Zelnorm™ (tegaserod) – Market re-introduction, updated indication

- On April 1, 2019, US WorldMeds announced the FDA approval of Zelnorm (tegaserod), for the treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation (IBS-C).
    - The safety and effectiveness of Zelnorm in men with IBS-C have not been established.
- Zelnorm was originally approved on July 24, 2002, for the short-term treatment of women with IBS-C. However, in 2007, Zelnorm was withdrawn from the U.S. market due to an imbalance in cardiovascular adverse events occurring with Zelnorm that had not been previously identified.
    - Zelnorm has remained available in the U.S. through an expanded access program.
- The approval to reintroduce Zelnorm comes after a complete safety review by the FDA and an FDA-assembled Gastrointestinal Drugs Advisory Committee (GIDAC). A positive GIDAC vote and FDA review both supported the reintroduction of Zelnorm for appropriate IBS-C patients.
- Zelnorm was also previously approved for the treatment of patients less than 65 years of age with chronic idiopathic constipation (CIC). This indication has been removed.
- Zelnorm is an agonist of serotonin type-4 (5-HT_4) receptors that stimulates the peristaltic reflex and intestinal secretion, inhibits visceral sensitivity, enhances basal motor activity, and normalizes impaired motility throughout the gastrointestinal tract.
- No new efficacy studies were added in support of the indication to the prescribing information; however, approval to reintroduce Zelnorm comes after a complete safety review by the FDA and an FDA-assembled Gastrointestinal Drugs Advisory Committee (GIDAC). The review focused on a retrospective analysis of the pooled clinical trial database data (involving 18,645 patients) of 29 placebo-controlled trials of IBS-C and other gastrointestinal motility disorders of at least four weeks duration.
    - An external adjudication of the reported cardiovascular ischemic (CVI) events identified an imbalance in patients taking Zelnorm (13 events, 0.1%) vs. placebo (1 event, 0.01%).
    - A second external adjudication was conducted with additional patient-level information, and used a comprehensive pre-specified methodology regarding both case selection and assessment. This adjudication confirmed seven CVI events (0.06%) in patients taking Zelnorm vs. one event (0.01%) in placebo-treated patients.
    - An imbalance in MACE events (defined as cardiovascular death, non-fatal MI, non-fatal stroke) was observed in patients taking Zelnorm vs. placebo, as reported in both external adjudications. The rate of MACE events for Zelnorm-treated patients ranged from 0.03% to 0.06% in the overall population and 0.01% to 0.03% in the female population less than 65 years of age without a history of CVI disease vs. zero in the placebo-treated group.
- Zelnorm is contraindicated in patients with a history of a history of myocardial infarction, stroke, transient ischemic attack, or angina; a history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment (eGFR < 15 mL/min/1.73 m^2) or end-stage renal disease; moderate and severe hepatic impairment (Child-Pugh B or C); a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions; and hypersensitivity to tegaserod.

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- In addition, the *Warnings and Precautions* section of the labeling was updated to include cardiovascular ischemic events (including MACE) and suicidal ideation and behavior.
- Other warnings and precautions include ischemic colitis and volume depletion associated with diarrhea.
- The most common adverse reactions (> 2%) with Zelnorm use were headache, abdominal pain, nausea, diarrhea, flatulence, dyspepsia, and dizziness.
- The recommended dosage of Zelnorm in adult women less than 65 years of age is 6 mg taken twice daily orally at least 30 minutes before meals. Zelnorm should be discontinued in patients who have not had adequate control of symptoms after 4 to 6 weeks of treatment.
- US WorldMeds' plans for reintroduction of Zelnorm are pending. Zelnorm will be available as a 6 mg tablet.