 2 randomized, double-blind, placebo-controlled trial (AR1001-ADP2-US01; NCT03625622) evaluated AR1001 (mirodenafil dihydrochloride) at doses of 10 mg and 30 mg daily for 26 weeks in 210 patients with mild to moderate Alzheimer's disease at 21 sites in the United States, followed by a 26-week optional open-label extension [16, 17].

Co-primary efficacy endpoints were changes from baseline at Week 26 in the ADAS-Cog 13 and the ADCS-CGIC. In the full intention-to-treat population, AR1001 did not meet the co-primary endpoints. In the pre-specified subgroup of patients receiving AR1001 30 mg as monotherapy (without concomitant acetylcholinesterase inhibitors or memantine), a statistically significant improvement was observed: ADAS-Cog 13 improvement of 4.019 points over baseline at Week 26 ($p = 0.012$), with concurrent reductions in plasma phosphorylated tau-181 of 1.361 pg/mL ($p = 0.023$) and in plasma phosphorylated tau-217 of 0.426 pg/mL compared to placebo [16, 17].

7.8 Alzheimer's disease Phase 3 trial (POLARIS-AD)

The POLARIS-AD trial (NCT05531526) is a Phase 3, double-blind, randomized, placebo-controlled, multicenter study evaluating AR1001 30 mg once daily for 52 weeks in approximately 1,150 participants with early Alzheimer's disease across approximately 200 sites globally [18, 21]. The primary endpoint is change from baseline in CDR-SB at 52 weeks. Secondary endpoints include ADAS-Cog 13, Amsterdam-IADL, Geriatric Depression Scale, MMSE, and changes in cerebrospinal fluid and

plasma biomarkers. FDA, EMA (in Czech Republic, Denmark, France, Germany, Italy, Spain, and the Netherlands), and MHRA authorization has been obtained. The trial is ongoing as of the monograph revision date; results have not been reported.

8. Sourcing and Quality Verification

Pharmaceutical-grade mirodenafil (Mvix brand, SK Chemicals Life Science) is the highest quality source for research applications where regulatory equivalence to clinical material is operationally important. The pharmaceutical-grade material is supplied as 50 mg and 100 mg oral tablets and as 50 mg ODF in South Korea. Sourcing outside South Korea requires importation under appropriate regulatory permits.

Research-grade mirodenafil is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Cayman Chemical, Selleckchem, BOC Sciences, MedKoo, Ambeed, and others) at greater than 98 percent purity by HPLC, typically as the free base or the dihydrochloride salt. Supply is in milligram to gram quantities. Pricing is moderate, in the range of \$100 to \$500 per 100 milligrams at typical research supplier scales at the time of monograph preparation.

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

- High-performance liquid chromatography area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (532.67 plus or minus 0.5 for the protonated free base $[M+H]^+$)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) confirmation of structural identity, particularly the pyrrolopyrimidinone core and piperazine ring proton environments
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography for common synthesis solvents

Third-party analytical laboratories (Janoshik Analytical, Anabolic Lab, and others) provide independent confirmation of vendor certificates of analysis. The research-grade mirodenafil market is moderately well established; lot-to-lot variability is observed and on-receipt analytical confirmation is appropriate for any investigation where dose-response precision is important.

9. Reconstitution and Handling

Mirodenafil dihydrochloride is soluble in water and in dimethyl sulfoxide (DMSO). For in vitro research applications, the compound is typically reconstituted in DMSO at stock concentrations of 10 to 50 mM, then diluted into aqueous assay buffer at the required working concentration. The final DMSO concentration in cell-based assays should be maintained below 0.1 to 0.5 percent (v/v) to avoid solvent cytotoxicity.

For in vivo research applications in rodent models, the compound has been administered by oral gavage dissolved in aqueous vehicle (0.5 percent carboxymethylcellulose or similar suspending agents) or in mixed solvent vehicles (DMSO/PEG-400/saline) at doses of 0.3 to 30 mg/kg [15, 25].

Storage of the solid compound should be at minus 20 degrees Celsius for long-term storage and at 2 to 8 degrees Celsius for working stock. The compound is stable at room temperature in dry conditions for short periods. Light protection is recommended. Aqueous stock solutions should be prepared fresh or aliquoted and stored at minus 20 degrees Celsius; stability in aqueous solution at room temperature is limited by the potential for hydrolysis of the sulfonamide bond and oxidation of the hydroxyethyl group.

DMSO stock solutions are stable at minus 20 degrees Celsius for at least 3 months. Repeated freeze-thaw cycles should be minimized; aliquoting into single-use volumes is recommended.

For the clinical (Mvix) tablet formulation, standard pharmaceutical storage at room temperature (15 to 30 degrees Celsius) in the original blister packaging is appropriate. No special reconstitution is required for the oral dosage forms.

10. Stack Interactions and Combinations

Mirodenafil interacts with several drug classes through its CYP3A4-mediated metabolism and through its pharmacodynamic mechanism. Investigators conducting research with mirodenafil, especially in chronic dosing regimens or in combination with other compounds, should consider:

CYP3A4 inhibitors. Strong inhibitors (ketoconazole, itraconazole, ritonavir, clarithromycin, nefazodone, grapefruit juice) substantially increase mirodenafil plasma exposure through inhibition of first-pass and systemic CYP3A4 metabolism. Dose reduction is required with concurrent use. The ketoconazole interaction study confirmed substantial AUC elevation [24].

CYP3A4 inducers. Strong inducers (rifampicin, carbamazepine, phenytoin, phenobarbital, St. John's wort) reduce mirodenafil plasma exposure by approximately 97 percent (as demonstrated with rifampicin), rendering the compound essentially ineffective at standard doses [24]. Concurrent use should be avoided or the dose should be substantially increased with pharmacokinetic monitoring.

Nitrates and nitric oxide donors. Concurrent use with organic nitrates (nitroglycerin, isosorbide mononitrate, isosorbide dinitrate) or nitric oxide donors (sodium nitroprusside, molsidomine, amyl nitrite) is absolutely contraindicated. The combination produces additive cGMP elevation in vascular smooth muscle, resulting in severe and potentially fatal hypotension. This contraindication applies to all PDE5 inhibitors without exception [7, 22].

Alpha-1 adrenergic receptor blockers. Concurrent use with alpha-blockers (tamsulosin, alfuzosin, doxazosin, terazosin) may produce additive hypotension through combined smooth muscle relaxation. The combination study of mirodenafil 100 mg with alpha-blockers in BPH patients did not demonstrate clinically significant hypotension, but caution is appropriate, particularly with non-uroselective alpha-blockers and at the time of peak drug concentrations [20].

Other PDE5 inhibitors. Concurrent use with another PDE5 inhibitor is pharmacologically redundant and produces additive vasodilatory effects without additional therapeutic benefit. The combination is not recommended.

Antihypertensive agents. Mirodenafil produces modest reductions in systemic blood pressure (typically 5 to 10 mmHg systolic) that are additive with antihypertensive medications. In the hypertensive erectile dysfunction trial, the combination of mirodenafil with antihypertensive therapy was well tolerated [10].

QT-prolonging agents. PDE5 inhibitors have not been associated with clinically significant QT interval prolongation in thorough QT studies. The combination of mirodenafil with QT-prolonging agents has not been specifically studied but is not expected to produce additive cardiac electrophysiological risk.

Cholinesterase inhibitors and memantine. In the AR1001 Alzheimer's disease Phase 2 trial, the monotherapy subgroup (without concurrent donepezil, rivastigmine, galantamine, or memantine) showed greater cognitive improvement than the full intention-to-treat population, raising the question of whether concurrent acetylcholinesterase inhibitor or memantine therapy attenuates the mirodenafil cognitive effect. The mechanism of this interaction, if confirmed, could involve competition at downstream cGMP/cholinergic signaling nodes. The POLARIS-AD Phase 3 trial is designed to address this question with stratified randomization [16, 18].

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at registered erectile dysfunction doses, compiled from published clinical trials, are:

- Flushing (3.3 to 24.1 percent; dose-dependent; reflects systemic vasodilation through PDE5 inhibition in vascular smooth muscle)
- Headache (1.8 to 14.8 percent; reflects cerebral vasodilation)
- Dyspepsia (0 to 4.4 percent)
- Dizziness (0 to 3.4 percent)
- Nasal congestion (1.1 to 2.2 percent)

Overall treatment-emergent adverse event rates ranged from 24.3 to 37.0 percent across published trials, with most events classified as mild or moderate in severity. Only one severe adverse event (facial flushing) has been reported across the published clinical trial literature [4, 8, 9, 10].

11.2 Distinguishing safety characteristics

Notably, no visual disturbances (blurred vision, chromatopsia, blue tinge) have been reported in any published mirodenafil trial. This is consistent with the compound's PDE6 selectivity profile: while the 30-fold PDE6 selectivity ratio is lower than that of tadalafil, it appears sufficient at clinical doses to avoid retinal PDE6 inhibition. For comparison, sildenafil (PDE6 selectivity approximately 7-fold) produces visual disturbances in 3 to 11 percent of patients, and vardenafil (PDE6 selectivity approximately 15-fold) produces visual disturbances in approximately 2 percent [4, 22].

No myalgia or back pain has been reported in published mirodenafil trials, consistent with the high PDE11 selectivity (greater than 10,000-fold). Tadalafil, with a PDE11 selectivity ratio of approximately 5-fold, produces myalgia and back pain in 5 to 7 percent of patients [22].

11.3 Cardiovascular safety

Published mirodenafil trials have not reported clinically significant cardiovascular adverse events. Blood pressure reductions are modest and consistent with the PDE5 inhibitor class effect. No serious cardiac events, including myocardial infarction or stroke, have been reported in the mirodenafil literature. The absolute contraindication with organic nitrates applies as with all PDE5 inhibitors.

11.4 Safety in the Alzheimer's disease program

The Phase 2 AR1001 trial reported a safety profile at the 30 mg daily dose that was comparable to placebo over 26 weeks of administration [16]. The lower dose used in the Alzheimer's disease program (30 mg daily, compared to 50 to 100 mg on demand for erectile dysfunction) is expected to produce lower peak plasma concentrations and a correspondingly reduced vasodilatory adverse event burden. The POLARIS-AD Phase 3 trial includes comprehensive safety monitoring as a secondary objective.

11.5 Pregnancy, lactation, and special populations

Mirodenafil is indicated for use in adult males and is not studied in women for the erectile dysfunction indication. Preclinical reproductive toxicology data have not been published in peer-reviewed form. Use in pediatric populations has not been studied. Geriatric use (greater than 65 years) has not been formally evaluated, although the Alzheimer's disease clinical program enrolls elderly participants and will provide safety data in this population.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five PDE5 inhibitor alternatives against mirodenafil, evaluated on five standards: novelty, effect size in the primary (erectile dysfunction) indication, promising potential (trajectory including non-erectile dysfunction indications), side-effect profile, and overall validation. The five comparators were selected as the principal PDE5 inhibitors with substantial clinical evidence and market presence, representing the full range of first-generation and second-generation agents.

12.1 Sildenafil (Viagra, Revatio)

Mechanism: Selective PDE5 inhibitor of the pyrazolopyrimidinone structural class. IC50 for PDE5: 3.5 nmol/L [7, 22].

Novelty: Low. Sildenafil was the first PDE5 inhibitor approved (FDA 1998) and established the therapeutic class. The mechanism and clinical application are fully characterized over more than 25 years of clinical experience.

Effect size: Meta-analytic IIEF-EF domain improvement of approximately 6.0 points over placebo. The compound is effective across broad-spectrum erectile dysfunction populations. Additional approved indications include pulmonary arterial hypertension (Revatio, 20 mg three times daily) [22].

Promising potential: Moderate. The compound is fully mature in erectile dysfunction and pulmonary arterial hypertension. PDE5 inhibition as a class mechanism is being explored for cardiac protection, Alzheimer's disease (epidemiological data suggest reduced incidence with chronic sildenafil use), and other indications, but sildenafil itself is not in active new-indication development programs comparable to the AR1001 Alzheimer's program.

Side-effect profile: Flushing (10 to 19 percent), headache (16 to 28 percent), dyspepsia (7 to 17 percent), visual disturbances (3 to 11 percent), nasal congestion (4 percent). The visual disturbance signal reflects the relatively low PDE6 selectivity

(approximately 7-fold). Overall adverse event rates (approximately 45 percent) are higher than those reported for mirodenafil [22].

Overall validation: Very high. Sildenafil is the reference standard for the PDE5 inhibitor class, with the most extensive global clinical experience and the broadest regulatory approval.

Comparison to mirodenafil: Mirodenafil has approximately 10-fold higher PDE5 affinity, substantially better PDE1 and PDE3 selectivity, and an absence of reported visual disturbances, reflecting its second-generation design. Sildenafil has vastly more extensive clinical experience, global regulatory approval, and the additional pulmonary arterial hypertension indication. Mirodenafil's Alzheimer's disease clinical program is more advanced than any sildenafil repositioning effort.

12.2 Tadalafil (Cialis, Adcirca)

Mechanism: Selective PDE5 inhibitor of the beta-carboline structural class. IC₅₀ for PDE5: 0.94 nmol/L. Distinguished by a long elimination half-life (17.5 hours) that supports both on-demand and once-daily dosing [22].

Novelty: Low. Approved FDA 2003 for erectile dysfunction and subsequently for pulmonary arterial hypertension and BPH/LUTS.

Effect size: Meta-analytic IIEF-EF domain improvement of approximately 7.49 points over placebo, the highest among marketed PDE5 inhibitors in aggregate comparisons. The once-daily 5 mg regimen for concurrent ED/LUTS/BPH is a unique clinical positioning [22].

Promising potential: Moderate. Fully mature in existing indications. Long half-life provides a theoretical advantage for chronic central nervous system dosing in potential repositioning applications, but no active Alzheimer's disease clinical program has been reported.

Side-effect profile: Headache (11 to 15 percent), dyspepsia (4 to 12 percent), back pain (6 percent), myalgia (5 to 7 percent), nasal congestion (3 percent), flushing (3 percent). The back pain and myalgia reflect the relatively low PDE11 selectivity (approximately 5-fold). Visual disturbances are rare (PDE6 selectivity greater than 700-fold). Overall adverse event rates (approximately 44 percent) are higher than mirodenafil [22].

Overall validation: Very high. Tadalafil is the second most widely prescribed PDE5 inhibitor globally, with uniquely broad indication coverage (ED, PAH, BPH/LUTS).

Comparison to mirodenafil: Mirodenafil has a shorter half-life and narrower indication portfolio. Tadalafil has the advantage of once-daily dosing versatility and the BPH/LUTS indication. Mirodenafil has the advantage of superior PDE11 selectivity (no myalgia/back pain signal) and the active Alzheimer's disease clinical development program.

12.3 Vardenafil (Levitra, Staxyn)

Mechanism: Selective PDE5 inhibitor of the piperazine-substituted pyrimidinone class. IC₅₀ for PDE5: 0.14 nmol/L, the most potent of the first-generation agents at the enzyme level [22].

Novelty: Low. Approved FDA 2003.

Effect size: Meta-analytic IIEF-EF domain improvement of approximately 7.11 points over placebo. Comparable to tadalafil and mirodenafil.

Promising potential: Low. No active new-indication development programs. Market share has declined relative to sildenafil and tadalafil.

Side-effect profile: Headache (15 percent), flushing (11 percent), dyspepsia (4 percent), nasal congestion (9 percent), visual disturbances (approximately 2 percent). PDE6 selectivity approximately 15-fold; PDE11 selectivity greater than 1,000-fold. Overall adverse event rates approximately 41.5 percent [22].

Overall validation: High. Extensive clinical experience and global regulatory approval, but declining commercial and research relevance.

Comparison to mirodenafil: Vardenafil has higher raw PDE5 potency (IC₅₀ 0.14 vs 0.34 nmol/L) but inferior PDE1 and PDE3 selectivity profiles. Mirodenafil has the advantage of the Alzheimer's disease program and the absence of visual disturbance reports. Both are on-demand, short-acting agents.

12.4 Udenafil (Zydena)

Mechanism: Selective PDE5 inhibitor of the pyrazolopyrimidinone class, also developed in South Korea (Dong-A Pharmaceutical). IC50 for PDE5: 8.25 nmol/L [22].

Novelty: Low. Approved in Korea 2005 for erectile dysfunction.

Effect size: Meta-analytic IIEF-EF domain improvement of approximately 5.66 points over placebo, the lowest among the five comparators. The compound has a longer half-life than mirodenafil (approximately 7 to 12 hours) providing extended duration of action.

Promising potential: Moderate. The FUEL trial (Fontan Udenafil Exercise Longitudinal) evaluated udenafil for exercise performance in Fontan-palliated single-ventricle heart disease, representing a novel cardiovascular repositioning. Results of the Phase 3 trial were mixed [27].

Side-effect profile: Flushing (19 percent), headache (7 percent), dyspepsia (2 percent). Visual disturbances reported at low frequency. Overall tolerability profile comparable to the first-generation class.

Overall validation: Moderate. Limited to South Korean approval; the Fontan cardiovascular indication represents a novel validation pathway but has not produced registration.

Comparison to mirodenafil: Both are Korean-developed second-generation PDE5 inhibitors, but mirodenafil has substantially higher PDE5 potency (0.34 vs 8.25 nmol/L), better PDE isoenzyme selectivity, and the more advanced Alzheimer's disease clinical program. Udenafil has the advantage of a longer half-life and the cardiovascular repositioning precedent.

12.5 Avanafil (Stendra, Spedra)

Mechanism: Selective PDE5 inhibitor of the pyrimidine class, designed for rapid onset of action. IC50 for PDE5: 5.2 nmol/L. Approved by FDA in 2012 [22].

Novelty: Moderate. Avanafil is the most recently approved PDE5 inhibitor and was designed to address the onset-of-action limitation of earlier agents.

Effect size: IIEF-EF domain improvement comparable to sildenafil (approximately 6 to 8 points over placebo in pivotal trials). The key differentiation is onset: avanafil reaches effective concentrations approximately 15 to 30 minutes after dosing, faster than sildenafil (30 to 60 minutes) and mirodenafil (30 to 90 minutes) [22].

Promising potential: Low. No active non-erectile dysfunction development programs.

Side-effect profile: Headache (6 to 10 percent), flushing (3 to 10 percent), nasal congestion (2 to 3 percent). Visual disturbances are rare (PDE6 selectivity approximately 100-fold). Overall adverse event rates are comparable to or lower than first-generation agents. Half-life approximately 5 hours [22].

Overall validation: Moderate. FDA-approved but with limited market penetration relative to sildenafil and tadalafil.

Comparison to mirodenafil: Avanafil has faster onset of action and FDA approval but lower PDE5 potency. Mirodenafil has higher PDE5 affinity, the active Alzheimer's disease program, and the orally dissolving film formulation. Neither has achieved broad international regulatory approval.

12.6 Comparator summary

The five comparator PDE5 inhibitors span the first-generation (sildenafil, tadalafil, vardenafil) and second-generation (udenafil, avanafil) developmental waves. **Sildenafil** and **tadalafil** have the broadest clinical validation and global regulatory approval, with tadalafil distinguished by its uniquely long half-life and the BPH/LUTS indication. **Vardenafil** has the highest raw PDE5 potency but declining commercial relevance. **Udenafil** is the closest structural and developmental comparator to mirodenafil (both Korean-developed, second-generation) but has lower potency and no Alzheimer's program. **Avanafil** has the fastest onset of action and recent FDA approval but limited development beyond erectile dysfunction.

Mirodenafil occupies a distinctive position in this comparator landscape: it has the highest PDE5 affinity among agents with published clinical data (second only to vardenafil at the enzyme level but with superior selectivity), the most favorable isoenzyme selectivity profile (particularly over PDE1, PDE3, and PDE11), the lowest reported visual disturbance and musculoskeletal adverse event rates, and the only active clinical development program for Alzheimer's disease among PDE5 inhibitors. The principal limitations are the narrow geographic approval (South

Korea only for erectile dysfunction), the short elimination half-life (limiting once-daily efficacy without metabolite contribution), and the absence of FDA or EMA approval for any indication.

The Alzheimer's disease repositioning is the most scientifically and commercially significant differentiator. If the POLARIS-AD Phase 3 trial produces a positive readout, mirodenafil would become the first PDE5 inhibitor approved for a neurodegenerative indication and the first PDE5 inhibitor to achieve global regulatory approval since avanafil in 2012. The multimodal mechanism (cGMP/PKG/CREB signaling, autophagy, GSK-3beta suppression, neuroinflammation, Wnt/beta-catenin restoration) distinguishes the Alzheimer's thesis from a simple vasodilatory mechanism and provides multiple endpoints for clinical validation.

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