Terlivaz® (terlipressin) – New orphan drug approval

- On September 14, 2022, Mallinckrodt announced the FDA approval of Terlivaz (terlipressin), to improve kidney function in adults with hepatorenal syndrome (HRS) with rapid reduction in kidney function.
    - Patients with a serum creatinine (SCr) > 5 mg/dL are unlikely to experience benefit.
- HRS involving rapid reduction in kidney function is an acute and life-threatening condition that occurs in people with advanced liver disease. HRS is classified into two distinct types – a rapidly progressive type that leads to acute renal failure where patients are typically hospitalized for their care and a more chronic type that progresses over weeks to months
    - HRS involving rapid reduction in kidney function is estimated to affect between 30,000 and 40,000 Americans annually.
- Terlivaz is a synthetic vasopressin analogue with twice the selectivity for vasopressin V_1 receptors vs. V_2 receptors. Terlivaz is thought to increase renal blood flow in patients with HRS by reducing portal hypertension and blood circulation in portal vessels and increasing effective arterial volume and mean arterial pressure.
    - Terlivaz is the first FDA-approved product to improve kidney function in adults with HRS.
- The efficacy of Terlivaz was established in a double-blind, randomized, placebo-controlled study (CONFIRM) in 300 patients with cirrhosis, ascites, and a diagnosis of HRS with a rapidly progressive worsening in renal function. Patients were randomized to treatment with Terlivaz or placebo. The primary endpoint was the incidence of Verified HRS Reversal, defined as the percentage of patients with 2 consecutive SCr values of ≤ 1.5 mg/dL, obtained at least 2 hours apart while on treatment by day 14 or discharge.
    - Verified HRS Reversal was achieved in 29.1% of patients with Terlivaz vs. 15.8% of patients with placebo ($p = 0.012$).
- Terlivaz carries a boxed warning for serious or fatal respiratory failure.
- Terlivaz is contraindicated in patients:
    - Experiencing hypoxia or worsening respiratory symptoms
    - In patients with ongoing coronary, peripheral or mesenteric ischemia.
- Additional warnings and precautions for Terlivaz include ineligibility for liver transplant, ischemic events, and embryo-fetal toxicity.
- The most common adverse reactions (≥ 10%) with Terlivaz use were abdominal pain, nausea, respiratory failure, diarrhea, and dyspnea.
- The recommended starting dosage of Terlivaz is 0.85 mg every 6 hours by slow intravenous bolus injection (over 2 minutes) on days 1 through 3. The dose should be adjusted on day 4 based on changes from baseline SCr. Refer to the drug label for complete dosing recommendations.

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    - Terlivaz should be administered through a peripheral or central line. A dedicated central line is not required.

- Mallinckrodt plans to launch Terlivaz in the coming weeks. Terlivaz will be available as a 0.85 mg (1 vial) lyophilized powder in a single-dose vial for reconstitution.