Zulresso™ (brexanolone) – New drug approval

- On March 19, 2019, the FDA announced the approval of SAGE Therapeutics' Zulresso (brexanolone), for the treatment of postpartum depression (PPD) in adults.
    - Zulresso is expected to be reviewed for controlled substance scheduling by the Drug Enforcement Administration within the next 90 days.
    - Zulresso is available only through a restricted program called the Zulresso REMS. Healthcare facilities must enroll in the program and ensure that Zulresso is only administered to patients who are enrolled in the Zulresso REMS.

- PPD is a major depressive episode that occurs following childbirth, although symptoms can start during pregnancy. PPD affects approximately one in nine women who have given birth in the U.S. and 400,000 women annually.

- Zulresso is the first medicine specifically approved for the treatment of PPD. The mechanism of action in the treatment of PPD in adults is not fully understood, but is thought to be related to its positive allosteric modulation of $GABA_A$ receptors.

- The efficacy of Zulresso was established in two studies in women with PPD. Study 1 included patients with severe PPD and study 2 included patients with moderate PPD. Patients were randomized to a 60-hour continuous intravenous (IV) infusion of Zulresso or placebo. The primary endpoint was the mean change from baseline in depressive symptoms as measured by the Hamilton Depression Rating Scale (HAM-D) total score at the end of the infusion (hour 60).
    - In both studies, titration to a target dose of Zulresso 90 mcg/kg/hour was superior to placebo in improvement of depressive symptoms. In a group of 38 patients in study 1, a Zulresso titration to a target dose of 60 mcg/kg/hour was also superior to placebo in improvement of depressive symptoms.

Study number	Treatment group (n)	HAM-D total score at hour 60	
		LS mean change from baseline (SE)	Placebo-subtracted difference (95% CI) p-value
1	Zulresso target dosage 90 mcg/kg/hour (n = 41)	-17.7 (1.2)	-3.7 (-6.9, -0.5); p = 0.0252
	Placebo (n = 43)	-14.0 (1.1)	
	Zulresso target dosage 60 mcg/kg/hour (n = 38)	-19.5 (1.2)	-5.5 (-8.8, -2.2); p = 0.0013
	Placebo (n = 43)	-14.0 (1.1)	
2	Zulresso target dosage 90 mcg/kg/hour (n = 51)	-14.6 (0.8)	-2.5 (-4.5, -0.5); p = 0.0160
	Placebo (n = 53)	-12.1 (0.8)	

Abbreviations: LS: least square; SE: standard error

- Zulresso carries a boxed warning for excessive sedation and sudden loss of consciousness.

- An additional warning and precaution for Zulresso is suicidal thoughts and behaviors.

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- The most common adverse reactions (≥ 5% and at least twice the rate of placebo) with Zulresso use were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush.

- Zulresso should be administered as a continuous IV infusion over a total of 60 hours (2.5 days) as follows:

    - 0 to 4 hours: initiate with a dosage of 30 mcg/kg/hour
    - 4 to 24 hours: increase dosage to 60 mcg/kg/hour
    - 24 to 52 hours: increase dosage to 90 mcg/kg/hour
    - 52 to 56 hours: decrease dosage to 60 mcg/kg/hour
    - 56 to 60 hours: decrease dosage to 30 mcg/kg/hour
    - If excessive sedation occurs at any time, the infusion should be stopped until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.
    - A healthcare provider must be available on site to continuously monitor the patient, and intervene as necessary, for the duration of the Zulresso infusion.
    - Refer to the Zulresso drug label for additional dosing and administration details.

- SAGE Therapeutics plans to make Zulresso available in late June. Zulresso will be available as a 100 mg/20 mL solution (5 mg/mL) in single-dose vials.