

Relugolix/Estradiol/Norethisterone (Norethindrone) Acetate: A Review in Symptomatic Uterine Fibroids

Uterine fibroids are common noncancerous tumors of the uterus. They are presumed to occur in over 70% of women of reproductive age. Uterine fibroids are usually asymptomatic or cause only mild symptoms.

However, one in four women with uterine fibroids requires treatment due to severe symptoms.

Hysterectomy is the definitive treatment, but it's invasive and prevents future childbearing. Less invasive procedures are available, but they do carry some safety and tolerability issues.

Drug treatments for uterine fibroids seek to optimize the levels of ovarian steroid hormones, especially those of estradiol, to alleviate symptoms.

A recently approved oral fixed-dose combination treatment, relugolix combination therapy, does this by combining relugolix, an antagonist of gonadotropin-releasing hormone, with estradiol and the synthetic progesterone norethisterone acetate in one pill.

Relugolix combination therapy is the only once-daily oral drug approved for symptomatic uterine fibroids. Once it's identified as an appropriate treatment, a relugolix combination tablet can be taken once daily beginning shortly after menses onset. It can be used for up to 24 months in the USA and until menopause in the EU.

Relugolix prevents the pituitary gland from releasing luteinizing hormone and follicle-stimulating hormone. This, in turn, decreases serum estradiol and progesterone to postmenopausal levels. The low estrogen levels, while effective in reducing uterine fibroid symptoms, could have adverse effects like bone mineral density loss.

The addition of low-dose estradiol in relugolix combination therapy helps negate these effects. And the norethisterone acetate protects the uterus from the potential negative effects of unopposed estrogen.

Clinical trials have shown that relugolix combination therapy is effective in reducing the heavy menstrual bleeding associated with uterine fibroids in premenopausal women. In two replicate trials, eligible patients received relugolix combination therapy, delayed relugolix combination therapy, or placebo for 24 weeks.

Almost three quarters of the relugolix combination therapy recipients showed a menstrual bleeding response, defined as menstrual blood loss of less than 80 milliliters and a reduction of 50% or more from baseline over the last 35 days of the treatment period.

In both clinical trials, the drug also significantly improved 6 of 7 key secondary endpoints versus placebo.

In a 28-week extension of the trials, approximately 88% of the patients still taking relugolix combination therapy and approximately 76% of those who switched from placebo achieved the menstrual bleeding response. The responders were then enrolled in a randomized withdrawal study that continued for up to 52 weeks.

Compared to those who were randomized to placebo, more of those who were randomized to relugolix combination therapy maintained the target reduction in menstrual blood loss at week 76. Similar results were seen for the proportion of patients who achieved or maintained amenorrhea.

In the LIBERTY 1 and 2 trials, relugolix combination therapy was generally well tolerated. The most common adverse reactions were vasomotor symptoms such as hot flush, hyperhidrosis, or night sweats; abnormal uterine bleeding; alopecia, and decreased or loss of libido.

Relugolix combination therapy did not induce clinically meaningful bone mineral density loss. No new safety signals were detected in the extension or randomized withdrawal study.

Overall, the data indicate that relugolix combination therapy is an effective, well-tolerated oral treatment for symptomatic uterine fibroids in



premenopausal women. With its convenient once-daily administration, it is a useful addition to the current drug treatment options for this indication.