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Brexanolone: An informative study

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Abstract: *The birth of a baby will cause the joy, satisfaction, fear and anxiety to mix up with powerful emotions. Yet it may also lead to something that you do not foresee-depression. Upon childbirth most new mothers experience "baby blues," which usually include mood swings, crying kinds, anxiety, and sleeping difficulty. Usually, baby blues start within a two- to three-day span and can last up to two weeks. However, some new moms experience more serious, chronic depression called postpartum depression. Our aim is to include an Informative Overview of Brexanolone (Zulresso) in postpartum depression (PPD), a new antidepressant with a new mechanism of action.*

Keywords: *Depression, Postpartum, Brexanolone, chronic*

I. Introduction

Brand name: Zulresso
Molecular Weight: 318.4976
Chemical Formula: $C_{21}H_{34}O_2$

Postpartum depression (PPD) is a form of depression that affects women following childbirth. It is a mood disorder that affects about 10–15 percent of adult mothers annually with depressive symptoms of 25–50 percent for those affected for more than 6 months [1]. Postpartum depression frequently develops in the span of several months to a year after birth. Some studies reported the onset of postpartum depression four years after birth [2]. However PPD may cause physiological, situational, or multifactorial causes [3]. For the treatment of postpartum depression (PPD), the FDA approved the GABAA receptor modulator brexanolone that came under the brand name of (Zulresso). On 19 March 2019, ZULRESSO was approved by the United States Food and Drug Administration (FDA). Brexanolone is the first drug to receive FDA approval for this indication [4].

Indication

Brexanolone prescription is a drug that is prescribed in adult women for treating postpartum depression. Brexanolone received FDA approval in March 2019. It is the first drug to obtain special approval for postpartum depression. Postpartum depression is a serious illness affecting 10 to 20 per cent of women around the world [5].

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Clinically, it acts after transmission as a significant sign of depression, and often coexists with anxiety [6]. Some 5 to 10 percent of these patients have serious postpartum depression [7]. Postpartum depression is one of the leading causes of maternal mortality and morbidity which eventually affects mother, infant, and their siblings' cognitive, emotional, behavioral, and physical well-being [8,9]. Hence, Brexanolone has been approved by the FDA as a Breakthrough Therapy Designation for the postpartum depression treatment.

Dosing and administration

Brexanolone injection is available as single-dose vial 100-mg/20-mL (5-mg/mL). Dilution is necessary before administering brexanolone.10For the duration of the brexanolone infusion, the healthcare provider must be on site to observe the patient constantly and intervene where appropriate. Brexanolone is administered as a continuous intravenous infusion over 60 hours (2.5 days). From 0 to 4 hours, the initial dose of brexanolone is 30 mcg/kg per hour; from 4 to 24 hours, the dose is increased to 60 mcg/kg per hour; from 24 to 52 hours, the dose is increased to 90 mcg/kg per hour (or, for patients unable to tolerate the 90-mcg/kg dose, a dose of 60 mcg/kg per hour can be considered). From 52 to 56 hours, the dose is decreased to 60 mcg/kg per hour; and from 56 to 60 hours, the dose is decreased to 30 mcg/kg per hour [10].

Preparation and Storage Instructions

Brexanolone is supplied in vials as a concentrated solution which need dilution before administration. After dilution, the product can be stored in infusion bags under refrigerated conditions for up to 96 hours. However, given that the diluted drug can only be used at room temperature for 12 hours, at least five infusion bags will be needed for each 60-hour infusion.

Diluted ZULRESSO storage instructions [10]

If not used immediately after dilution, store into refrigerated conditions for up to 96 hours. Long-term room temperature storage can promote adventitious microbe production. Each prepared bag of diluted ZULRESSO may be used for up to 12 hours of infusion time at room temperature. After 12 hours of infusion, discard any unused ZULRESSO; Table 1 depicts the preparation phases for ZULRESSO.

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	Visually inspect the vials of ZULRESSO for particulate matter and discoloration prior to administration. Brexanolone is a clear, colorless solution. Don’t use if the solution is discolored or particulate matter is present.
	The 60-hour infusion will generally require the preparation of 5 infusion bags. Additional bags will be needed for patients weighing ≥90 kg

	For each infusion bag: • Prepare and store in a polyolefin, non-DEHP, nonlatex bag, only. Dilute in the infusion bag immediately after the initial puncture of the drug product vial. • Take 20 mL of ZULRESSO from the vial and place it into the infusion bag. Dilute with 40 mL of Sterile Water for Injection, and further dilute with 40 mL of 0.9% Sodium Chloride Injection (total volume of 100 mL) to achieve a target concentration of 1 mg/mL.
	Immediately place the infusion bag under refrigerated conditions until use

Dosage formulations and strength

Injection: 100 mg/20 mL (5 mg / mL) in a single-dose vial with a transparent, colorless solution.

Description

ZULRESSO contains brexanolone, a gamma-aminobutyric acid (GABA) neuroactive steroid, a receptor-positive modulator chemically similar to endogenous allopregnanolone; ZULRESSO injection is a solution that is sterile, dry, colorless and without preservative. ZULRESSO 5 mg / mL is hypertonic, and should be diluted as an intravenous infusion before administration. Every mL of a solution contains 5 mg brexanolone, 250 mg betadex sulfobutyl ether sodium, 0.265 mg citric acid monohydrate, 2.57 mg sodium citrate dihydrate, and injection water. During production, hydrochloric acid or sodium hydroxide can be used to change the pH. Action mechanism Exact mechanism of action of brexanolone is not completely understood. Brexanolone is an aqueous allopregnanolone product and is a major progesterone metabolite. Allopregnanolone levels appear to increase with progesterone at the highest in the third trimester [11] during pregnancy. Allopregnanolone is a strong, endogenous neuroactive steroid that modulates neuronal excitability through positive allosteric regulation of synaptic and extrasynaptic gamma-aminobutyric acid (GABA) type A receptors [12]. Extrasynaptic GABA type A receptors mediate tonic inhibition that makes the mechanism of allopregnanolone special in comparison with benzodiazepines that mediate phasic inhibitors.

Pharmacodynamics

Brexanolone potentiated GABA-mediated currents from recombinant human GABAA receptors in mammalian cells expressing α1β2-2 subunits of receptors, α4β3-3-subunits of receptors and α6β3-3-subunits. Exposure-response associations with Brexanolone and the pharmacodynamic response time course are unclear.

Pharmacokinetics

It demonstrated dose-proportional pharmacokinetics over a dosage range of 30 mcg / kg / hour to 270 mcg / kg / hour (3 times the recommended maximum dosage). Mean steady state exposure was about 52 ng / mL and 79 ng / mL at 60 mcg / kg / hour and 90 mcg / kg / hour respectively.

Distribution: The brexanolone distribution volume was around 3 L / kg, indicating broad distribution into tissues. Binding plasma protein reached 99 per cent and is independent of plasma concentrations.

Elimination: Brexanolone's terminal half-life was about nine hours. Brexanolone's gross plasma clearance is around 1 litre / hour / kg.

Metabolism: Brexanolone is extensively metabolized through 3 key routes via non-CYP-based pathways: keto-reduction (AKRs), glucuronidation (UGTs), and sulphation (SULTs). There are 3 main circulating metabolites, which are pharmacologically inactive and do not contribute to ZULRESSO's overall effectiveness.

Excretion: 47% is recovered in feces (primarily as metabolites) and 42% in urine (with less than 1% as unchanged brexanolone) following administration of radiolabeled brexanolone.

Specific Populations: There were no clinically relevant variations in brexanolone pharmacokinetics reported based on a study of renal impairment (severe) or hepatic impairment (mild, moderate, severe).

Synthesis[12]

Allopregnanolone is a progesterone Neuroactive metabolite. Allopregnanolone is synthesized by the sequential action of two enzymes, 5α-reductase type I (5α-RI), which transforms progesterone into 5α-dihydroprogesterone, and 3α-hydroxysteroid dehydrogenase (3α-HSD), which transforms 5α-dihydroprogesterone into allopregnanolone. Allopregnanolone on the GABAA receptor is a potent positive allosteric modulator for GABA action. Allopregnanolone reduces the rate of recovery from desensitization of the GABAA receptor, and can increase the rate of entry into quick desensitized states.

II. Discussion and Conclusion

PPD is a psychiatric disorder which is extremely prevalent, underdiagnosed and undertreated. Brexanolone, approved by the FDA under a REMS in March 2019, provides promise for PPD as a targeted pharmacotherapeutic intervention, with minimal side effects and interactions between drugs. There is a need for more studies to clarify the etiology of postpartum depression, broaden treatment options and turn results into effective patient care. Postpartum depression is a common form of depression with no previous FDA-approved treatment. Traditional antidepressants have limitations in practical use. Brexanolone provides a new mechanism and promise for rapid remission of symptoms. Logistic, safety, and financial issues may limit widespread use.

Conflict of interest

The authors declare none.

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