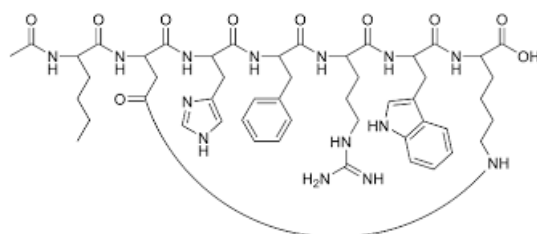


## Professional Monograph

### PT-141 (Bremelanotide)



#### INDICATION and USAGE SUMMARY

- Central melanocortin receptor agonist (high affinity for MC4R)
- Used in male or female sexual dysfunction
  - Improves Female Sexual Dysfunction, including hypoactive sexual desire disorder (HSDD) and Female Sexual Arousal Disorder
  - Improves erectile dysfunction in men
- General dosage = 2mg (0.2ml), injected SubQ, 1 hour before sex
  - If initiating PT-141 therapy for the first time, test 1mg (0.1ml) SubQ, wait 30 minutes to determine if any blood pressure or GI effects are going to occur. Inject 1mg (0.1ml) SubQ additional if no problems.
  - Duration of effects after administration is 24-72 hours
- Not recommended to use more than 2 injections weekly

**Name(s):** PT-141, bremelanotide

**Sequence:** Ac-Nle-cyclo[Asp-His-D-Phe-Arg-Trp-Lys]-OH

**Molecular formula:** C<sub>50</sub>H<sub>68</sub>N<sub>14</sub>O<sub>10</sub>

**Molar Mass:** 1025.2

**Structural Names:** cyclo-[Nle<sup>4</sup>, Asp<sup>5</sup>, D-Phe<sup>7</sup>, Lys<sup>10</sup>]alpha-MSH-(4-10)

- Dosage Route:** SubQ injection
- Mixing:**
- Allow refrigerated vial to warm to room temperature.
  - Use aseptic technique and reconstitute lyophilized powder (10mg vial) with 1ml bacteriostatic water or buffering agent. A buffered solution for reconstitution will improve stability.
- Stability:**
- Un-reconstituted lyophilized powder should be stored under refrigeration per vial's instruction.
  - After reconstitution with bacteriostatic water, refrigerate solution and **use within 30 days**. If buffered solution is used, stability will improve.
- Dosage:**
- SubQ (men and women)
    - 2mg starting dose, 1 hour before sex
    - Recommended to inject 1mg for test dose, then add 1mg more 30 minutes later
    - Titration may be needed to achieve desired response
    - Dose 2 x weekly initially, then may increase if tolerated

## Background

It is estimated that 43% of women (30 million in the US) suffer from female sexual dysfunction. Approximately 15 million women suffer from hypoactive sexual desire disorder (HSDD) in the US, characterized by low sexual desire that leads to marked distress or relationship anxiety.<sup>1</sup> It is also estimated that 30 million men suffer from ED (erectile dysfunction), with incidence increasing 2-3 fold between the ages of 40-70.<sup>2</sup>

The most common method of treating male sexual dysfunction include PDE5 inhibitors (phosphodiesterase type 5), including Viagra (sildenafil) tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®), and avanafil (Stendra®).<sup>3</sup> However, PDE5 inhibitors can produce side effects such as dyspepsia, headaches, flushing and priapism (erection lasting more than 4 hours), and they can be involved with serious drug interactions, including with nitrates. Also, PDE5's are reported effective in only 40-80% of patients.<sup>4</sup> Sildenafil and vardenafil have similar half-lives of 4 hours,

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<sup>1</sup> U.S. Census Bureau, 2014; Shifren et al, Sexual Problems and Distress in United States Women; Obstetrics & Gynecology, Vol. 112, No. 5, November 2008.

<sup>2</sup> Laumann EO, Palik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;28(16):537-44.

<sup>3</sup> Aversa A, Mazizzilli F, Rossi T, et al. Effects of sildenafil (Viagra) administration on seminal parameters and post-ejaculatory refractory time in normal males. Hum Reprod. 2000;15(1):131-4.

<sup>4</sup> Padma-Nathan H, Steers WD, Wicker PA. Efficacy and safety of oral sildenafil in the treatment of erectile dysfunction: a double-blind, placebo-controlled study of 329 patients. Int J Clin Pract. 1998; 52: 375-379.

while tadalafil has the longest (17.5 hours) and avanafil has the shortest (3 hours). Vardenafil should be used with caution in patients with prolonged QT interval.<sup>5</sup>

Addyi (flibanserin), called the “female viagra”, was approved in 2015 for the treatment of hypoactive sexual desire disorder (HSDD) in premenopausal women and is classified as a multifunctional serotonin agonist antagonist (MSAA). Addyi carries a black box warning claiming the product may cause fainting and hypotension and should not be combined with alcohol.<sup>6</sup>

Fortunately, there now is a safe and efficacious alternative for clinicians wishing to treat male or female sexual dysfunction – the peptide PT-141 (bremelanotide).

### **PT-141**

PT-141, or bremelanotide, is a synthetic, central melanocortin receptor agonist that increases  $\alpha$ -melanocyte stimulating hormone ( $\alpha$ -MSH) in the body. It has been reported to aid in sexual experiences for men and women.<sup>7,8</sup> PT-141 is a deaminated derivative and likely metabolite of Melanotan II, another synthetic melanocortin receptor agonist initially used for tanning purposes. During treatment with Melanotan II, researchers, clinicians and patients noticed an increase in sexual activity.<sup>9</sup> However, Side effects reported with melanotan II include nausea, vomiting, yawning, and a delayed onset of erection (approximately 2 hours).<sup>10</sup> So researchers began to look for alternatives to melanotan II, and bremelanotide was synthesized in 2000 and trials began.

Unlike the FDA approved PDE5 inhibitors that improved sexual function by improving nitric oxide and vascular function, **PT-141 works on the CNS, thus eliciting a more desirous sexual response.**<sup>11</sup> Of the 5 melanocortin receptors (1-5), PT-141 has the highest affinity for melanocortin receptor 4 (MC4R). In the hypothalamus,  $\alpha$ -MSH suppresses appetite (MC4R receptor), with MC4R defects are reported to be a cause for autosomal dominant obesity, accounting for approximately 6% of all cases of early onset obesity.<sup>12</sup> MC4R stimulation also

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<sup>5</sup> Patel CK, Bennett N. Advances in the treatment of erectile dysfunction: what's new and upcoming? Version 1.2016: 5: F1000 Faculty Rev-369.

<sup>6</sup> Gelman F, Atrio J. Flibanserin for hypoactive sexual desire disorder: place in therapy. *Ther Adv Chronic Dis.* 2017;8(1):16-25.

<sup>7</sup> King SH, Mayorov AV, Balse-Srinivasan P, et al. Melanocortin receptors, melanotropic peptides and penile erection. *Curr Top Med Chem.* 2007;7(11):1098-1106.

<sup>8</sup> Clayton AH, Althof SE, Kingsberg S, et al. Bremelanotide for female sexual dysfunctions in premenopausal women: a randomized, placebo-controlled dose-finding trial. *Women's Health.* 2-16;12(3):325-337.

<sup>9</sup> Wessells H, Levine N, Hadley ME, et al. Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. *Int J Impot Res.* 2000;12 (Suppl 4):S74-9.

<sup>10</sup> Wessells H, Levine N, Hadley ME, et al. : Melanocortin receptor agonists, penile erection, and sexual motivation: human studies with Melanotan II. *Int J Impot Res.* 2000;12(Suppl 4):S74-9.

<sup>11</sup> Rosen RC, Diamond LE, Earle DC, et al. Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT\_141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra. *Int J Impotence Res.* 2004;16:315-42.

<sup>12</sup> Baltatzi M, Hatzitollios A, Tziomalos K, et al. Neuropeptide Y and alpha-melanocyte stimulating hormone: interaction in obesity and possible role in the development of hypertension. *Int J Clin Prac.* 2000;62(9):1432-40.

contributes to improved sexual function in both men (improving penile erections) and women (increasing desire and arousal).<sup>13,14</sup>

## Research

Current research validates use of melanocortinergic agents for the treatment of both male and female sexual dysfunction.<sup>15</sup> PT-141, with a high affinity for MC4R (melanocortin receptor 4), has been clinically studied in both males and females with sexual issues.<sup>16,17, 18</sup> In laboratory studies, administration of bremelanotide significantly promoted solicitational behavior in female rats, and appears to be the first “true” aphrodisiac.<sup>19</sup> Studies using animal models have demonstrated that pre-copulatory behaviors in female rats analogous to sexual arousal are evoked, and preliminary clinical data also suggest a role in promoting sexual desire and arousal in women.<sup>20</sup> Studies have also reported that melanocortin peptides also affect dopaminergic neurotransmission, which can also affect sexuality via reward-based neuropharmacology.<sup>21</sup>

Improvements in erection response in men with mild to moderate erectile dysfunction as well as improvement in both arousal and subjective excitement in premenopausal women with FSAD is reported when using bremelanotide.<sup>22,23</sup> Based on clinical observations, **International Peptide Society (IPS) recommends not using the injection of PT-141 concurrently with PDE5 inhibitor due to risk of hypertension and/or priapism in men.**

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<sup>13</sup> King SH, Mayorov AV, Balse-Srinivasan P, et al. Melanocortin receptors, melanotropic peptides and penile erection. *Curr Top Med Chem.* 2007;7(11):1098-1106.

<sup>14</sup> Ven der Ploeg LHT, Martin WJ, Howard AD, et al. A role for the melanocortin 4 receptor in sexual function. *PNAS.*2002;99(17):11381-11386.

<sup>15</sup> Shadiack AM, Sharma SD, Earle DC, Spana C, Hallam TJ. Melanocortins in the treatment of male and female sexual dysfunction. *Curr Top Med Chem.* 2007;7(11):1137-44.

<sup>16</sup> Molinoff PB, Shadiack AM, Earle D, Diamond LE, Quon CY. PT-141: a melanocortin agonist for the treatment of sexual dysfunction. *Ann. NY Acad. Sci.* 994, 96–102 (2003).

<sup>17</sup> Clayton AH, Althof SE, Kingsberg S, et al. Bremelanotide for female sexual dysfunctions in premenopausal women: a randomized, placebo-controlled dose-finding trial. *Women’s Health.* 2-16;12(3):325-337.

<sup>18</sup> Bremelano, Clayton AH, Althof SE, Kingsberg S, et al. Bremelanotide for female sexual dysfunctions in premenopausal women: a randomized, placebo-controlled dose-finding trial. *Womens Health (Lond).* 2016;12(3):325-37.

<sup>19</sup> Pfaus JG, Shadiack A, Soest TV, et al. Selective facilitation of sexual solicitation in the female rat by a melanocortin receptor agonist. *PNAS.* 2004;101(27):10201-10204.

<sup>20</sup> Shadiack AM, Sharma SD, Earle DC, et al. Melanocortins in the treatment of male and female sexual dysfunction. *Curr Top Med Chem.* 2007;7(11):1137-44.

<sup>21</sup> Shadiack AM, Althof S. Preclinical effects of melanocortins in male sexual dysfunction. *Int J Impot Res.* 2008;20(Suppl 1):S11-6.

<sup>22</sup> Rosen RC, Diamond LE, Earle DC, et al. Evaluation of the safety, pharmacokinetics and pharmacodynamic effects of subcutaneously administered PT\_141, a melanocortin receptor agonist, in healthy male subjects and in patients with an inadequate response to Viagra. *Int J Impotence Res.* 2004;16:315-42.

<sup>23</sup> Diamond LE, Earle DC, Garcia WD, Spana C. Co-administration of low doses of intranasal PT-141, a melanocortin receptor agonist, and sildenafil to men with erectile dysfunction results in an enhanced erectile response. *Urology.* 2005 Apr;65(4):755-9.

Data from Phase II clinical trials using intranasal bremelanotide supported the use of melanocortin-based therapy for erectile dysfunction.<sup>24</sup> Unfortunately, intranasal use led to hypertension and clinical trials using intranasal bremelanotide were discontinued in 2008.

Palatin, Inc. reformulated the bremelanotide for SubQ use via an autoinjector. In early 2017, Palatin Technologies successfully completed two Phase III Reconnect clinical trials using injectable (SubQ) bremelanotide for FDS (female sexual dysfunction) specifically hypoactive sexual desire disorder (HSDD). Each double-blind, placebo-controlled, randomized parallel group study with over 600 patients were treated with Rekynda, SubQ for 24 weeks. The side effects encountered were mild to moderate nausea, flushing and/or headache. Palatin has exclusively licensed North American rights to develop and commercialize bremelanotide to AMAG Pharmaceuticals, Inc. with a trade name of Rekynda™, and continues licensing to countries around the world. The anticipated filing date in the U.S. for a new drug application for bremelanotide, is early 2018, with an anticipated approval and launch by early 2019. Off label uses for male sexual dysfunction will still be available.

### **Potential Side Effects and/or Contraindications**

- As with all injections, redness and pain at the site of injection may be present.
- GI distress (including nausea) may occur. Administration of an antihistamine in sensitive individuals is recommended by the International Peptide Society (IPS) to help decrease the incidence of any nausea that may occur.
- Flushing and headache may also occur
- Using before bedtime may affect sleep patterns
- If tachycardia develops, discontinue use. Twice-weekly usage is recommended by the International Peptide Society (IPS) to decrease the incidence of developing tachycardia.
- Discontinue use if priapism develops in men (an erection lasting longer than 4 hours).
- Use with caution if a history of hypertension is present.<sup>25</sup> A case study reported that PT-141 injection led to elevated blood pressure in existing hypertensive patients (2 patients).<sup>26</sup> Anecdotal reports of short-term increases in blood pressure after injection are also reported, especially in those pre-disposed to hypertension.
- It is NOT recommended to use PT-141 injection concurrently with a PDE5 inhibitor in men due to risk of priapism.
- A Phase 1 study (n=24 -12 men, 12 women) using SubQ bremelanotide and ethanol concurrently reported no synergistic side effects between them.<sup>27</sup>

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<sup>24</sup> King SH, Mayorov AV, Balse-Srinivasan P, et al. Melanocortin receptors, melanotropic peptides and penile erection. *Curr Top Med Chem.* 2007;7(11):1098-1106.

<sup>25</sup> White WB, Myers MG, Jordan R, et al. Usefulness of ambulatory blood pressure monitoring to assess the melanocortin receptor agonist bremelanotide. *J Hypertens.* 35(4):761-68.

<sup>26</sup> Diamond LE., Earle DC, Rosen RC, et al. Double-blind, placebo-controlled evaluation of the safety, pharmacokinetic properties and pharmacodynamic effects of intranasal PT-141, a melanocortin receptor agonist, in healthy males and patients with mild-to-moderate erectile dysfunction. *Int. J Impot Res.* 2004;16(1):51-9.

<sup>27</sup> Clayton AH, Lucas J, DeRogatis LR, et al. Phase 1 randomized placebo-controlled, double blind study of the safety and tolerability of bremelanotide coadministered with ethanol in healthy male and female participants. *Clin Ther.* 2017;39(3):514-526.

**DISCLAIMER:** Statements made are for educational purposes and have not been evaluated by the US Food and Drug Administration (FDA). They are not intended to diagnose, treat, cure, or prevent any disease. Peptides should only be administered by licensed and qualified health care professionals.