

RESEARCH MONOGRAPH . COMPOUND PROFILE

Dapoxetine

A naphthalene-derived phenylpropylamine SSRI originally developed at Eli Lilly as an antidepressant candidate, repositioned as the first and only oral pharmacotherapy specifically approved for on-demand treatment of premature ejaculation, distinguished from conventional SSRIs by rapid absorption, short initial half-life, and suitability for event-based rather than chronic dosing.

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AUTHOR	Kodiac bioLabs Research
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ABSTRACT

Dapoxetine (LY 210448) is a short-acting selective serotonin reuptake inhibitor (SSRI) and the first oral pharmacotherapy specifically developed and approved for the on-demand treatment of premature ejaculation (PE) in adult men aged 18 to 64 years. Originally synthesized at Eli Lilly and Company as an antidepressant candidate in the late 1980s, the compound was shelved after failing to demonstrate sufficient efficacy in depression, subsequently licensed to Pharmaceutical Product Development (PPD) in 2003, and then advanced through Phase 3 clinical development by ALZA Corporation (a Johnson and Johnson subsidiary) for the PE indication. Dapoxetine received its first regulatory approvals in Finland and Sweden in 2009 under the trade name Priligy and has since been registered in over 60 countries across Europe, Asia, Latin America, and Oceania. The compound has not been approved by the United States Food and Drug Administration, which issued a not-approvable letter in 2005 citing the need for additional efficacy and safety data.

The pharmacological mechanism of dapoxetine is inhibition of the serotonin transporter (SERT) at both peripheral and central sites, increasing serotonin availability at postsynaptic receptors in the ejaculatory pathway. Preclinical electrophysiology studies in anaesthetized rats demonstrated that dapoxetine inhibits the ejaculatory expulsion reflex at a supraspinal level, specifically modulating activity of lateral paragigantocellular nucleus (LPGi) neurons that project to spinal ejaculatory motor centers. The compound exhibits high selectivity for the serotonin transporter over the norepinephrine and dopamine transporters, with Ki

values of approximately 1.0 nM for SERT, 66 nM for the norepinephrine transporter, and greater than 1000 nM for the dopamine transporter.

The critical pharmacokinetic distinction of dapoxetine from conventional SSRIs (paroxetine, fluoxetine, sertraline, citalopram) is its rapid absorption and elimination profile. After oral administration, dapoxetine reaches maximum plasma concentration (C_{max}) within approximately 1.0 to 1.3 hours, with an initial distribution half-life of 1.3 to 1.4 hours and a terminal elimination half-life of 18.7 to 21.9 hours. Oral bioavailability is approximately 42 percent, with substantial interindividual variability (range 15 to 76 percent) attributable to first-pass hepatic metabolism. Metabolism proceeds through CYP3A4, CYP2D6, and flavin-containing monooxygenase 1 (FMO1) pathways, producing dapoxetine N-oxide (inactive), N-desmethyldapoxetine (active), and N,N-didesmethyldapoxetine (active) as the principal circulating metabolites. Plasma protein binding exceeds 99 percent.

Five pivotal Phase 3 randomized, double-blind, placebo-controlled trials enrolling 6,081 men across more than 25 countries established the clinical efficacy of dapoxetine at 30 mg and 60 mg on-demand doses. Integrated analysis demonstrated that mean intravaginal ejaculatory latency time (IELT) increased from a baseline of 0.9 minutes to 3.2 minutes with dapoxetine 30 mg and 3.5 minutes with dapoxetine 60 mg, compared to 1.9 minutes with placebo. Statistically significant improvements were observed across all patient-reported outcome domains including ejaculatory control, satisfaction with sexual intercourse, ejaculation-related personal distress, and interpersonal difficulty. The safety profile is consistent with the SSRI pharmacological

class; the most common adverse events are nausea (8.7 to 20.1 percent), dizziness (5.8 to 10.9 percent), headache (5.6 to 8.8 percent), diarrhea (3.9 to 6.8 percent), and somnolence. A specific safety concern is vasovagal-mediated syncope, observed at rates of 0.06 percent with 30 mg and 0.23 percent with 60 mg compared to 0.05 percent with placebo. Dapoxetine is contraindicated with potent CYP3A4 inhibitors, monoamine oxidase inhibitors, other serotonergic agents, and in patients with significant cardiovascular disease or a history of syncope.

This monograph reviews the chemistry, synthesis, and stereochemistry of dapoxetine; the serotonin transporter pharmacology and supraspinal ejaculatory reflex modulation mechanism in molecular and electrophysiological detail; the comprehensive human pharmacokinetic record including CYP2D6 and CYP3A4 metabolic polymorphism; the clinical evidence base across premature ejaculation and combination therapy with phosphodiesterase type 5 inhibitors; the reconstitution, sourcing, and quality verification considerations for laboratory work; stack-interaction implications; adverse-event signal including syncope and serotonin syndrome risk; and a comparative assessment of five alternative premature ejaculation pharmacotherapies against dapoxetine on five competency standards (novelty, effect size, promising potential, side-effect profile, and overall validation).

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Dapoxetine.

Marketed names: Priligy (Menarini; Europe, Australia, New Zealand, South Korea, and other jurisdictions), Westoxetin (generic markets), Kutub (generic), Dumax (generic), Joypox (generic).

Development codes: LY 210448 (Eli Lilly). The development code is the canonical identifier in the early pharmacology literature and in the initial patent filings from the Eli Lilly discovery program [1].

Chemical Abstracts Service registry numbers: 119356-77-3 (free base), 129938-20-1 (hydrochloride salt). The hydrochloride salt is the formulated pharmaceutical form; the free base is the synthetic intermediate and is available from research chemical suppliers.

International Union of Pure and Applied Chemistry name: (S)-N,N-dimethyl-3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine. The compound is a chiral aryloxyphenylpropylamine, bearing a naphthyloxy ether at the 3-position and a dimethylamino group at the 1-position of a phenylpropane backbone.

1.2 Structural class and chemistry

Dapoxetine is a phenylpropylamine derivative belonging to the aryloxyphenylpropylamine structural class, which also includes fluoxetine, atomoxetine, nisoxetine, and duloxetine. The structural class is characterized by a 3-aryloxy-1-phenylpropan-1-amine backbone in which variations at the aryloxy substituent and the amine nitrogen determine transporter selectivity and pharmacokinetic properties. In dapoxetine, the aryloxy group is 1-naphthyloxy and the amine is N,N-dimethyl, producing high SERT selectivity and the rapid-onset, short-acting pharmacokinetic profile that distinguishes the compound from other members of the class [2].

Molecular formula: C₂₁H₂₃NO (free base); C₂₁H₂₄ClNO (hydrochloride salt).

Exact mass: 305.1780 g/mol (free base, monoisotopic).

Molecular weight: 305.41 g/mol (free base); 341.87 g/mol (hydrochloride salt).

Physical properties: White to off-white crystalline powder. The hydrochloride salt is freely soluble in water and methanol; sparingly soluble in ethanol; practically insoluble in apolar organic solvents. The free base is soluble in most common organic solvents including dichloromethane, ethyl acetate, and methanol. Melting point of the hydrochloride salt is approximately 178 to 180 degrees Celsius.

Stereochemistry: Dapoxetine contains one stereocenter at carbon 1 of the phenylpropane backbone and is supplied exclusively as the (S)-enantiomer. The (S)-configuration is essential for pharmacological activity at the serotonin transporter; the (R)-enantiomer exhibits substantially reduced SERT affinity and is not the clinically active material. Investigators acquiring research-grade dapoxetine should confirm enantiomeric purity by chiral high-performance liquid chromatography or by optical rotation measurement against a validated reference standard.

1.3 Synthesis

The published synthesis of dapoxetine proceeds through several principal routes that can be categorized as achiral resolution approaches and asymmetric synthesis approaches.

The achiral resolution approach begins with racemic 3-(naphthalen-1-yloxy)-1-phenylpropan-1-amine, prepared from cinnamaldehyde or phenylpropanediol intermediates, followed by chiral resolution using tartrate salts or chiral HPLC to isolate the (S)-enantiomer. The resolved amine is then N,N-dimethylated to produce dapoxetine free base, which is converted to the hydrochloride salt by addition of stoichiometric hydrogen chloride in diethyl ether or dioxane [3].

A commonly described four-step synthesis starts from (R)-1-phenyl-1,3-propanediol: selective tosylation of the primary hydroxyl group with p-toluenesulfonyl chloride and triethylamine in the presence of 4-dimethylaminopyridine (DMAP); condensation of the tosylate with 1-naphthol under basic conditions to install the naphthyloxy ether; conversion of the secondary alcohol to the corresponding mesylate with methanesulfonyl chloride; and displacement of the mesylate with dimethylamine to afford dapoxetine free base with retention of configuration [3, 4].

Asymmetric synthesis approaches employ chiral catalysis (metal-catalyzed asymmetric reduction of prochiral ketone intermediates or enzyme-catalyzed resolution of racemic intermediates) to produce the (S)-enantiomer directly without

classical resolution. Industrial manufacturing typically employs the asymmetric route for cost efficiency at scale, achieving enantiomeric excess greater than 99 percent. The hydrochloride salt is prepared by recrystallization and is characterized by nuclear magnetic resonance spectroscopy, mass spectrometry, melting point, optical rotation, and high-performance liquid chromatography purity determination.

2. Abstract

Dapoxetine (LY 210448) is a potent and selective inhibitor of the serotonin reuptake transporter (SERT) and the only oral pharmacotherapy specifically developed and approved for the on-demand treatment of premature ejaculation in adult men [5, 6]. The compound occupies a unique pharmacological position within the SSRI class: it shares the serotonin transporter inhibition mechanism with the antidepressant SSRIs (fluoxetine, paroxetine, sertraline, citalopram, escitalopram) but is distinguished by rapid oral absorption (T_{max} approximately 1.0 to 1.3 hours), rapid initial distribution ($t_{1/2}$ alpha approximately 1.3 to 1.4 hours), and correspondingly rapid onset and offset of serotonergic activity at the supraspinal ejaculatory control centers [7].

The premature ejaculation indication exploits the well-established observation that serotonergic inhibition of the ejaculatory reflex, first characterized as a side effect of chronic SSRI antidepressant therapy, can be achieved acutely with a rapidly absorbed and rapidly eliminated SSRI administered 1 to 3 hours before anticipated sexual activity [8]. The critical pharmacokinetic advantage of dapoxetine over off-label use of conventional SSRIs is the avoidance of chronic daily dosing with its attendant antidepressant discontinuation effects, sexual dysfunction, and steady-state serotonergic side effects.

Five pivotal Phase 3 clinical trials enrolling 6,081 men across more than 25 countries established the clinical efficacy and safety profile [9, 10]. Dapoxetine 30 mg and 60 mg administered on-demand produced statistically and clinically significant increases in intravaginal ejaculatory latency time (IELT) and improvements in patient-reported control over ejaculation, ejaculation-related distress, interpersonal difficulty, and sexual satisfaction compared to placebo. Effect sizes were moderate: mean IELT increased from 0.9 minutes at baseline to 3.2 minutes with 30 mg and 3.5 minutes with 60 mg, compared to 1.9 minutes with placebo.

The compound is registered in over 60 countries; it has not been approved by the United States Food and Drug Administration. The principal safety concerns are vasovagal-mediated syncope (dose-related, occurring at rates of 0.06 to 0.23 per-

cent), serotonin syndrome risk with concurrent serotonergic agents, and the typical SSRI gastrointestinal and central nervous system adverse events (nausea, dizziness, headache, diarrhea, somnolence).

This monograph documents the chemistry, synthesis, pharmacology, pharmacokinetics, clinical evidence base, sourcing, reconstitution, stack interactions, adverse events, and comparative positioning of dapoxetine against five alternative premature ejaculation pharmacotherapies.

3. Discovery and Development History

3.1 Origin

Dapoxetine was synthesized at Eli Lilly and Company in the late 1980s as part of a structure-activity exploration of aryloxyphenylpropylamine SERT inhibitors within the same medicinal chemistry program that produced fluoxetine (Prozac). The compound, designated LY 210448, was advanced into Phase 1 clinical trials as an antidepressant candidate on the basis of potent serotonin reuptake inhibition and favorable oral bioavailability in preclinical species. However, the rapid-onset, short-duration pharmacokinetic profile that would later become the compound's principal advantage for the PE indication was a liability for the antidepressant application, where sustained serotonergic activity through chronic daily dosing is the therapeutic model. Dapoxetine did not demonstrate sufficient antidepressant efficacy in early clinical assessment and was shelved by Eli Lilly in the early 1990s [1, 11].

3.2 Repositioning for premature ejaculation

The rationale for repositioning dapoxetine as a PE treatment derived from the long-standing clinical observation that ejaculatory delay is a common and dose-dependent side effect of chronic SSRI antidepressant therapy. Waldinger and colleagues had demonstrated in the 1990s that daily paroxetine, sertraline, fluoxetine, and clomipramine significantly increased IELT in men with PE [12]. However, chronic SSRI dosing for PE carried the disadvantages of antidepressant discontinuation syndrome, sexual side effects (paradoxically including erectile dysfunction and anorgasmia), and the requirement for daily medication for an episodic condition. A short-acting SSRI that could be administered on-demand before sexual activity would address all of these limitations.

3.3 Licensing and Phase 3 development

In December 2003, Eli Lilly sold the dapoxetine patent portfolio to Pharmaceutical Product Development (PPD) for approximately \$65 million. PPD had previously licensed the compound from Lilly in 1998 and developed it through Phase 2 proof-of-concept trials demonstrating dose-dependent IELT increases [11]. PPD subse-

quently out-licensed dapoxetine to ALZA Corporation, a wholly owned subsidiary of Johnson and Johnson, which conducted the five pivotal Phase 3 trials beginning in 2004 [9, 10].

3.4 FDA review and international approval

Johnson and Johnson submitted a New Drug Application to the United States Food and Drug Administration in 2004. In October 2005, the FDA issued a not-approvable letter, citing the need for additional clinical efficacy and safety data, specifically regarding the syncope signal and the adequacy of the benefit-risk profile for an on-demand sexual medicine [11]. Johnson and Johnson completed three additional Phase 3 efficacy and safety studies in response.

The expanded dossier was submitted to European and other international health authorities. Dapoxetine received its first regulatory approvals in Finland and Sweden in February 2009 under the trade name Priligy [13]. Subsequent approvals followed in Austria, Germany, Italy, Spain, Portugal, South Korea, Mexico, New Zealand, Australia, and numerous additional jurisdictions through 2010 and beyond. The compound is now registered in over 60 countries. Menarini Group holds the European marketing authorization; other licensees market the product in their respective jurisdictions.

3.5 Current regulatory status

Dapoxetine has not been approved by the United States Food and Drug Administration. The compound is available by prescription in all jurisdictions where it is registered, at doses of 30 mg and 60 mg film-coated tablets for on-demand oral administration. Generic competition has commenced in most jurisdictions following patent expiry.

4. Mechanism of Action

Dapoxetine is a monoamine reuptake inhibitor with high selectivity for the serotonin transporter (SERT). Its principal molecular activity is inhibition of the presynaptic serotonin reuptake pump, increasing serotonin availability in the synaptic cleft at both central and peripheral serotonergic synapses involved in ejaculatory reflex control. This activity operates at functionally relevant concentrations achieved by the registered on-demand oral dose and produces the observed ejaculatory delay.

4.1 Serotonin transporter inhibition

The serotonin transporter (SLC6A4/SERT) is a 12-transmembrane domain sodium- and chloride-dependent monoamine transporter responsible for the reuptake of serotonin (5-hydroxytryptamine, 5-HT) from the synaptic cleft into presynaptic terminals. SERT is expressed at high density throughout the central nervous system, particularly in the dorsal raphe nucleus, limbic system, hypothalamus, and brainstem nuclei involved in ejaculatory control, as well as peripherally in enteric neurons and platelets.

Dapoxetine binds SERT with high affinity (K_i approximately 1.0 nM) and inhibits serotonin reuptake with an IC_{50} of approximately 1.0 to 1.4 nM in human platelet and synaptosomal preparations [2, 14]. Selectivity over the norepinephrine transporter (NET) is approximately 66-fold (K_i approximately 66 nM) and over the dopamine transporter (DAT) is greater than 1000-fold (K_i greater than 1000 nM). This selectivity profile is comparable to paroxetine and escitalopram and superior to fluoxetine and sertraline in SERT specificity.

The functional consequence of acute SERT inhibition is an immediate increase in synaptic serotonin concentration at the postsynaptic 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2C}, and other serotonin receptor subtypes that modulate the ejaculatory reflex arc. Unlike chronic SSRI administration (where therapeutic effect in depression requires weeks of dosing to produce somatodendritic 5-HT_{1A} autoreceptor desensitization and downstream neuroplastic adaptation), the ejaculatory delay effect of dapoxetine is acute and occurs on the first dose, consistent with direct serotonergic inhibition of the ejaculatory reflex [8].

4.2 Supraspinal modulation of the ejaculatory reflex

The ejaculatory reflex is a coordinated spinal reflex mediated by lumbar spinothalamic cells, with supraspinal modulatory input from the nucleus paragigantocellularis (nPGi), the medial preoptic area (MPOA), the paraventricular nucleus of the hypothalamus, and other brainstem and forebrain structures. Serotonergic descending projections from the nPGi to the lumbar spinal cord exert tonic inhibitory control over the ejaculatory reflex; increased serotonergic activity in this pathway raises the ejaculatory threshold and delays ejaculation [15].

Clement and colleagues demonstrated in anaesthetized male rats that acute intravenous administration of dapoxetine inhibited the ejaculatory expulsion reflex at a supraspinal level, specifically modulating the firing pattern of lateral paragigantocellular nucleus (LPGi) neurons [16]. This supraspinal site of action distinguishes the mechanism from purely peripheral serotonergic effects and supports the clinical observation of central ejaculatory delay without significant alteration of penile sensation or erectile function.

4.3 Receptor-level pharmacology

The downstream serotonergic effects relevant to ejaculatory control involve multiple receptor subtypes. Postsynaptic 5-HT_{2C} receptor activation in the spinal cord and brainstem is inhibitory to ejaculation; 5-HT_{1A} receptor activation at somatodendritic autoreceptors on raphe neurons initially attenuates serotonin release (a mechanism relevant to chronic SSRI dosing latency in depression but less relevant to the acute on-demand dapoxetine paradigm). The net acute effect of SERT inhibition by dapoxetine at the registered on-demand dose is an increase in postsynaptic 5-HT_{2C}-mediated inhibition of the ejaculatory reflex, with contribution from 5-HT_{1B} receptor-mediated presynaptic feedback at serotonergic terminals in the spinal ejaculatory generator [15, 17].

Dapoxetine does not exhibit clinically significant binding at muscarinic, histaminergic, alpha-adrenergic, or dopaminergic receptors at therapeutic concentrations, which accounts for the absence of anticholinergic, antihistaminic, and adrenergic side effects at the registered doses.

4.4 Composite pharmacology and selectivity

At the registered on-demand doses (30 mg and 60 mg), dapoxetine achieves peak plasma concentrations of approximately 297 ng/mL (30 mg) and 498 ng/mL (60 mg) within 1.0 to 1.3 hours of oral administration. Correcting for the greater than 99 percent plasma protein binding, free plasma concentrations at C_{max} are in the low nanomolar range (approximately 1 to 2 nM), which exceeds the SERT K_i (approximately 1.0 nM) and produces substantial transporter occupancy. The rapid decline in plasma concentration after C_{max} (initial half-life 1.3 to 1.4 hours) ensures that SERT occupancy returns to sub-therapeutic levels within hours, supporting the on-demand dosing paradigm and minimizing carryover serotonergic effects between dosing events [7].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Dapoxetine is rapidly absorbed from the gastrointestinal tract after oral administration. Maximum plasma concentration (C_{max}) is reached within approximately 1.01 hours at the 30 mg dose (C_{max} approximately 297 ng/mL) and 1.27 hours at the 60 mg dose (C_{max} approximately 498 ng/mL) [7, 18]. Absolute oral bioavailability is approximately 42 percent, with substantial interindividual variability (range 15 to 76 percent) attributable to the extent of first-pass hepatic and intestinal metabolism. Food has a minor effect on absorption: a high-fat meal delays T_{max} by approximately 40 minutes and modestly reduces C_{max} (by approximately 10 percent) without significantly affecting overall exposure (AUC). The prescribing information permits administration with or without food.

5.2 Distribution

Dapoxetine exhibits a large volume of distribution (approximately 162 L), reflecting extensive tissue partitioning. Plasma protein binding exceeds 99 percent, predominantly to albumin and alpha-1-acid glycoprotein. The high protein binding limits the free fraction available for pharmacological activity but is consistent with the rapid initial distribution phase (t_{1/2} alpha 1.3 to 1.4 hours) observed in pharmacokinetic studies [7].

The compound crosses the blood-brain barrier; central nervous system penetration is assumed based on the supraspinal site of action demonstrated in preclinical electrophysiology studies and the central adverse-event profile (dizziness, somnolence) observed clinically. Formal positron emission tomography or cerebrospinal fluid pharmacokinetic studies characterizing central compartment distribution have not been published for dapoxetine.

5.3 Metabolism

Dapoxetine is metabolized extensively in the liver and kidney by multiple enzyme systems. The principal metabolic transformations are N-demethylation, N-oxidation, hydroxylation, glucuronidation, and sulfation, mediated chiefly by CYP3A4, CYP2D6, and flavin-containing monooxygenase 1 (FMO1) [18, 19].

The three principal circulating metabolites are:

- Dapoxetine N-oxide: produced by FMO1-mediated N-oxidation; pharmacologically inactive at the serotonin transporter.
- N-desmethyldapoxetine (DED): produced by CYP3A4- and CYP2D6-mediated N-demethylation; pharmacologically active at SERT but with lower potency than the parent compound.
- N,N-didesmethyldapoxetine: produced by sequential demethylation of N-desmethyldapoxetine; pharmacologically active but at further reduced potency.

The active metabolites are conjugated (glucuronidated and sulfated) and excreted primarily in urine. Less than 3 percent of an administered dose is excreted unchanged in urine.

The dual CYP3A4/CYP2D6 metabolic pathway creates a clinically significant pharmacokinetic drug-interaction liability and a pharmacogenomic variable. CYP2D6 poor metabolizers (approximately 5 to 10 percent of European-ancestry populations) exhibit increased dapoxetine exposure; concomitant use of potent CYP3A4 inhibitors produces approximately 2-fold increases in exposure. The combination of CYP2D6 poor metabolizer status and moderate CYP3A4 inhibitor co-administration can produce markedly elevated plasma concentrations.

5.4 Elimination

The plasma concentration-time profile of dapoxetine is biphasic, with an initial rapid distribution phase ($t_{1/2}$ alpha approximately 1.3 to 1.4 hours) and a longer terminal elimination phase ($t_{1/2}$ beta approximately 18.7 hours at 30 mg and 21.9 hours at 60 mg) [7]. The initial rapid decline is responsible for the short duration of pharmacological effect that supports on-demand dosing; the longer terminal half-life reflects slow redistribution from deep tissue compartments and elimination of

conjugated metabolites. Renal excretion of conjugated metabolites is the principal elimination pathway. Hepatic impairment can substantially prolong elimination; the compound is not recommended in moderate to severe hepatic impairment.

5.5 Routes of administration

Dapoxetine is administered exclusively by the oral route in registered clinical practice. The approved formulations are 30 mg and 60 mg film-coated tablets of dapoxetine hydrochloride for on-demand oral use, administered 1 to 3 hours before anticipated sexual activity. The recommended starting dose is 30 mg; if the response is insufficient and side effects are tolerable, the dose may be increased to 60 mg. The maximum recommended dosing frequency is one tablet per 24-hour period.

No parenteral, sublingual, or topical formulations of dapoxetine are registered or in clinical development. Research-grade dapoxetine hydrochloride is supplied as a powder suitable for reconstitution in aqueous or organic solvent systems for in vitro and in vivo research applications.

5.6 Special populations

CYP2D6 poor metabolizers exhibit increased dapoxetine exposure. Prescribing information recommends caution in known poor metabolizers and dose restriction when concurrent moderate CYP3A4 inhibitors are used. Renal impairment does not require dose adjustment at the registered doses. Hepatic impairment: the compound is not recommended in moderate to severe hepatic impairment. Geriatric use: limited data are available in men older than 64 years; the approved indication is restricted to ages 18 to 64. Pediatric use: dapoxetine is not indicated in children or adolescents. Pregnancy and lactation: the compound is indicated for use in men only and is not recommended for use in women.

6. Preclinical Pharmacology

6.1 In vitro pharmacology

In vitro binding studies in human recombinant and native tissue preparations established the selectivity profile of dapoxetine. The compound inhibits [3H]-serotonin uptake in human platelet preparations with an IC₅₀ of approximately 1.0 to 1.4 nM and displaces [3H]-citalopram from SERT binding sites with a K_i of approximately 1.0 nM [2, 14]. Selectivity ratios over NET (K_i approximately 66 nM) and DAT (K_i greater than 1000 nM) confirm the SERT-selective profile. No significant binding was observed at muscarinic M1 through M5, histamine H1, alpha-1 and alpha-2 adrenergic, dopamine D1 through D5, or opioid receptors at concentrations up to 10 micromolar.

6.2 In vivo pharmacology

In preclinical rat models of ejaculatory function, dapoxetine administered acutely (single intravenous or intraperitoneal dose) produced dose-dependent increases in ejaculatory latency without significant effects on erectile function, mount latency, or intromission frequency [16, 20]. The effect was abolished by pretreatment with the 5-HT_{2C} receptor antagonist SB 242084, supporting the hypothesis that the ejaculatory delay is mediated through postsynaptic 5-HT_{2C} receptor activation in the spinal ejaculatory generator.

The Clement et al. electrophysiology studies in anaesthetized rats demonstrated that intravenous dapoxetine (0.5 to 5 mg/kg) dose-dependently inhibited the ejaculatory expulsion reflex evoked by electrical stimulation of the dorsal penile nerve, with the site of action localized to the lateral paragigantocellular nucleus (LPGi) of the brainstem [16]. This supraspinal inhibition was abolished by lesion of the LPGi, confirming the critical role of descending serotonergic pathways in the dapoxetine mechanism.

6.3 Toxicology

Preclinical toxicology studies in rats and dogs at oral doses up to 100 mg/kg/day for 26 weeks did not produce target organ toxicity or carcinogenicity signals beyond the expected serotonergic pharmacological effects (decreased food consumption, decreased body weight gain at high doses). Reproductive toxicology studies did not demonstrate teratogenicity or effects on fertility at doses up to approximately 10 times the maximum recommended human dose on a mg/m² basis. Genetic toxicology (Ames test, in vitro chromosomal aberration, in vivo micronucleus) was negative.

7. Clinical Evidence Base

7.1 Phase 2 proof-of-concept

Early Phase 2 studies conducted by PPD and ALZA in men with lifelong and acquired PE established the dose-response relationship for dapoxetine. A randomized, double-blind, placebo-controlled crossover study in 130 men demonstrated that dapoxetine 60 mg on-demand produced a significant increase in geometric mean IELT compared to placebo (approximately 2.8-fold increase from baseline), with corresponding improvements in patient-reported ejaculatory control [11, 21]. The 30 mg dose produced a smaller but statistically significant effect. These results supported advancement to Phase 3.

7.2 Phase 3 pivotal trials

Five randomized, multicenter, double-blind, placebo-controlled Phase 3 studies were conducted across more than 25 countries in 6,081 men aged 18 years or older who met DSM-IV-TR diagnostic criteria for premature ejaculation, with four studies requiring a baseline IELT of 2 minutes or less [9, 10].

Study designs: Four studies evaluated dapoxetine 30 mg and 60 mg on-demand (administered 1 to 3 hours before sexual intercourse) for 12 or 24 weeks. One study evaluated dapoxetine 60 mg administered daily versus on-demand for 9 weeks. In all studies, participants recorded IELT with a validated stopwatch methodology and completed patient-reported outcome instruments including the Clinical Global Impression of Change (CGI-C), the Premature Ejaculation Profile (PEP), and subject-rated scales of control, satisfaction, and distress.

Primary efficacy results (integrated analysis): Mean average IELT increased from a baseline of 0.9 minutes to 3.2 minutes with dapoxetine 30 mg (approximately 3.6-fold increase) and 3.5 minutes with dapoxetine 60 mg (approximately 3.9-fold increase), compared to 1.9 minutes with placebo (approximately 2.1-fold increase) [9]. Both active doses produced statistically significant increases compared to placebo (p less than 0.001 for both comparisons). The placebo effect was substantial, consistent with the recognized high placebo response rate in sexual medicine trials.

Patient-reported outcomes: Both dapoxetine doses produced statistically significant improvements compared to placebo on all patient-reported domains: perceived control over ejaculation, satisfaction with sexual intercourse, ejaculation-related personal distress, and ejaculation-related interpersonal difficulty. The proportion of men rating their condition as "much better" or "very much better" on the CGI-C was approximately 26 percent with placebo, 36 percent with dapoxetine 30 mg, and 43 percent with dapoxetine 60 mg [9, 10].

Subgroup analyses: Efficacy was consistent across age groups, baseline IELT categories, PE subtypes (lifelong versus acquired), and geographic regions. Men with concurrent mild erectile dysfunction showed similar IELT improvements to those without erectile dysfunction. The on-demand dosing paradigm was confirmed as non-inferior to daily dosing in the study that compared the two regimens.

7.3 Long-term extension studies

Open-label extension studies of up to 9 months duration demonstrated sustained efficacy of dapoxetine on-demand without evidence of tachyphylaxis or tolerance [22]. IELT improvements were maintained or further increased with continued treatment. No new safety signals emerged during long-term exposure. Discontinuation rates attributable to adverse events were approximately 4 to 5 percent per year at the 60 mg dose and 2 to 3 percent at the 30 mg dose.

7.4 Combination with phosphodiesterase type 5 inhibitors

Premature ejaculation and erectile dysfunction frequently co-occur, and combination therapy with dapoxetine and phosphodiesterase type 5 (PDE5) inhibitors (sildenafil, tadalafil, vardenafil) has been evaluated in multiple studies. Pharmacokinetic interaction studies demonstrated that dapoxetine does not significantly alter the pharmacokinetics of tadalafil or sildenafil, and that PDE5 inhibitors do not significantly alter dapoxetine exposure [23, 24]. Combination use is permitted in prescribing information with the caveat that concurrent administration may increase the risk of orthostatic hypotension. Clinical studies of the combination have reported additive benefits on both IELT and erectile function endpoints in men with co-occurring PE and ED.

7.5 Real-world evidence and meta-analyses

Multiple meta-analyses of randomized controlled trial data have confirmed the efficacy of dapoxetine for PE. A 2014 meta-analysis of 11 randomized controlled trials (including the five pivotal Phase 3 studies) reported weighted mean differences in IELT of 1.15 minutes for dapoxetine 30 mg versus placebo and 1.53 minutes for 60 mg versus placebo [25]. A 2015 Cochrane-methodology meta-analysis reported similar effect sizes and confirmed the dose-response relationship [26]. Real-world observational studies in European and Asian populations have generally confirmed the randomized trial findings, with some evidence of greater satisfaction in real-world settings where patients self-select into treatment.

8. Sourcing and Quality Verification

Pharmaceutical-grade dapoxetine (Priligy brand or licensed generic) is the highest quality source for research applications where regulatory equivalence to clinical material is operationally important. The pharmaceutical-grade material is supplied as 30 mg and 60 mg film-coated tablets of dapoxetine hydrochloride. Pharmaceutical sourcing is feasible in all jurisdictions where the compound is registered.

Research-grade dapoxetine hydrochloride is supplied by multiple chemical and pharmaceutical research suppliers (Cayman Chemical, Sigma-Aldrich/Merck, MedChemExpress, Selleckchem, Santa Cruz Biotechnology, Tocris, BOC Sciences, and others) at greater than 98 percent purity by HPLC. Supply is in milligram to gram quantities as the hydrochloride salt; the free base is also available from selected suppliers. Pricing is moderate, typically in the range of \$30 to \$150 per gram of research-grade material 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 (306.19 for the protonated free base $[M+H]^+$, or 342.15 for the hydrochloride adduct)
- Chiral HPLC or optical rotation measurement to confirm enantiomeric purity (greater than 99 percent enantiomeric excess of the (S)-enantiomer)
- Nuclear magnetic resonance spectroscopy (1H and ^{13}C) for structural confirmation
- 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 provide independent confirmation of vendor certificates of analysis. The research-grade dapoxetine market is well established given the broad commercial availability of the pharmaceutical product; counterfeit

material is uncommon but lot-to-lot variability in research-grade preparations warrants on-receipt analytical confirmation.

9. Reconstitution and Handling

Dapoxetine hydrochloride is freely soluble in water and methanol at room temperature. For research applications, the compound is supplied as a crystalline powder and is reconstituted as needed. Stock solutions are typically prepared at 10 to 50 mM in dimethyl sulfoxide (DMSO) for in vitro cell-based assays, at 1 to 10 mg/mL in normal saline or phosphate-buffered saline for in vivo studies, or at 1 to 10 mg/mL in methanol or acetonitrile for analytical reference standard preparation.

Storage of the solid compound should be at room temperature (15 to 25 degrees Celsius) or at refrigerated conditions (2 to 8 degrees Celsius), protected from light and moisture. The compound is stable under these conditions for at least 2 years based on manufacturer stability data.

Aqueous stock solutions should be prepared fresh or stored at refrigerated conditions (2 to 8 degrees Celsius) and used within 7 to 14 days. DMSO stock solutions are stable at minus 20 degrees Celsius for at least 6 months. Repeated freeze-thaw cycles of DMSO stocks should be minimized; aliquoting into single-use volumes at the time of preparation is recommended.

For oral gavage administration in rodent research, dapoxetine hydrochloride is dissolved in water, normal saline, or 0.5 percent methylcellulose vehicle at concentrations appropriate to the target dose (typically 1 to 30 mg/kg) and administration volume (typically 5 to 10 mL/kg in mice and rats). The compound is stable in these vehicles at room temperature for the duration of a typical dosing session (4 to 8 hours).

10. Stack Interactions and Combinations

Dapoxetine interacts with several drug classes through its CYP3A4/CYP2D6-mediated metabolism and through its serotonergic pharmacology. Investigators conducting research with dapoxetine, especially in chronic or combination dosing paradigms, should consider:

Potent CYP3A4 inhibitors: Ketoconazole (200 mg twice daily for 7 days) increased dapoxetine C_{max} by 35 percent and AUC by 99 percent. Concomitant use of potent CYP3A4 inhibitors (ketoconazole, itraconazole, ritonavir, nelfinavir, atazanavir, telithromycin, nefazodone) is contraindicated [18, 19].

Moderate CYP3A4 inhibitors: Erythromycin, clarithromycin, fluconazole, amprenavir, fosamprenavir, aprepitant, verapamil, and diltiazem may significantly increase dapoxetine and desmethyldapoxetine exposure, especially in CYP2D6 poor metabolizers. The maximum dose should be restricted to 30 mg in patients concomitantly treated with moderate CYP3A4 inhibitors.

CYP2D6 inhibitors: Potent CYP2D6 inhibitors (fluoxetine, paroxetine, bupropion, quinidine) increase dapoxetine exposure. Concomitant use with SSRIs and SNRIs is contraindicated owing to both the CYP2D6 interaction and the pharmacodynamic risk of serotonin syndrome.

Serotonergic agents: Concomitant use with monoamine oxidase inhibitors (MAOIs), SSRIs, SNRIs, tricyclic antidepressants, triptans, tramadol, tryptophan, St. John's wort, and other serotonergic agents is contraindicated owing to the risk of serotonin syndrome. A 14-day washout period is recommended after discontinuation of an MAOI before dapoxetine initiation; a 7-day washout is recommended after discontinuation of dapoxetine before MAOI initiation [18].

Phosphodiesterase type 5 inhibitors: Pharmacokinetic interactions are minimal. Dapoxetine does not alter the pharmacokinetics of tadalafil, sildenafil, or vardenafil, and these agents do not significantly alter dapoxetine pharmacokinetics [23,

24]. However, the combination may increase the risk of orthostatic hypotension through additive vasodilatory effects. Patients should be advised to rise slowly from sitting or lying positions and to maintain adequate hydration.

Alpha-adrenergic blockers: Concomitant use with tamsulosin and other alpha-blockers has not been formally studied. Additive orthostatic hypotension risk is theoretically possible and should be considered.

Ethanol: Concurrent alcohol use with dapoxetine increases the incidence and severity of central nervous system adverse events (dizziness, somnolence, impaired cognition) and significantly increases the risk of vasovagal syncope. Alcohol use in the period surrounding dapoxetine administration is contraindicated in the prescribing information.

Thioridazine: Concomitant use is contraindicated. Thioridazine prolongs the QTc interval, and increased dapoxetine exposure (through CYP2D6 inhibition by thioridazine) may exacerbate this effect.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at registered on-demand doses, derived from the integrated Phase 3 database, are:

- Nausea (8.7 percent at 30 mg, 20.1 percent at 60 mg, versus 1.9 percent placebo; dose-dependent; reflects central serotonergic activation in the chemoreceptor trigger zone)
- Dizziness (5.8 percent at 30 mg, 10.9 percent at 60 mg, versus 1.4 percent placebo)
- Headache (5.6 percent at 30 mg, 8.8 percent at 60 mg, versus 4.0 percent placebo)
- Diarrhea (3.9 percent at 30 mg, 6.8 percent at 60 mg, versus 1.4 percent placebo)
- Somnolence (3.1 percent at 30 mg, 6.0 percent at 60 mg, versus 0.5 percent placebo)
- Insomnia (2.1 percent at 30 mg, 3.9 percent at 60 mg, versus 0.7 percent placebo)
- Fatigue (2.0 percent at 30 mg, 4.1 percent at 60 mg, versus 0.4 percent placebo)

These adverse events are generally mild to moderate in severity, self-limiting, and temporally related to the dosing event. They are consistent with the acute serotonergic pharmacological profile and decrease in frequency with continued use [9, 10].

11.2 Syncope

Vasovagal-mediated (neurocardiogenic) syncope is the principal safety concern specific to dapoxetine. In the integrated Phase 3 database, syncope was reported in 0.05 percent of placebo-treated men, 0.06 percent of dapoxetine 30 mg-treated men, and 0.23 percent of dapoxetine 60 mg-treated men [27]. The mechanism is serotonin-mediated activation of vagal afferent pathways producing reflex bradycardia

and hypotension, consistent with the neurocardiogenic syncope phenotype. Prodromal symptoms (nausea, dizziness, lightheadedness, diaphoresis) typically precede the syncopal event and provide warning.

The syncope signal was the principal basis for the FDA not-approvable letter in 2005. Subsequent studies with dedicated cardiovascular monitoring and prodromal symptom counseling demonstrated that the risk could be managed with patient education, adequate hydration, and avoidance of alcohol and concomitant vasodilatory agents [27]. Dapoxetine is contraindicated in patients with a history of syncope or significant cardiovascular disease.

11.3 Serotonin syndrome

The risk of serotonin syndrome is a class effect of all serotonergic agents, including dapoxetine. Serotonin syndrome is a potentially life-threatening condition characterized by neuromuscular excitation (tremor, clonus, hyperreflexia), autonomic instability (hyperthermia, tachycardia, diaphoresis), and altered mental status. The risk is principally present with concomitant serotonergic agents (MAOIs, SSRIs, SNRIs, tramadol, triptans, recreational serotonergic drugs including MDMA and LSD). Dapoxetine monotherapy at registered doses has not produced confirmed cases of serotonin syndrome [18].

11.4 Cardiovascular safety

Dedicated cardiovascular safety studies, including thorough QT/QTc studies, demonstrated that dapoxetine at supratherapeutic doses (up to 240 mg) did not produce clinically significant QTc prolongation. The compound does not carry a QT warning in the prescribing information. Orthostatic hypotension is observed at low frequency (approximately 0.1 to 0.3 percent) and is more common when dapoxetine is co-administered with PDE5 inhibitors or alcohol [27].

11.5 Discontinuation effects

Unlike conventional SSRIs used chronically, on-demand dapoxetine does not produce antidepressant discontinuation syndrome owing to the absence of steady-state serotonergic receptor adaptation. However, if dapoxetine has been used at high frequency (daily or near-daily for extended periods), abrupt cessation may

theoretically produce mild serotonergic withdrawal symptoms (insomnia, irritability, dizziness). The prescribing information does not include a discontinuation-tapering recommendation.

11.6 Psychiatric adverse events

The SSRI class carries regulatory warnings regarding suicidality in young adults with depression. As dapoxetine is not indicated for depression and produces acute rather than chronic serotonergic effects, the standard SSRI suicidality warning is applied to the prescribing information as a class precaution. No signal of increased suicidality has been identified in the dapoxetine clinical trial database. Mood changes, anxiety, and agitation have been reported at low frequency in postmarketing surveillance.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative pharmacotherapies for premature ejaculation against dapoxetine, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile (clinical or in vitro), and overall validation. The five comparators were selected as the principal pharmacological alternatives with substantive clinical evidence in PE treatment.

12.1 Paroxetine (daily, off-label)

Mechanism: Selective serotonin reuptake inhibitor (SSRI). Paroxetine has the highest SERT affinity among marketed SSRIs (K_i approximately 0.1 nM) and additionally inhibits the norepinephrine transporter at higher concentrations. Unlike dapoxetine, paroxetine has a long elimination half-life (approximately 21 hours) and achieves steady-state serotonergic effects suitable for chronic daily dosing.

Clinical evidence: Paroxetine administered daily at 10 to 40 mg has been the most extensively studied off-label SSRI for PE. Meta-analyses consistently identify paroxetine as producing the largest ejaculation delay among SSRIs, with an approximately 8.8-fold increase in IELT from baseline [12, 28]. Waldinger et al. demonstrated that daily paroxetine 20 mg increased geometric mean IELT from 15.4 seconds to 113.6 seconds after 6 weeks of treatment. The effect requires 1 to 2 weeks of daily dosing to reach maximum; acute single-dose administration produces a smaller and less consistent effect.

Novelty: Low. Off-label use of a conventional antidepressant SSRI represents the repurposing baseline.

Effect size: High. Among the SSRIs studied for PE, paroxetine produces the largest absolute IELT increase, with fold-increases of approximately 8 to 10-fold from baseline in meta-analytic estimates [28]. This exceeds the 3.5 to 3.9-fold increase observed with on-demand dapoxetine in the Phase 3 integrated analysis.

Promising potential: Moderate. Paroxetine will not be developed or approved for PE, but it remains the most widely prescribed off-label SSRI for this indication in jurisdictions where dapoxetine is not available, including the United States.

Side-effect profile: Daily paroxetine carries the full chronic SSRI adverse-event burden: sexual dysfunction (anorgasmia, decreased libido, erectile dysfunction, paradoxically complicating PE treatment), weight gain, somnolence, dry mouth, constipation, and antidepressant discontinuation syndrome on abrupt cessation [29]. These chronic side effects are the principal clinical disadvantage relative to on-demand dapoxetine.

Overall validation: High. The clinical evidence for daily paroxetine in PE is extensive, reproducible, and supported by multiple meta-analyses. The compound is the off-label SSRI standard of care.

Comparison to dapoxetine: Paroxetine produces larger absolute IELT increases than dapoxetine but requires daily dosing with corresponding chronic SSRI side effects. Dapoxetine offers the advantage of on-demand dosing with no carryover sexual, metabolic, or discontinuation effects. The clinical decision between the two agents depends on the frequency of sexual activity and patient preference for on-demand versus daily treatment.

12.2 Sertraline (daily, off-label)

Mechanism: Selective serotonin reuptake inhibitor with modest dopamine transporter affinity. Elimination half-life approximately 26 hours; chronic dosing required for PE efficacy.

Clinical evidence: Daily sertraline at 25 to 100 mg has been studied in multiple randomized controlled trials for PE. Meta-analytic IELT fold-increase from baseline is approximately 4.1 to 5.4-fold, lower than paroxetine but higher than fluoxetine [28]. Sertraline is the second most commonly prescribed off-label SSRI for PE.

Novelty: Low. Off-label repurposing of a conventional antidepressant SSRI.

Effect size: Moderate. The IELT fold-increase is intermediate between paroxetine and fluoxetine, and comparable to or slightly greater than on-demand dapoxetine.

Promising potential: Low to moderate. Like paroxetine, sertraline will not be developed for PE but remains in clinical use off-label.

Side-effect profile: Daily sertraline carries the chronic SSRI adverse-event burden. Gastrointestinal effects (nausea, diarrhea) are somewhat more prominent with sertraline than with paroxetine; sexual side effects (erectile dysfunction, anorgasmia) are similar. Discontinuation syndrome is milder than with paroxetine.

Overall validation: Moderate to high. Multiple randomized trials and meta-analyses support efficacy.

Comparison to dapoxetine: Sertraline offers slightly larger IELT fold-increases than dapoxetine on some meta-analytic estimates but requires daily dosing. Dapoxetine offers superior convenience and side-effect profile through on-demand dosing.

12.3 Tramadol (on-demand, off-label)

Mechanism: Centrally acting analgesic with dual mechanism: weak mu-opioid receptor agonism and serotonin-norepinephrine reuptake inhibition. The serotonergic component contributes to ejaculatory delay; the opioid component may additionally modulate ejaculatory threshold through descending inhibitory pathways.

Clinical evidence: On-demand tramadol at 25 to 50 mg administered 2 hours before sexual activity has been studied in multiple randomized controlled trials. IELT fold-increases of approximately 4 to 7.3-fold from baseline have been reported, with the larger effects at higher doses [30]. A 2012 meta-analysis by Bar-Or et al. confirmed efficacy but raised concerns about the heterogeneity of study designs and outcome measures.

Novelty: Moderate. The dual opioid-serotonergic mechanism is distinct from pure SERT inhibition and represents an alternative pharmacological approach.

Effect size: Moderate to high. IELT fold-increases are comparable to or somewhat greater than on-demand dapoxetine in individual studies, though cross-study comparison is limited by methodological heterogeneity.

Promising potential: Low. Tramadol carries opioid-related abuse liability and regulatory scheduling concerns that preclude formal development for PE. Off-label use is discouraged by most PE treatment guidelines as second-line therapy [31].

Side-effect profile: Opioid-related adverse events include nausea, dizziness, constipation, somnolence, and risk of dependence with chronic use. Seizure risk is elevated at higher doses. Serotonin syndrome risk is present with concurrent serotonergic agents, including dapoxetine, precluding combination use [30]. The abuse liability is the principal safety concern relative to dapoxetine.

Overall validation: Moderate. Multiple randomized trials support efficacy, but the opioid regulatory classification and abuse liability limit clinical adoption.

Comparison to dapoxetine: Tramadol offers comparable on-demand efficacy but carries opioid-class risks (dependence, abuse liability, seizure, serotonin syndrome) that dapoxetine does not. Dapoxetine is the preferred on-demand oral agent in guidelines that address both options [31].

12.4 Lidocaine-prilocaine topical cream/spray (on-demand)

Mechanism: Topical local anesthetic desensitization of penile glans afferent nerves, reducing sensory input to the ejaculatory reflex arc. The mechanism is peripheral (penile sensory threshold elevation) rather than central (supraspinal ejaculatory reflex modulation).

Clinical evidence: Lidocaine-prilocaine combination (EMLA cream 2.5%/2.5% or proprietary spray formulations such as Fortacin/TEMPE) has been evaluated in multiple randomized controlled trials for PE. A randomized controlled trial comparing oral dapoxetine 30 mg to topical 10 percent lidocaine spray found that lidocaine produced significantly greater IELT increases (179.4 seconds mean increase from baseline) compared to dapoxetine (63.4 seconds mean increase), with effectiveness reported by 78 percent of the lidocaine group versus 29 percent of the dapoxetine group [32]. Other studies have reported more modest differences.

Novelty: Low to moderate. Topical anesthetics have been used for PE for decades; the novelty is in standardized metered-dose formulations (Fortacin).

Effect size: Moderate to high. Individual studies suggest IELT increases comparable to or greater than on-demand dapoxetine. The principal limitation is the hypoesthesia (reduced penile sensation) that accompanies the therapeutic effect, which some patients find unacceptable.

Promising potential: Moderate. Fortacin (lidocaine-prilocaine metered-dose spray) is approved in the European Union for PE. The topical approach offers the advantage of minimal systemic exposure and a favorable systemic safety profile.

Side-effect profile: Local adverse events include penile hypoesthesia (the therapeutic mechanism itself), burning or tingling at the application site, and transfer of anesthetic to the partner's genitalia producing vulvovaginal hypoesthesia (mitigated by use of a condom or by washing before intercourse). Systemic adverse events are rare at topical doses.

Overall validation: Moderate. Clinical evidence supports efficacy; regulatory approval in the EU confirms the evidence base. The principal limitation is patient acceptance of reduced penile sensation.

Comparison to dapoxetine: Topical lidocaine-prilocaine and dapoxetine represent complementary approaches (peripheral desensitization versus central reflex modulation). Dapoxetine preserves penile sensation, which is preferred by many patients. The topical approach avoids systemic serotonergic effects and syncope risk. Combination of both approaches has been proposed for refractory PE.

12.5 Clomipramine (on-demand or daily, off-label)

Mechanism: Tricyclic antidepressant with potent serotonin reuptake inhibition (K_i approximately 0.14 nM for SERT) and secondary activity at norepinephrine, histamine H₁, muscarinic M₁, and alpha-1 adrenergic receptors. The serotonergic mechanism drives ejaculatory delay; the secondary pharmacology drives the adverse-event profile.

Clinical evidence: Clomipramine has been studied for PE at daily doses of 25 to 50 mg and at on-demand doses of 25 mg administered 4 to 6 hours before sexual activity. On-demand clomipramine 25 mg has been reported to increase IELT approximately 4 to 6-fold from baseline [28, 33]. Daily dosing produces larger and more consistent IELT increases. Clomipramine was the first antidepressant systematically studied for PE and remains a recommended option in international PE treatment guidelines [31].

Novelty: Low. Off-label use of a first-generation antidepressant.

Effect size: Moderate to high. Comparable to paroxetine on daily dosing; somewhat lower than paroxetine on on-demand dosing. Larger than on-demand dapoxetine in some comparisons.

Promising potential: Low. Clomipramine will not be developed for PE. Off-label use continues, particularly in resource-limited settings.

Side-effect profile: The tricyclic pharmacology produces a broad adverse-event profile: anticholinergic effects (dry mouth, constipation, urinary retention, blurred vision), antihistaminic effects (sedation, weight gain), alpha-adrenolytic effects (orthostatic hypotension), and cardiac conduction effects (QTc prolongation, risk of arrhythmia in overdose). Sexual side effects (erectile dysfunction, anorgasmia) are common with daily use. The adverse-event burden is substantially greater than dapoxetine [33].

Overall validation: Moderate. Clinical evidence supports efficacy; the compound is recommended in treatment guidelines. The adverse-event profile limits clinical adoption relative to SSRIs and dapoxetine.

Comparison to dapoxetine: Clomipramine offers comparable or larger IELT increases but at the cost of a substantially broader adverse-event profile. Dapoxetine is preferred in current treatment guidelines for its SERT selectivity, narrow adverse-event profile, and on-demand dosing convenience.

12.6 Comparator summary

The five comparators occupy distinct positions in the PE pharmacotherapy landscape. **Paroxetine** represents the off-label daily SSRI standard, producing the largest absolute IELT increases but requiring chronic dosing with corresponding chronic SSRI adverse events. **Sertraline** offers an intermediate daily SSRI alternative with a somewhat milder discontinuation profile. **Tramadol** provides an on-demand alternative with a distinct opioid-serotonergic mechanism but carries abuse liability and scheduling concerns. **Lidocaine-prilocaine** offers a topical peripheral approach with minimal systemic effects but at the cost of penile hypoesthesia. **Clomipramine** is a potent serotonergic option limited by its broad tricyclic adverse-event profile.

Dapoxetine occupies a unique position in this landscape: it is the only compound specifically developed and approved for PE, the only approved on-demand oral treatment, and the compound with the most favorable balance of efficacy, conve-

nience, and tolerability for the on-demand treatment paradigm. Its clinical evidence base is the largest and most rigorous (five pivotal Phase 3 trials, 6,081 randomized patients, integrated analysis published). Its principal limitation relative to the comparators is the moderate effect size (3.5 to 3.9-fold IELT increase from baseline), which is smaller than daily paroxetine (approximately 8.8-fold) and comparable to or slightly smaller than on-demand tramadol (approximately 4 to 7.3-fold) and on-demand clomipramine (approximately 4 to 6-fold). However, the superior safety profile (no opioid liability, no tricyclic adverse events, no chronic SSRI burden) and the regulatory validation (approved indication in over 60 countries) support the positioning of dapoxetine as the first-line on-demand pharmacotherapy for PE in the jurisdictions where it is available.

The principal practical question for the clinical positioning of dapoxetine is whether the moderate effect size is sufficient for the individual patient. For patients with very short baseline IELT (less than 30 seconds) or for those who require larger IELT increases, daily paroxetine or combination therapy (dapoxetine plus topical anesthetic) may offer superior outcomes. For patients who prefer on-demand treatment with minimal systemic effects and no chronic dosing requirement, dapoxetine is the established standard of care.

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