PT-141 (Bremelanotide)

A Clinical Learning Guide for Medical Providers

Melanocortin Receptor Agonist (MC4R) • Vyleesi • Hormonal & Sexual Health (2 of 3)

Evidence base at a glance: The second peptide in the Hormonal & Sexual Health group — and the rare FDA-APPROVED one. Three facts dominate: (1) it is the first and only FDA-approved on-demand injectable for female sexual desire (Vyleesi, approved 2019 for acquired, generalized HSDD in premenopausal women), so for that indication this is approved medicine, not a research peptide; (2) its mechanism is CENTRAL and motivational — an MC4R agonist acting in the hypothalamus/limbic reward circuitry to raise dopamine and increase DESIRE — fundamentally different from PDE5 inhibitors (peripheral vasodilation) and from kisspeptin (upstream hormone signaling); and (3) it treats desire and distress, NOT performance — the Phase 3 trials showed significant gains in desire and distress but NO increase in satisfying sexual events, so expectation-setting is essential. Contraindicated in uncontrolled hypertension / known CVD. Male use is entirely off-label (Phase I–II only).

1. Peptide Profile

Name: PT-141 / Bremelanotide (brand: Vyleesi)

Classification: Synthetic cyclic heptapeptide; nonselective melanocortin receptor (MCR) agonist acting primarily at MC4R; derived from α-MSH via Melanotan II

Receptor potency: MC1R > MC4R > MC3R > MC5R > MC2R — but MC4R (CNS) drives the sexual-desire effect; MC1R (melanocytes) drives the hyperpigmentation side effect

FDA status: APPROVED June 21, 2019 (NDA 210557) for acquired, generalized HSDD in premenopausal women. NOT approved for men (off-label/investigational)

Pharmacokinetics: ~100% SC bioavailability; Tmax ~1 h; half-life ~2.7 h; Cmax plateaus at ~7.5 mg (no benefit exceeding the approved dose)

Route & dose (approved, women): 1.75 mg SC (autoinjector, abdomen/thigh) on demand, ≥45 min before activity; max 1 dose/24 h and ≤8 doses/month

Mechanism note: FDA officially lists the exact mechanism for HSDD as “unknown”; the working model is central MC4R → dopamine in sexual-behavior circuitry

Where It Sits in the Hormonal & Sexual Health Group

This is the second of three peptides in the Hormonal & Sexual Health category, and it occupies a very different niche from the first. Kisspeptin-10 (guide 1) acts on the HORMONAL axis — the upstream switch for GnRH/LH/FSH and sex-steroid production. PT-141 acts on the DESIRE circuitry — the central melanocortin/dopamine pathways that govern sexual motivation, largely independent of hormone levels. In other words, kisspeptin addresses the hardware of the reproductive endocrine system, while PT-141 addresses the software of wanting. It is also the only FDA-approved agent in the entire collection, which changes its risk–benefit framing substantially.

A Critical Expectation: Desire, Not Performance

The single most important framing point, emphasized repeatedly by Dr. Seeds, is that PT-141 is a DESIRE drug, not a performance or "hedonistic" drug. It is designed to help someone (classically a premenopausal woman who has lost desire, sometimes after stress or trauma) want intimacy again and feel less distress about the loss — it does not, in the trial data, increase the number of satisfying sexual events. Patients who expect a performance or frequency boost will be disappointed; patients who understand it targets desire and distress are the right candidates.

2. Modes of Action & Mechanisms

PT-141 works centrally, not peripherally. By agonizing MC4R in hypothalamic and limbic reward regions, it increases dopaminergic (and noradrenergic) tone in the circuits that generate sexual desire — a motivational mechanism distinct from vascular or hormonal approaches.

Melanocortin Receptor System

- **MC4R (the therapeutic target):** expressed in hypothalamus (medial preoptic area, paraventricular nucleus), limbic system, and reward centers; agonism upregulates dopamine/norepinephrine to modulate sexual behavior
- **MC1R (the side-effect target):** on melanocytes; activation increases melanin → focal hyperpigmentation (face, gingiva, breasts)
- **MC3R:** hypothalamic; may contribute to appetite/energy regulation (the basis of the weight/appetite signal)
- **Mechanism caveat:** the FDA officially lists the precise mechanism for HSDD benefit as unknown — the dopamine model is a well-supported inference, not a proven pathway

CNS Sexual Pathway Modulation (fMRI evidence)

A randomized fMRI study in 31 women with HSDD (Comninos 2022) gave unusually direct mechanistic insight. MC4R agonism enhanced activity in the cerebellum and supplementary motor area during erotic stimuli, DEACTIVATED the secondary somatosensory cortex (S2) — interpreted as reducing self-monitoring or "spectatoring" — and enhanced amygdala–insula connectivity. In plain terms: it appears to turn up sexual processing while turning down self-conscious self-observation. Small transient rises in LH, FSH, and testosterone occurred, with no change in estradiol.

Peripheral & Endocrine Effects

Effect	Detail
Hyperpigmentation (MC1R)	Focal melanin increase (face, gingiva, breasts); dose-frequency dependent; higher risk in darker skin
Blood pressure / heart rate	Transient +6 mmHg SBP / +3 mmHg DBP (peak 2–4 h), HR down up to 5 bpm; resolves within ~12 h
HPG axis	Small transient ↑ LH (+1.1 IU/L) and FSH (+0.35 IU/L); no estradiol change
Gastric motility	Slows gastric emptying — may reduce absorption of concomitant oral drugs

Effect	Detail
Cardiac (QTc)	No clinically relevant QTc prolongation even at supratherapeutic (20 mg intranasal) dose

Mechanistic takeaway: PT-141 is the only sexual-health agent that works on the brain's DESIRE circuitry (central MC4R → dopamine), reducing self-monitoring and enhancing sexual processing — not vasodilation (PDE5i) and not hormone signaling (kisspeptin). Its main side effects (pigmentation, transient BP rise) come from the same melanocortin family acting at MC1R and on vascular tone.

3. Points of Clinical Relevance

1. It is FDA-approved — but only for a specific population and indication

For acquired, generalized HSDD in PREMENOPAUSAL WOMEN, PT-141 (Vyleesi) is approved medicine with Phase 3 support — a different footing from the research peptides elsewhere in this series. That approval does not extend to men, post-menopausal women, or HSDD from other causes; outside the labeled population it is off-label and should be treated as investigational.

2. It improves desire and distress — but NOT satisfying sexual events

The RECONNECT Phase 3 trials showed statistically significant improvement in sexual desire (FSFI-D) and in associated distress (FSDS-DAO), but NO significant increase in satisfying sexual events (SSEs) versus placebo. This is the central counseling point: set expectations around feeling more desire and less distress, not around more or "better" sexual events.

3. Central desire mechanism — complementary to, not interchangeable with, PDE5i

Because PT-141 acts centrally on desire/arousal while PDE5 inhibitors act peripherally on erection (and require existing desire/stimulation to work), the two address different problems. In men (off-label), this is why PT-141 may help PDE5i non-responders (~33% rescue in one study) and why a PT-141 + low-dose PDE5i combination is of interest — desire plus performance. Kisspeptin, by contrast, works on hormone production, a third distinct lever.

4. Nausea is common but front-loaded; pretreatment can help

Nausea affects ~40% overall but is highest with the FIRST dose (~21%) and falls to ~3% with subsequent doses. Flushing (~20%) and headache (~11%) are next most common. An anti-emetic (e.g. ondansetron 4 mg PO ~30 min before) can be considered for the first dose, and a first in-office dose lets you manage both nausea and the transient BP rise.

5. Cardiovascular and pigmentation safety define candidacy

PT-141 is contraindicated in uncontrolled hypertension and known cardiovascular disease due to a transient pressor effect, so BP control and CVD risk gate eligibility. Focal hyperpigmentation (MC1R-mediated) is uncommon at the labeled ≤8 doses/month (~1%) but rises sharply with daily dosing (~38% at 8 days) and is more likely in darker skin — a discussion point at consent.

Dr. Seeds notes that in his clinical experience the pigmentation has resolved after discontinuation, though the FDA label does not confirm resolution in all patients.

6. Key drug interactions: naltrexone and oral-drug absorption

PT-141 significantly DECREASES oral naltrexone levels — risking treatment failure in patients using naltrexone for alcohol/opioid dependence — making that a practical exclusion. By slowing gastric emptying it can also reduce absorption of concomitant oral medications, so avoid co-dosing with oral drugs that depend on threshold concentrations (e.g. some antibiotics). Notably, there is no significant alcohol interaction (a practical advantage over flibanserin).

4. General Dosing & Delivery Options

FDA-approved dosing exists for premenopausal women with HSDD (below). Male and other off-label dosing is extrapolated from Phase I–II data and is investigational. Cmax plateaus near 7.5 mg — exceeding the approved dose adds risk, not benefit.

FDA-Approved Protocol (Premenopausal Women, HSDD)

- **Dose:** 1.75 mg SC (autoinjector) in the abdomen or thigh
- **Timing:** ≥45 minutes before anticipated sexual activity (optimal timing is patient-determined by experience)
- **Frequency limits:** maximum 1 dose per 24 hours and no more than 8 doses per month (receptor desensitization rationale)
- **Stop rule:** discontinue if no improvement after 8 weeks

Off-Label Male Protocols (investigational — not FDA-approved)

Use	Dose / Route	Notes
Male ED / low desire	1.0–2.0 mg SC, ~45 min before activity	Phase I–II evidence only; monitor BP before/after first dose
PDE5i non-responders	PT-141 + low-dose PDE5i	May rescue ~33% of non-responders; combination under study (Palatin Phase 2)
Intranasal (historical research)	7.5–15 mg IN	Used in early ED trials; not a current clinical route

Administration, Anti-Emesis & Storage

- **First-dose strategy:** consider an in-office first dose to observe BP (2–4 h) and nausea; consider ondansetron 4 mg PO ~30 min prior
- **Dose ceiling:** no benefit exceeding ~7.5 mg (Cmax plateau) — higher doses raise side-effect risk only
- **Renal/hepatic impairment:** exposure (AUC) rises with impairment (mild ~1.2×; moderate ~1.5–1.7×; severe renal ~2×) — use caution
- **Storage:** follow product labeling for the Vyleesi autoinjector; protect from freezing

5. Evidence Profile

Evidence tier distribution: HIGH for female HSDD (two Phase 3 RCTs, n=1,247, plus a 52-week open-label extension); MODERATE for long-term safety and the fMRI mechanism; LOW–MODERATE for male ED (Phase I–II only); LOW for PDE5i-combination and weight effects; and NOT DEMONSTRATED for satisfying-sexual-event improvement. This is, by some distance, the best human evidence base in the series.

Female HSDD — RECONNECT Phase 3 (the approval basis)

Endpoint	Bremelanotide	Placebo	Significance
Desire (FSFI-D change)	+0.5 to +0.6	+0.2	p<0.001 (significant)
Distress (FSDS-DAO Q13)	−0.7	−0.4	p<0.001 (significant)
Satisfying sexual events (SSE)	~0.0	~0.0	NS (not significant)

- 24-week double-blind RCT; mean age 39; median use 2–3×/month; all FSFI domains (desire, arousal, lubrication, orgasm, satisfaction, pain) improved on post-hoc analysis
- 52-week open-label extension (n=684): sustained FSFI-D improvement (~+1.25 to +1.30); no new safety signals; discontinuation 18% (drug) vs 2% (placebo)

Mechanism — fMRI (moderate)

- Comninos 2022 (RCT, n=31): MC4R agonism enhanced cerebellar/SMA activity, deactivated S2 (less self-monitoring), and enhanced amygdala–insula connectivity during erotic stimuli

Male ED — Phase I–II (low–moderate; all off-label)

- Diamond 2004: significant erectile response with intranasal PT-141 (RigiScan); ~30-min onset
- Safarinejad 2008 (n=342 sildenafil non-responders): 33.5% vs 8.5% positive response — NOTE: this study carries a published Expression of Concern
- Combination (n=19): IN PT-141 7.5 mg + sildenafil 25 mg gave greater rigidity than sildenafil alone; real-world refill rates 65–73%

Other Signals (low)

- Weight/appetite (Phase 1, obese women): −~400 kcal/day and −2.1 vs −0.7 kg over 16 days (MC4R appetite role; related drug setmelanotide approved for rare genetic obesity)

Critical gaps: SSE improvement was NOT demonstrated — manage expectations. The exact HSDD mechanism is officially unknown. Male efficacy rests entirely on Phase I–II / off-label data with no completed Phase 3 (and one key male study carries an Expression of Concern). There is no head-to-head trial vs flibanserin, long-term hyperpigmentation outcomes are not fully characterized by the FDA, and approval does not extend beyond premenopausal women with acquired, generalized HSDD.

6. Clinical Considerations

Contraindications

- **Uncontrolled hypertension or known cardiovascular disease:** contraindicated (transient pressor effect)
- **High cardiovascular risk:** not recommended
- **Oral naltrexone (alcohol/opioid dependence):** PT-141 lowers naltrexone levels — risk of treatment failure; avoid
- **Severe needle phobia:** SC injection required
- **HSDD from relationship conflict, medications, or untreated depression:** treat the underlying cause first — poor candidate

Drug Interactions

- **Naltrexone (oral):** significantly decreased levels — clinically important interaction
- **Oral threshold-dependent drugs (e.g. some antibiotics):** delayed gastric emptying may reduce absorption — separate dosing
- **Alcohol:** no significant interaction (advantage over flibanserin), though flushing may increase

Monitoring Protocol

Timepoint	Assessment	Action
Pre-treatment	BP, HR, skin exam, CVD risk	Defer if uncontrolled HTN / CVD
First dose (in-office)	BP at 2–4 h; nausea	Anti-emetic PRN; hold for BP concern
4 weeks	Efficacy; skin for pigmentation	Discontinue if new hyperpigmentation
8 weeks	Efficacy (FSFI-D)	Discontinue if no improvement (FDA stop rule)
Quarterly / annually	BP, skin, med reconciliation, CVD review	Adjust or discontinue as indicated

Comparison: PT-141 vs Flibanserin vs PDE5 Inhibitors

Feature	PT-141 (Vyleesi)	Flibanserin (Addyi)	PDE5 inhibitors
Mechanism	Central MC4R → dopamine (desire)	5-HT1A agonist / 5-HT2A antagonist	Peripheral NO/cGMP (erection)
Use pattern	On-demand SC	Daily oral (bedtime)	On-demand oral
Alcohol	No significant interaction	Severe hypotension risk	Caution
Targets	Desire / distress (women)	Desire (women)	Erection only (no desire)

Adverse Events & Safety Profile

- Most common (Phase 3): nausea 40% (front-loaded, improves to ~3%), flushing 20%, injection-site reactions 13%, headache 11%; discontinuation 18% vs 2% placebo
- Hyperpigmentation (MC1R): ~1% at ≤8 doses/month, much higher with daily dosing; more likely in darker skin; lecturer reports resolution after discontinuation though FDA does not confirm in all
- Transient BP rise / HR drop resolving within ~12 h; no QTc concern; favorable overall within the approved population

Regulatory Status

PT-141 / bremelanotide (Vyleesi) is FDA-APPROVED for acquired, generalized HSDD in premenopausal women (2019). All other uses — men, post-menopausal women, other HSDD subtypes — are off-label and investigational and require clinical judgment and documented informed consent. (Note: melanocortin agonists may be subject to anti-doping rules in sport; verify if relevant.)

7. Final Note

As the second of three peptides in the Hormonal & Sexual Health group, PT-141 stands apart in two ways: it is the only FDA-approved agent in this collection, and it works on the brain's desire circuitry rather than on hormones or blood flow. Where kisspeptin (guide 1) modulates the upstream reproductive endocrine axis, PT-141 modulates motivation — agonizing central MC4R to raise dopaminergic tone and, per fMRI data, enhance sexual processing while quieting self-monitoring. For acquired, generalized HSDD in premenopausal women it has genuine Phase 3 support, an on-demand dosing advantage over daily flibanserin, and no significant alcohol interaction.

The honest framing centers on expectations and boundaries. PT-141 improves desire and the distress that accompanies its loss, but it did NOT increase satisfying sexual events in the trials — it is not a performance or "hedonistic" drug, and patients seeking that will be disappointed. Its mechanism is officially "unknown" to the FDA even as the dopamine model fits the data. Outside the approved population — most notably in men — the evidence is Phase I–II and off-label, with no completed Phase 3 and one key study under an Expression of Concern. Safety is manageable but real: cardiovascular contraindications, front-loaded nausea, dose-dependent hyperpigmentation, and the naltrexone interaction all shape candidacy.

For the clinician, PT-141 is a genuinely useful, approved tool for the right patient — a premenopausal woman with distressing acquired HSDD, controlled blood pressure, no CVD, who prefers on-demand dosing and understands the desire-not-performance distinction. Used off-label in men or in combination with a PDE5 inhibitor, it is reasonable to consider in PDE5i non-responders but should be framed as investigational, with cardiovascular screening, expectation-setting, and structured BP/skin monitoring throughout.

Bottom line: The FDA-approved, on-demand injectable for female HSDD (premenopausal) and the second peptide in the Hormonal & Sexual Health group — a central MC4R agonist that raises desire and lowers distress via hypothalamic/limbic dopamine, distinct from PDE5i (peripheral) and kisspeptin (hormonal). Phase 3 proven for desire/distress but NOT for

satisfying sexual events; mechanism officially "unknown." Contraindicated in uncontrolled HTN/CVD; watch nausea (front-loaded), hyperpigmentation (MC1R, dose-dependent), and the naltrexone interaction. Male and combination use are off-label/investigational (Phase I–II). Approved for women with HSDD; off-label otherwise.

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For educational and research purposes only. Not medical advice. PT-141 / bremelanotide (Vyleesi) is FDA-approved for acquired, generalized HSDD in premenopausal women; all other uses (including all male use) are off-label and investigational. It improves desire and distress but did NOT increase satisfying sexual events in Phase 3 trials, and its exact mechanism is officially unknown to the FDA. Contraindicated in uncontrolled hypertension and known cardiovascular disease; interacts with oral naltrexone. Second of three peptides in the Hormonal & Sexual Health series. Based on lecture materials by William Seeds, MD — SSRP Institute | Cellular Medicine Education.