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

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Abstract
An oral fixed-dose combination of relugolix/estradiol/norethisterone (also known as norethindrone) acetate (Ryeqo®; Myfembree®) has been approved for the management of heavy menstrual bleeding associated with uterine fibroids in the USA and management of moderate to severe symptoms of uterine fibroids in the EU. Relugolix is a gonadotropin releasing hormone (GnRH) receptor antagonist that decreases serum estradiol and progesterone concentrations to postmenopausal levels. The addition of estradiol/norethisterone acetate to relugolix ameliorates relugolix-induced bone loss and hot flush. In the two phase 3 LIBERTY trials, relugolix + estradiol/norethisterone substantially decreased menstrual bleeding and improved a range of other uterine fibroid symptoms in women with uterine fibroids-associated heavy menstrual bleeding. The combination was generally well tolerated, with vasomotor symptoms being the most common adverse reaction. Treatment with this combination for over up to 2 years did not induce a clinically meaningful bone loss in the majority of women. Relugolix/estradiol/norethisterone acetate, with its convenient once-daily administration, is a useful addition to current pharmacological treatment options for premenopausal women with symptomatic uterine fibroids.

Plain Language Summary
Uterine fibroids are a common type of noncancerous tumours that grow in the uterus. In some women, these tumours cause debilitating symptoms, such as heavy menstrual bleeding, pelvic pain and passing of blood clots. Hysterectomy is the only definitive treatment for this condition, but is associated with some disadvantages. Less invasive procedures and medical treatments are now available to treat these symptoms. Recently, a fixed-dose tablet comprising relugolix, estradiol and norethisterone acetate (Ryeqo®; Myfembree®) has been approved to treat symptoms of uterine fibroids. This combination works by suppressing ovarian hormone levels. In clinical trials, relugolix + estradiol/norethisterone substantially reduced menstrual bleeding and improved several other symptoms in women with uterine fibroids-associated heavy menstrual bleeding. The combination was generally well tolerated and had a minimal impact on bone loss, a known adverse effect of such therapies. With its convenient once-daily administration, relugolix/estradiol/norethisterone acetate is a useful addition to current medical treatment options for premenopausal women with symptomatic uterine fibroids.
1 Introduction

Uterine fibroids (also known as leiomyomas or myomas) are benign, clonal, smooth muscle tumours of the uterus, arising primarily in three anatomical locations (submucosal, intramural and subserosal) [1]. These tumours are driven by ovarian steroids, oestrogen and progesterone, and are the most common reproductive tract tumours in women of reproductive age [1, 2]. Uterine fibroids are presumed to occur in over 70% of women of reproductive age [1, 3]. While they cause no symptoms in most cases, ≈ 25% of women with these tumours develop symptoms severe enough to require treatment [1, 3]. Uterine fibroids symptoms can be classified into one of three categories: abnormal uterine bleeding, pelvic pressure and pain (bulk symptoms) and reproductive dysfunction [4], all of which negatively impact health-related quality of life [5]. Heavy menstrual bleeding (HMB), the cardinal symptom of uterine fibroids, can lead to life-threatening anaemia and is a major source of social embarrassment [1, 5].

Hysterectomy is the only definitive treatment for uterine fibroids-associated HMB, but is associated with the loss of future childbearing, increased risk of complications, late morbidities and potential loss of ovarian function (when oophorectomy is also involved) [1, 6]. For patients who wish to preserve the uterus and fertility, several less invasive procedures are available, including myomectomy (robotic, hysteroscopic, laparoscopic or abdominal), endometrial ablation, uterine artery embolization and MRI-guided focused ultrasound (MRgFUS). These procedures are not without safety and tolerability issues, and some (uterine artery embolization, MRgFUS) require specialised expertise to perform [1, 6].

Given that oestrogen and progesterone are the key drivers of uterine fibroids, optimising levels of these steroids (particularly estradiol) lies at the root of pharmacotherapy for managing symptomatic uterine fibroids [1]. Until recently, approved treatments included selective progesterone receptor modulators (e.g. ulipristal acetate) and gonadotropin releasing hormone (GnRH) receptor agonists (e.g. leuprolerin) [6, 7]. In addition, a plethora of unapproved options are available, including oral contraceptives, levonorgestrel intrauterine device, androgenic steroids, aromatase inhibitors, antifibrinolytics and nonsteroidal anti-inflammatories [6, 7]. Sustained low levels of ovarian hormones, while effectively reduce the symptoms of uterine fibroids, have harmful consequences, such as loss of bone mineral density (BMD) and hot flush [8]. A pharmacotherapy for symptomatic uterine fibroids that can be used for long term without these consequences is an unmet medical need [5, 7].

GnRH receptor antagonists (e.g. elagolix and relugolix) have similar benefits to GnRH receptor agonists, with additional advantages of rapid onset of action and no flare effect [1]. BMD loss and hot flush induced by these agents can be ameliorated by adding back low levels of oestrogen and progesterin (‘add-back therapy’) [9, 10]. An oral fixed-dose combination (FDC) of relugolix/estradiol/norethisterone (also known as norethindrone) acetate 40/1/0.5 mg [Ryeqo® (EU); Myfembree® (USA)] has been approved for use in women with symptomatic uterine fibroids [11, 12]. This article reviews the clinical efficacy and tolerability of this FDC for the management of symptomatic uterine fibroids, with a brief overview of its pharmacological properties.

2 Pharmacodynamic Properties

Relugolix is a nonpeptide GnRH receptor antagonist that competitively binds to, and blocks, GnRH receptors in the anterior pituitary gland [13]. This action prevents the release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), resulting in decreased serum estradiol and progesterone concentrations to postmenopausal levels [13, 14]. Low levels of ovarian hormones prevent hormone-dependent proliferative effects on endometrium, resulting in reduced uterine fibroids-associated HMB. Estradiol is an oestrogen that may reduce the risk of bone loss and hot flush associated with relugolix; norethisterone is a progestin which may protect the uterus from the effect of unopposed oestrogen [15, 16].

In vitro, relugolix binds to human GnRH receptors with high affinity [half maximal inhibitory concentration (IC₅₀) 0.12 nmol/L] and specificity, and inhibits GnRH-induced [³H] arachidonic acid release in a dose-dependent manner; in vivo, relugolix suppressed the hypothalamic-pituitary-gonadal axis in female human GnRH receptor knock-in mice [14].

In two phase 1 trials in healthy adult premenopausal women, relugolix dose-dependently reduced serum levels of LH, FSH, estradiol and progesterone, with no effect on levels of endogenous growth hormone, prolactin, thyrotropin and adrenocorticotropic hormone [7]. Near maximal reductions in estradiol were seen with relugolix 40 mg [7]. In a dose-finding phase 2 trial, relugolix 10, 20 and 40 mg once daily dose-dependently reduced uterine fibroids-associated HMB [17]. In a phase 3 trial, relugolix 40 mg once daily was noninferior to leuprorelin acetate 1.88 or 3.75 mg injections once every 4 weeks for improvement in uterine fibroids associated HMB [18]. Relugolix also improved uterine fibroid-associated pain in a placebo-controlled, phase 3 trial [19].

In a phase 1 trial in healthy premenopausal women, relugolix 40 mg coadministered with estradiol/norethisterone...
acetate 1/0.5 mg [hereafter referred to as relugolix combination therapy (CT)] once daily resulted in estradiol plasma concentrations that mitigated the hypoestrogenic effects (BMD loss and hot flush) associated with relugolix alone [20]. In another phase 1 trial in healthy premenopausal women, relugolix CT once daily for 84 days inhibited ovulation in all subjects [21].

### 3 Pharmacokinetic Properties

In healthy postmenopausal women taking a single relugolix/estradiol/norethisterone acetate 40/1/0.5 mg oral FDC tablet under fasted conditions, time to maximum plasma drug concentration ($C_{max}$) was 2.00, 7.00 and 1.0 h for relugolix, unconjugated estradiol and norethisterone, respectively [7, 11]. After reaching $C_{max}$, relugolix concentrations declined rapidly in the first 6–16 h postdose, followed by a slower decline between 12–24 h; the majority of the total exposure to relugolix occurred within the first 24 h. Following once-daily administration of the oral FDC tablet, relugolix concentrations reached steady state within 12 days, with an accumulation of $\approx$ 2-fold, and estradiol and norethisterone concentrations reached steady state within 14 days, with an accumulation of 33–47%. The mean terminal half-life of relugolix, estradiol and norethisterone was 10.9 h, respectively. Food did not have a clinically meaningful effect on the exposure to any of the drug components. Pharmacokinetic bioequivalence between the relugolix CT and the relugolix/estradiol/norethisterone acetate 40/1/0.5 mg FDC tablet has been established in healthy postmenopausal women [7, 11].

The absolute bioavailability of relugolix is 11.6% [7, 11]. In humans, 68–71% of relugolix is bound to plasma protein, mainly to albumin and to a lesser extent to α1-acid glycoprotein, with a mean blood-to-plasma ratio of 0.78. In vitro, relugolix is metabolized mainly by CYP3A and to a lesser extent by CYP2C8. Following oral administration of a single dose of radiolabelled relugolix 80 mg, $\approx$ 81% of the radioactivity was recovered in faeces (4.2% as unchanged) and 4.1% in urine (2.2% as unchanged) [7, 11]. Estradiol and norethisterone are bound to sex hormone binding globulin (36–37%) and to albumin (61%) [7, 11]. Estradiol is reversibly dehydrogenated by 17β-hydroxysteroid dehydrogenase into estrone, and both estradiol and estrone can be converted to estriol, a major urinary metabolite. Estradiol also undergoes hepatic recirculation via sulfation and glucuronidation, as well as oxidative metabolism by CYP enzymes (such as CYP3A4). Estradiol is excreted in the urine as glucuronide and sulfate conjugates. After oral administration, norethisterone acetate is hydrolysed in the intestine and liver to norethisterone, which is primarily metabolized by steroid reductases to other active metabolites. Norethisterone also undergoes biotransformation via sulfation, glucuronidation and oxidation by CYP enzymes (such as CYP3A4), and is primarily excreted in the urine as various polar metabolites [7, 11].

Relugolix pharmacokinetics are not affected to a clinically significant extent by age (19–53 years), race/ethnicity (Asian, White, Black/African American), bodyweight (38–144 kg), mild to severe kidney function impairment (creatinine clearance 15–89 mL/min) and mild or moderate liver function impairment (Child-Pugh A or B) [11]. The effects of kidney failure with or without haemodialysis on the relugolix pharmacokinetics have not been assessed. The effects of kidney or liver function impairment on the pharmacokinetics of estradiol or norethisterone have not been studied, although estradiol blood concentrations are expected to be increased in patients with liver function impairment compared to patients with normal liver function [11].

Avoid coadministration of relugolix/estradiol/norethisterone acetate with P-glycoprotein inhibitors (which may increase the exposure to relugolix and therefore, increase the risk of adverse reactions) or with combined P-glycoprotein and strong CYP3A inducers (which may decrease the exposure to relugolix, estradiol and norethisterone acetate and therefore, decrease the therapeutic effect) [11, 12]. If coadministration with P-glycoprotein inhibitors is unavoidable, take relugolix/estradiol/norethisterone acetate first, with P-glycoprotein inhibitor dosing separated by ≥ 6 h [11, 12].

### 4 Therapeutic Efficacy

#### 4.1 LIBERTY Trials

The efficacy of relugolix CT in women with uterine fibroids-associated HMB was evaluated in two replicate randomized, double-blind, placebo-controlled, multinational, phase 3 studies (LIBERTY 1 and LIBERTY 2; Fig. 1) [9]. These trials enrolled premenopausal women aged 18–50 years with a diagnosis of uterine fibroids confirmed by transvaginal ultrasound. At least one uterine fibroid had to be verified by a central reader to meet at least one of the following criteria: subserosal, intramural or < 50% intracavitary submucosal fibroid with a diameter ≥ 2 cm; or, multiple small fibroids with a total uterine volume ≥ 130 cm³. Patients had to have HMB, defined as a menstrual blood loss (MBL) volume of ≥ 80 mL per cycle for two cycles or ≥ 160 mL during one cycle, assessed by alkaline haematin method. Exclusion criteria included: baseline z score less than − 2.0 for BMD at the lumbar spine, total hip or femoral neck; HMB due to causes other than uterine fibroids; medical procedures to treat uterine fibroids in the previous 6 months; haemoglobin levels < 8 g/dL; or, rapidly enlarging uterine fibroids in the investigator’s opinion [9].
Stratified by baseline MBL volume (< 225 vs ≥ 225 mL) and geographic region (North America vs rest of world), patients were randomized to relugolix CT, delayed relugolix CT (relugolix 40 mg monotherapy for 12 weeks, followed by relugolix CT for 12 weeks) or placebo once daily for 24 weeks [9]. The primary endpoint was the proportion of patients with a menstrual bleeding response, defined as MBL volume < 80 mL and a ≥ 50% reduction from baseline over the last 35 days of the treatment period. Seven key secondary endpoints (amenorrhea, MBL volume, distress from bleeding and pelvic discomfort, anaemia, pain, uterine fibroid volume and uterine volume) were also assessed. Distress from bleeding and pelvic discomfort, and pain were assessed using patient-reported Bleeding and Pelvic Discomfort Scale (BPDS) [range 0–100; higher the score greater the symptom severity] and numerical rating scale (NRS) [0 = no pain; 10 = worst imaginable pain] scores, respectively. The primary and the key secondary endpoints were compared between the relugolix CT and placebo groups in the modified intention-to-treat population, following a statistical hierarchy. The delayed relugolix CT group was included to compare BMD and hot flush between the relugolix CT and relugolix monotherapy groups during the first 12 weeks of the trial [9].

Demographics and clinical characteristics at baseline were well balanced between the treatment groups within each trial [9]. Across both trials, at baseline, 51% of patients were Black, 43% were White, mean patient age was 41.3–42.5 years, mean body mass index was 30.8–32.3, mean MBL volume was 211.8–246.7 mL, 33–37% of patients had a MBL volume ≥ 225 mL, mean haemoglobin level was 11.1–11.4 g/dL, mean uterine fibroid volume was 71.8–93.8 cm³, mean uterine volume was 379.1–469.9 cm³, mean BPDS score was 66.8–72.0 and 84–95% of patients had maximum NRS score ≥ 4 [9].

In both LIBERTY 1 and LIBERTY 2, more than two-thirds of patients were responders to relugolix CT over the last 35 days of the treatment period [9]. The proportion of women achieving a menstrual bleeding response was significantly higher in the relugolix CT than in the placebo group (Table 1; primary endpoint). The observed treatment effect for the primary endpoint appeared to be consistent across the stratification factors and other baseline characteristics, such as age, race, ethnicity, uterine volume and body mass index (odds ratio for relugolix CT vs placebo > 10 in most subgroups) [9].

Relugolix CT was associated with significant improvement relative to placebo for six of seven key secondary endpoints in both trials (Table 1) [9]. In the relugolix CT group, amenorrhea occurred in ≥ 50% of women and MBL volume decreased from baseline by ≈ 84%, with a substantial reduction (> 60%) in MBL seen as early as week 4. Among relugolix CT recipients who had anaemia at baseline, haemoglobin levels increased by > 2 g/dL in > 50% of women. Relugolix CT also decreased distress from bleeding and pelvic discomfort, pain, and uterine volume. Reductions in the primary uterine fibroid volume did not differ significantly between the relugolix CT and placebo groups [9].

Among other secondary endpoints, more relugolix CT than placebo recipients reported a clinically meaningful reduction in distress from bleeding and pelvic discomfort, which was defined a reduction of ≥ 20 points from baseline.
Table 1  Efficacy of relugolix 40 mg coadministered with estradiol/norethisterone acetate 1/0.5 mg in women with fibroid-associated heavy menstrual bleeding in phase 3 clinical trials [9]

| Endpoints                              | LIBERTY 1 | LIBERTY 2 |
|----------------------------------------|-----------|-----------|
|                                        | PL (n = 127) | RCT (n = 128) | DRCT (n = 127) | PL (n = 129) | RCT (n = 125) | DRCT (n = 127) |
| Menstrual bleeding response (%) pts    | 19        | 73***     | 80          | 15          | 71***        | 73          |
| Key secondary endpoints (%) pts        |           |           |             |             |             |             |
| Amenorrhea (%)                        | 6         | 52***     | 58          | 3           | 50***        | 50          |
| Menstrual blood loss volume (Δ %)      | –23.2     | –84.3***  | –88.2       | –15.1       | –84.3***     | –89.4       |
| BPDS score (Δ)                        | –16.1     | –45.0***  | –51.3       | –18.3       | –51.7***     | –48.9       |
| Anaemia improved (%) pts [n]          | 22 [23]   | 50 [30]*  | 56 [32]     | 5 [37]      | 61 [31]***   | 58 [31]     |
| Maximum NRS score ≤ 1Δ (%) pts [n]    | 10 [69]   | 43 [58]***| 42 [65]     | 17 [82]     | 47 [68]***   | 41 [58]     |
| Primary uterine fibroid volume (Δ %)  | –0.3      | –12.4     | –22.7       | –7.4        | –17.4        | –30.2       |
| Uterine volume (Δ %)                  | 2.2       | –12.9***  | –17.9       | –1.5        | –13.8**      | –17.7       |

See main text for randomized treatment details

Δ change from baseline at week 24, BPDS Bleeding and Pelvic Discomfort scale, DRCT delayed relugolix combination therapy, NRS numerical rating scale, PL placebo, RCT relugolix combination therapy

*p ≤ 0.05, **p = 0.008, ***p ≤ 0.001 versus placebo

aStatistical comparisons were conducted for RCT versus PL; DRCT group was included to compare different endpoints (see main text for details)

bPrimary endpoint; defined as menstrual blood loss volume < 80 mL and a ≥ 50% reduction from baseline over the last 35 days of the treatment period, as measured by alkaline haematin method

cTested if the primary end point was significant (p < 0.05 vs PL) in the following hierarchical order: first four endpoints in LIBERTY 1, and 1st, 2nd, 3rd and 5th endpoints in LIBERTY 2, followed by other endpoints using Hochberg step-up procedure

dOver the last 35 days of treatment period; for NRS score, data are for pain evaluation subgroup

eHaemoglobin levels ≤ 10.5 g/dL at baseline and an increase of > 2 g/dL at week 24

in BPDS score at week 24 (61.7% vs 27.6% in LIBERTY 1; 63.2% vs 28.7% in LIBERTY 2) [9].

4.2 LIBERTY Extension

Patients who completed the 24-week LIBERTY trials were enrolled in a long-term extension study (Fig. 1) [7, 22]. A total of 477 patients (n = 163, 150 and 164 from the relugolix CT, delayed relugolix CT and placebo groups, respectively) were enrolled and all patients received open-label relugolix CT for 28 weeks (total treatment period 52 weeks from randomization). Treatment benefits were sustained through week 52 in the relugolix CT and delayed relugolix CT groups. At 52 weeks, 87.7% of patients in the relugolix CT group achieved a bleeding response (i.e. MBL volume < 80 mL and a ≥ 50% reduction from baseline over the last 35 days of the treatment period); similar proportion of patients met the criteria for the individual primary endpoint component. Responder rates in subgroups based on baseline characteristics (geographical region, MBL volume at baseline, race, uterine volume, body mass index) were consistent with that in the overall population [7, 22]. In the relugolix CT group, 19% of women were European and the response rate was 100% in this subgroup [23]. At 52 weeks, 70.6% of patients in the relugolix CT group achieved amenorrhea over the last 35 days of treatment. MBL volume was reduced by 89.8% from baseline, and 23 of 39 (59%) patients with anaemia at baseline achieved a > 2 g/dL increase in haemoglobin levels [7].

Patients who received placebo in the parent trials experienced substantial treatment benefits after transitioning to relugolix CT [7]. At week 52, the responder rate was 75.6%, MBL was reduced by 91.9% from baseline, 57.9% of patients achieved amenorrhea over the last 35 days of treatment and 16 of 38 (42.1%) patients with anaemia at baseline achieved a > 2 g/dL increase in haemoglobin levels [7].

In the extension study, relugolix CT was associated with sustained improvements in symptom severity and uterine fibroid-related quality of life (assessed by the Uterine Fibroid Symptom & Health-Related Quality of Life Questionnaire) and HMB-related quality of life (assessed by Menorrhagia Impact Questionnaire) [7].

4.3 Randomized Withdrawal Study

Patients who met the responder criteria in the LIBERTY extension study (MBL volume < 80 mL and a ≥ 50% reduction from the parent study baseline at week 48) were randomized to relugolix CT (n = 115) or placebo (n = 114) once daily for up to 52 weeks, providing efficacy data for a total treatment period of 104 weeks (Fig. 1) [24]. Patients who had a relapse (MBL volume ≥ 80 mL) during the study received open-label relugolix CT. A significantly greater proportion of relugolix CT than placebo recipients maintained MBL volume < 80 mL at week 76 (78.4% vs 15.1%; primary endpoint). Similar results were seen for the proportion of patients who achieved or maintained amenorrhea [24].
5 Safety and Tolerability

Relugolix CT was generally well tolerated in women with uterine fibroids-associated HMB in the LIBERTY 1 and 2 trials [9, 11]. In both trials combined, 3.9% of 254 relugolix CT recipients and 4.3% of 256 placebo recipients discontinued treatment because of adverse events during the 24-week double-blind treatment [9]. The most common adverse reaction leading to discontinuation of relugolix CT was uterine bleeding (1.2%), which typically occurred within the first 3 months of treatment. Serious adverse reactions occurred in 3.1% and 2.3% of patients in the respective groups [9]. Serious adverse reactions with relugolix CT included uterine myoma expulsion and menorrhagia, uterine prolapse, cholecystitis and pelvic pain, each occurring in one patient. The most common adverse reactions (incidence ≥ 3% in the relugolix CT group and greater than that in the placebo group) included hot flush, hyperhidrosis or night sweats (10.6% vs 6.6%), abnormal uterine bleeding (6.3% vs 1.2%), alopecia (3.5% vs 0.8%) and decreased or loss of libido (3.1% vs 0.4%). In LIBERTY 1, adverse reaction of new or worsening hypertension occurred in 7.0% of relugolix CT recipients and 0.8% of placebo recipients. The less common adverse reactions with relugolix CT included irritability, dyspepsia and breast cyst [11]. No new safety signals were detected in the LIBERTY extension or in the randomized withdrawal study [7]. There were no cases of endometrial hyperplasia or endometrial cancer among patients treated with relugolix CT for up to 52 weeks [7].

5.1 Bone Mineral Density

The addition of estradiol/norethisterone acetate mitigated relugolix-induced BMD loss, as assessed by dual-energy X-ray absorptiometry [9]. For instance, in LIBERTY 1, relugolix monotherapy for 12 weeks induced a greater BMD loss from baseline than relugolix CT; least squares mean (LSM) change was −2.00% versus −0.47% at the lumbar spine and −0.95% versus −0.01% in total hip. The BMD loss with relugolix monotherapy reached a plateau and remained stable thereafter. After initiation of relugolix CT from week 12 onwards [9], relugolix CT did not induce a clinically meaningful BMD loss (defined as −2.2%) in women with uterine fibroids-associated HMB [12, 25, 26]. In LIBERTY 1 and 2 combined, LSM change from baseline in lumbar spine BMD at 24 weeks was −0.229% (95% CI −0.693 to 0.236) with relugolix CT and +0.241% (95% CI −0.243 to 0.716) with placebo [12]. In the LIBERTY extension, LSM change from baseline in lumbar spine BMD at week 52 was −0.804% (95% CI −1.358 to −0.250) in patients who continued relugolix CT (n = 132) and −0.775% (95% CI −1.325 to −0.226) in those who switched from placebo to relugolix CT (n = 120). In 32 patients who received relugolix CT for 104 weeks (in the LIBERTY trials, 52-week LIBERTY extension and the randomized withdrawal study), LSM change from baseline in BMD was 0.04% [12]. Low-trauma fractures were rare (0.6% of 634) in relugolix CT recipients in the LIBERTY trials and their extension [11].

In a separate prospective observational study, 262 untreated women with uterine fibroids age matched to LIBERTY trial participants were enrolled [11, 27]. In this cohort, LSM change from baseline in lumbar spine BMD was 0% at month 6 and −0.41% at month 12 [11]. At 12 months, a decline in lumbar spine BMD of > 3% was seen in 23% of women in the LIBERTY extension study and 17.4% of those in the observational study; a decline of > 8% was seen in 1% and 0.9% of women in the respective studies [11].

6 Dosage and Administration

Relugolix/estradiol/norethisterone acetate 40/1/0.5 mg FDC oral tablet is indicated for the treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age in the EU [12] and for the management of uterine fibroids-associated HMB in premenopausal women in the USA [11]. The recommended dosage is one tablet once daily at approximately the same time, with or without food [11, 12]. In the EU, relugolix/estradiol/norethisterone acetate should be started within 5 days of the onset of menses and can be continued without interruption until menopause, at which time treatment discontinuation should be considered [12]. In the USA, relugolix/estradiol/norethisterone acetate should be started as early as possible, and no later than 7 days, after the onset of menses and the recommended total duration of treatment is 24 months [11].

Contraindications to relugolix/estradiol/norethisterone acetate use include a high risk of thrombotic or thromboembolic disorders, pregnancy, osteoporosis, liver function impairment or liver disease (USA), severe liver function impairment (EU), hormone-sensitive malignancies and undiagnosed abnormal uterine bleeding [11, 12]. Concomitant use of hormonal contraceptives with relugolix/estradiol/norethisterone acetate is contraindicated in the EU [12] and should be avoided in the USA [11]. The US prescribing information for relugolix/estradiol/norethisterone acetate carries a boxed warning of the risk of thrombotic or thromboembolic disorders [11]. Local prescribing information should be consulted for detailed information, including contraindications, special warnings, precautions, drug interactions and use in special patient populations.

7 Place of Relugolix/Estradiol/ Norethisterone Acetate in the Medical Management of Uterine Fibroids

In the USA, two GnRH receptor antagonists plus add-back therapy FDCs are specifically approved for the management of uterine fibroids-associated HMB in premenopausal women: elagolix/
stradiol/norethisterone acetate [28] and relugolix/estradiol/norethisterone acetate [11], both recommended for a duration of 24 months. Relugolix/estradiol/norethisterone acetate is also approved in the EU for a broader indication (treatment of moderate to severe uterine fibroid symptoms in adult women of reproductive age) and it can be taken without interruption until menopause, at which time discontinuation should be considered [12]. In addition, ulipristal acetate is indicated in the EU for the intermittent treatment of moderate to severe uterine fibroid symptoms; however, because of concerns for serious liver injury, its use is restricted to women who are not eligible for surgical treatment options [29]. GnRH agonists are available in both the EU and USA for short-term (3 months) preoperative hematologic improvement in women with anemia caused by uterine fibroids [6, 7].

Relugolix reduces uterine fibroids-associated HMB by decreasing serum levels of estradiol and progesterone (Sect. 2). Following a 40 mg oral dose, exposure to relugolix remained maximal in the first 24 h, making a once-daily regimen possible (Sect. 3). In the two well-designed, replicate, phase 3 LIBERTY trials, relugolix CT substantially reduced menstrual bleeding in women with uterine fibroids-associated HMB (Sect. 4.1). The treatment also led to amenorrhea in the majority of patients, reduced MBL volume, improved distress from bleeding and pelvic discomfort, improved anaemia, decreased fibroid-related pain and reduced uterine, but not fibroid, volume (Sect. 4.1). In a small exit interview substudy of the LIBERTY trials, the most commonly reported symptoms were HMB, pelvic pain and passing of blood clots [30], highlighting the impact of relugolix/estradiol/norethisterone acetate in reducing the burden of uterine fibroids. The efficacy of this combination was sustained in the long term in an extension study (Sect. 4.2) and was confirmed in a randomized withdrawal study (Sect. 4.3). Relugolix CT was generally well tolerated, with the most common adverse reaction being hot flush, hyperhidrosis or night sweats (Sect. 5). Treatment with this combination for up to 2 years did not induce a clinically meaningful BMD loss in the majority of patients (Sect. 5.1).

A comparative effectiveness review conducted by the Agency for Healthcare Research and Quality in the USA in 2017 concluded that the current state of evidence base does not permit drawing definitive conclusions about the relative risks, benefits and costs of available treatment options for uterine fibroids [31]. This deficit is, perhaps, reflected in the low quality of national and international treatment guidelines for uterine fibroids, where there are several areas of disagreement and uncertainty, with very little consensus [32]. Accentuating this reality, current NICE guidelines for the medical treatment of HMB due to uterine fibroids in women of reproductive age includes several treatments that are not specifically approved for use in this population [33]. Relugolix/estradiol/norethisterone acetate (and elagolix/estradiol/norethisterone acetate) is yet to feature in uterine fibroid treatment guidelines.

Relugolix/estradiol/norethisterone acetate is administered once daily [11, 12], whereas elagolix/estradiol/norethisterone acetate requires two administrations: the FDC in the morning and only elagolix in the evening [28]. Randomized head-to-head comparison of these two FDCs would be useful in determining their relative roles in the treatment of symptomatic uterine fibroids. Further data on real-world experience, longer-term safety and cost effectiveness of relugolix/estradiol/norethisterone acetate would also be of interest.

In conclusion, relugolix/estradiol/norethisterone acetate is an effective and well tolerated oral treatment for symptomatic uterine fibroids. With its convenient oral once-daily administration, the FDC is a useful addition to current pharmacological treatment options for premenopausal women with symptomatic uterine fibroids.

### Data Selection Relugolix/Estradiol/Norethisterone Acetate: 136 Records Identified

| Duplicate records removed | 37 |
|---------------------------|----|
| Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial) | 36 |
| Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase II/III trials) | 30 |
| Cited efficacy/tolerability articles | 8 |
| Cited articles not efficacy/tolerability | 25 |

Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were relugolix, Orgovyx, RVT-601, Relumina, TAK-385, Ryeqo, Myfembree, uterine fibroids, uterine leiomyomas and menstrual bleeding. Records were limited to those in English language. Searches last updated 21 September 2022.
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