Vyleesi (bremelanotide)

BENEFIT APPLICATION

Benefit determinations are based on the applicable contract language in effect at the time the services were rendered. Exclusions, limitations or exceptions may apply. Benefits may vary based on contract, and individual member benefits must be verified. Wellmark determines medical necessity only if the benefit exists and no contract exclusions are applicable. This medical policy may not apply to FEP. Benefits are determined by the Federal Employee Program.

DESCRIPTION

Vyleesi (bremelanotide) is a melanocortin receptor (MCR) agonist that nonselectively activates several receptor subtypes with the following order of potency: MC1R, MC4R, MC3R, MC5R, MC2R.

FDA-Approved Indications
Vyleesi (bremelanotide) is indicated for the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), as characterized by low sexual desire that causes marked distress or interpersonal difficulty and is not due to a co-existing medical or psychiatric condition, problems with the relationship, or the effects of a medication or drug substance.

Limitations of Use
- Vyleesi is not indicated for the treatment of HSDD in postmenopausal women or in men
- Vyleesi is not indicated to enhance sexual performance

POLICY

Vyleesi (bremelanotide) is considered **not covered** for all indications, including the treatment of premenopausal women with acquired, generalized hypoactive sexual desire disorder (HSDD), due to the limited clinical benefits demonstrated in clinical trials, high cost, and increased risk of nausea.

CLINICAL RATIONALE

Hypoactive sexual desire disorder (HSDD) is a disease that represents a subset of symptoms associated with “desire” within the overarching diagnosis of sexual dysfunction. HSDD was a stand-alone diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV. In DSM V, HSDD is now incorporated into female sexual interest/ arousal disorder (FSIAD). FSIAD is defined as a lack of, or significantly reduced, sexual interest or arousal for 6 months or greater when a patient meets 3 of the 6 diagnostic criteria.

Vyleesi (bremelanotide) is the second agent, after Addyi (flibanserin) in 2015, to receive an FDA-approval for the treatment of premenopausal women with acquired, generalized HSDD that is not due to a co-existing medical or psychiatric condition, problems within the relationship, or the effects of a medication or other drug substance. The approval was based on two identical, 24-week, phase III, randomized, double-blind, placebo-controlled trials in 1,247 premenopausal women with acquired, generalized HSDD. Patients were randomized to subcutaneous (SC) injections of Vyleesi or placebo on an as-needed basis. The co-primary endpoints in the studies were change from baseline to end of study (EOS) in the Desire domain from the

Female Sexual Function Index (FSFI Q1 & Q2) and change from baseline to EOS in the score for feeling bothered by low sexual desire as measured by the Female Sexual Distress Scale – Desire/Arousal/Orgasm Question 13 (FSDS-DAO Q13). In both studies, Vyleesi showed a statistically significant increase in the FSFI Desire Domain score and a statistically significant decrease in the FSDS-DAO Q13 score from baseline to the EOS visit vs. placebo. There was no significant difference between the two treatment groups in the number of satisfying sexual events, a secondary endpoint.

Summary of Efficacy Results for Reconnect Study

RECONNECT	Study 1		Study 2	
	Vyleesi	Placebo	Vyleesi	Placebo
FSFI-Desire Domain Score Score range: 1.2 to 6.0, with higher scores indicating greater desire				
Mean change from baseline (SD)	0.5 (1.1)	0.2 (1.0)	0.6 (1.0)	0.2 (0.9)
Median change from baseline	0.6	0	0.6	0
p-value	0.0002		< 0.0001	
FSDS-DAO Q13 Score Score range: 0 to 4, with higher scores indicating greater bother				
Mean change from baseline (SD)	-0.7 (1.2)	-0.4 (1.1)	-0.7 (1.1)	-0.4 (1.1)
Median change from baseline	-1	0	-1	0
p-value	< 0.0001		0.0053	
Number of Satisfying Sexual Events (SSEs)				
Mean change from baseline (SD)	0.0 (1.4)	-0.1 (1.4)	0.0 (1.3)	0.0 (1.2)
Median change from baseline	0	0	0	0
p-value	0.76		0.70	

*Results using modified intent to treat population defined as all patients who were randomized, used at least one dose of double-blind study drug, and had at least one double-blind follow-up visit.

Although Vyleesi showed a statistically significant increase in the FSFI Desire Domain score and a statistically significant decrease in the FSDS-DAO Q13 score from baseline to the EOS visit vs. placebo, it has a relatively moderate effect. Approximately 25% of patients had an increase of 1.2 or more in their sexual desire score on the Female Sexual Function Index (FSFI), compared to 17% on placebo. And about one-third (35%) of patients had a decrease of 1 point or more on the four-point Female Sexual Distress Scale-Desire/Arousal/Orgasm (FSDS-DAO), compared with 31% of those taking placebo. That translates to only 4% of patients gaining any benefit over placebo when sexual distress was evaluated and only 8% seeing better results versus placebo in terms of sexual desire.

Serious adverse reactions occurred in 1.1% of women treated with bremelanotide (compared with 0.5% with placebo). Common adverse reactions included nausea (40%; mostly with first injection; 13% of women required anti-emetic medications), vomiting (5%), flushing (20%), headache (11%), and hyperpigmentation (1%; possibly permanent). Some women had a transient increase in blood pressure, and bremelanotide should not be used in women with uncontrolled hypertension or known cardiovascular disease.

Among the 856 patients who completed the double-blind core study phase, approximately 80% (684 patients) elected to participate in an open-label extension trial. This included 87% (430/493) of patients from the placebo groups and 70% (254/363) of patients from the bremelanotide groups. The open-label extension demonstrated safety of bremelanotide up to 76 weeks as well as sustained improvements in symptoms in women with hypoactive sexual desire disorder. One patient was diagnosed with acute hepatitis that resolved without further complications and was regarded as possibly related to study drug. There were

no other new safety signals or findings observed compared to Study 1 and Study 2. The authors did mention notable limitations of the study which included selection bias and high discontinuation rates.

A differential study withdrawal rate was observed in both studies (Study 1: 41.9% bremelanotide vs 16.0% placebo; Study 2: 43.8% bremelanotide vs 28.4% placebo). The most common reasons for the study discontinuation attributed to adverse events (Study 1: 23.4%; Study 2: 18.7%) and withdrawal of consent (17.6% and 19.0%). In Study 1, patients who did not complete the open-label extension discontinued during the first 20 weeks (150/363 patients [41.3%]). In Study 2, a similar number of patients discontinued the open-label extension throughout the 52-week period, except for week 4 and week 28 when higher numbers of patients discontinued (43 [13.4%] patients and 36 [11.2%] patients, respectively). Only about 40% of patients who enrolled in the open-label extension completed the 52-week treatment period. As the major reason for study discontinuation was adverse events (21.2%), the authors note that it is likely that the incidence of adverse events is higher in the "real world" compared with the population who participated in the open-label extension.

The co-primary efficacy endpoint results were assessed using a modified intent-to-treat (mITT) population, which was defined as all patients in the safety population who had one or more double-blind follow-up visits, rather than using the intention-to-treat (ITT) principle, in which all subjects are included in the final analysis and analyzed in the groups which they were originally randomized. The mITT analysis allows for a subjective approach in entry criteria, which can lead to confusion, inaccurate results and bias. With the high rate of withdrawals in these studies, the efficacy of Vyleesi is likely overstated when using mITT compared to if the gold-standard ITT analysis was used.

The National Women's Health Network (the NWHN) released a statement following the FDA's decision to approve Vyleesi (bremelanotide) urging women to avoid using the drug until more is known about its safety and effectiveness. NWHN stated "Women simply do not have enough information to make an informed decision about whether the drug is safe and effective".

HSDD is a very complex condition and the mechanism by which Vyleesi improves sexual desire and related distress is unknown. Although there is an unmet need and Vyleesi has demonstrated some improvement in treating HSDD, evidence demonstrates that Vyleesi only modestly increases sexual desire in some women, may slightly lessen distress over a lack of desire, and has no effect on the number of satisfying sexual events. Vyleesi is associated with an increased risk of nausea at any time throughout treatment that may require antiemetic therapy and must be self-administered as an injection about 45 minutes before a sexual encounter. Continued assessment of long-term benefits and risks associated with Vyleesi and the safety and efficacy in postmenopausal women and in women whose comorbidities include psychiatric disorders requiring medication are still warranted. In summary, Vyleesi is associated with a manageable yet poor adverse effect profile and high cost that does not justify the limited clinical benefit it provides.

APPENDIX

Co-primary Endpoints Response Options

FSFI Question 1: Over the past 4 weeks, how **often** did you feel sexual desire or interest?	5=Almost always or always 4=Most times (more than half the time) 3=Sometimes (about half the time) 2=A few times (less than half the time) 1=Almost never or never

FSFI Question 2: Over the past 4 weeks, how would you rate your **level** (degree) of sexual desire or interest?	5=Very high 4=High 3=Moderate 2=Low 1=Very low or none at all
FSDS-DAO Question 13: How **often** did you feel bothered by low sexual desire?	4=Always 3=Frequently 2=Occasionally 1=Rarely 0=Never

FSFI: Female Sexual Function Index
FSDS-DAO: Female Sexual Distress Scale-Desire/Arousal/Orgasm

PROCEDURES AND BILLING CODES

To report provider services, use appropriate CPT* codes, Alpha Numeric (HCPCS level 2) codes, Revenue codes, and/or ICD diagnostic codes.

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POLICY HISTORY

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