DRUG UPDATE

Linzagolix

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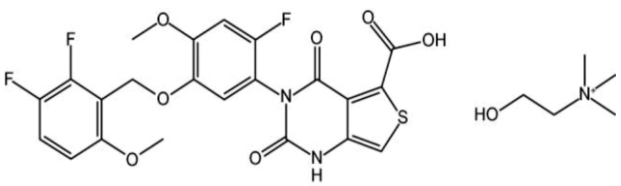
Linzagolix has been recently approved for the management of moderate-to-severe symptoms associated with leiomyomas (in the reproductive age group females) in the European Union (EU), whereas it is under regulatory review status in the United States of America (USA). Linzagolix is awaiting its entry in the Indian markets.

In the reproductive age group females, there are Oestrogen-related disorders like fibroids (uterine leiomyomas), endometriosis (endometrium-like tissue outside the uterine cavity) and adenomyosis (pathologically endometrial glands and stroma in uterine wall muscle).

Leiomyomas symptomatically present as- heavy menstrual bleeding (can result in anaemia), dysmenorrhea, pelvic pain, frequent urination, dyspareunia and it also increases risk for pregnancy complications, which are mainly managed surgically (mainly hysterectomy), Pharmacological management options available are like Gonadotropin releasing hormone (GnRH) agonists, Progestin-releasing IUD and Tranexamic acid. In recent studies, a promising alternative has emerged that is Linzagolix. It has been found to effectively improve symptoms with significant reduction in uterine volume.[1]

Chemical Name

3-{5-[(2,3-difluoro-6-methoxyphenyl)methoxyl]-2-fluoro-4-methoxyphenyl}-2,4-dioxo-1,2,3,4-tetrahydrothieno [3,4-d] pyrimidine-5-carboxylic acid



Linzagolix is a selective, non-peptide, orally active Gonadotropin releasing hormone (GnRH) antagonist, indicated for treatment of moderate-to-severe symptoms related with leiomyomas in reproductive age group females[2].

Preclinical data

In animal studies on ovariectomized cynomolgus monkey models reduction in serum LH levels at 8 hours was found which sustained for over 24 hours. Whereas, in intact female cynomolgus monkeys, dose -dependent partial or complete blockage of GnRHsignalling was seen, with resumption of normal menstrual cycles and hormonal secretion within one cycle on withdrawal[3].

Clinical trials data

In phase 1 trials, it was found that Linzagolix can be orally administered (taken with or without food) and gets rapidly absorbed. It is highly bound to plasma proteins, with a half-life of 15 hours. It is mainly excreted in urine, then in faeces, majorly unchanged[3].

Linzagolix in phase 2 and phase 3 trials effectively reduced pain and other symptoms and uterine and fibroid size as a selective GnRH receptor antagonist, blocking the hypothalamic pituitary-gonadal axis, resulting in dose dependent reduction in serum levels of luteinising hormone (LH), follicle-stimulating hormone (FSH) and estradiol. The GnRH receptors are coupled with Gaq/11 which on activation increases intracellular Ca^{2+} flux, Linzagolix dose-dependently inhibits GnRH-stimulated Ca^{2+} flux.

Linzagolix improved dysmenorrhea and non-menstrual pelvic pain in the randomised, double-blind, placebo-controlled phase 3 conducted in Europe and the USA in women with moderate-to-severe endometriosis-associated pain[3].

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Treatment with high-dose linzagolix 200 mg once daily for 12 weeks followed by a 100 mg/day maintenance dosage for a further 12 weeks significantly reduced uterine volume and adenomyosis-related symptoms, including pelvic pain and dysmenorrhea, in an exploratory phase 2 trial in 8 premenopausal women with symptomatic uterine adenomyosis[3] .

In clinical studies, the most common adverse events associated with Linzagolix were hot flushes and headache, more commonly at higher doses. These events were less frequent with Linzagolix with add-back therapy.

In phase 3 trials, less than 6 month use of Linzagolix 200 mg daily, reduction in size of leiomyomas was found, which may increase in size on cessation of drug. It should not be given more than 6 months due to risk of reduction of Bone Mineral Density on long term use[3].

In phase 3 trials, high lipid levels (LDL cholesterol, HDL cholesterol and triglycerides) were seen, which generally were higher in Linzagolix without add-back therapy (ABR). These levels reduced after the treatment but had not reached the baseline levels[3].

It should be given cautiously to patient with a history of depression and/or suicidal ideation as mood disorders like emotional lability, alteration in mood and depression are seen with use of GnRH antagonists including Linzagolix[3].

Relatively contraindicated for patients with moderate or severe kidney impairment or with end stage kidney disease and patients with severe hepatic impairment, as in these conditions unbound Linzagolix mean exposure is found increased[3].

Contraindicated in pregnancy or breastfeeding and patients with osteoporosis or genital bleeding of unknown aetiology.

Current status

Oral contraceptives and progestogens were effective in almost two-third females suffering from symptomatic leiomyomas. It is clinically known that oestrogen plays an important role in pathogenesis, oral GnRH antagonists may prove effective, especially in non-respondents to progestogens[4].

Linzagolix is approved for treatment of moderate-to-severe symptoms of leiomyomas in reproductive females in EU (17 June 2022) and in USA under regulatory review and under phase 3 clinical development for management of pain associated with endometriosis[3].

REFERENCES

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