Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2442

relugolix 40mg, estradiol 1mg, norethisterone acetate 0.5mg film-coated tablets (Ryeqo®)

Gedeon Richter

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and, following review by the SMC Executive, advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission

relugolix, estradiol, norethisterone acetate tablets (Ryeqo®) is accepted for restricted use within NHSScotland.

Indication under review: treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

SMC restriction: for use in patients who have failed or are unsuitable for conventional therapies (first line treatments), such as tranexamic acid, hormonal contraceptives and intrauterine delivery systems.

Relugolix, estradiol, norethisterone acetate tablets (Ryeqo®), compared with placebo, significantly reduced menstrual blood loss volume in patients with uterine fibroids and heavy menstrual bleeding.

Chairman
Scottish Medicines Consortium

Indication

Treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.[1]

Dosing Information

One tablet of relugolix, estradiol and norethisterone acetate (relugolix combination therapy [CT]) taken once daily, at about the same time with or without food. Tablets should be taken with some liquid as needed. When starting treatment, the first tablet must be taken within 5 days of the onset of menstrual bleeding. If treatment is initiated on another day of the menstrual cycle, irregular and/or heavy bleeding may initially occur.

Pregnancy must be ruled out prior to initiating treatment. Any hormonal contraception needs to be stopped prior to initiation of treatment and non-hormonal methods of contraception must be used for at least 1 month after initiation of treatment. In patients with risk factors for osteoporosis or bone loss, a dual X-ray absorptiometry (DXA) is recommended prior to starting treatment. Discontinuation should be considered when the patient enters menopause, as uterine fibroids are known to regress when menopause begins. A DXA scan is recommended after one year of treatment.[1]

Product availability date

November 2021

Summary of evidence on comparative efficacy

Relugolix CT tablets contain the gonadotrophin releasing hormone (GnRH) antagonist, relugolix, the estrogen receptor agonist, estradiol, and the progestogen, norethisterone acetate. Relugolix inhibits GnRH receptors in the anterior pituitary gland, thereby decreasing release of luteinising hormone (LH) and follicle-stimulating hormone (FSH) from this gland. The reduction in FSH concentration prevents follicular growth, thereby reducing estrogen production. Prevention of a LH surge inhibits ovulation and development of the corpus luteum, which precludes production of progesterone. Estradiol alleviates symptoms associated with a hypoestrogenic state, such as vasomotor symptoms and bone mineral density loss. Norethisterone acetate reduces estrogen-induced risk of endometrial hyperplasia in non-hysterectomised patients.[1] Relugolix CT is used in the treatment of uterine fibroids, which are benign smooth muscle tumours in the uterus that are hormone-sensitive, requiring estrogen for growth. This growth is also influenced by other hormones such as progesterone and local growth factors.[2]

The company has requested that SMC considers relugolix CT when positioned for use in patients who have failed or are unsuitable for conventional therapies (first line treatments), such as tranexamic acid, hormonal contraceptives and intrauterine delivery systems.

Two double-blind phase III studies (LIBERTY-1 and -2) recruited pre-menopausal women (18 to 50 years) with uterine fibroids and regular heavy menstrual periods, defined as menstrual blood loss (MBL) ≥160mL during cycle 1 or ≥80mL per cycle for two cycles. Randomisation was stratified by region (North America or rest of the world) and screening MBL volume (<225mL or ≥225mL). Patients were equally assigned to relugolix CT one tablet daily for 24 weeks or placebo or 'delayed relugolix CT' comprising relugolix 40mg orally once daily for 12 weeks then relugolix CT one tablet daily for 12 weeks. The primary outcome was the proportion of patients with response, defined as MBL volume <80mL and a reduction from baseline of at least 50% in MBL, during the last 35 days of the treatment phase (measured by alkaline hematin). The primary comparison was between relugolix CT and placebo. This was assessed in the modified intention-to-treat population, which comprised all randomised patients who received at least one dose of study medication. Delayed relugolix CT is not licensed and results for it are not presented here.[3]

The proportion of patients achieving a response for the primary outcome was significantly higher with relugolix CT compared with placebo, as detailed in Table 1 below. Secondary outcomes were assessed in the hierarchical order listed in this table (except in LIBERTY-2 where the fourth and fifth secondary outcomes were assessed in the reverse order). All secondary outcomes noted in the table were significantly improved with relugolix CT compared with placebo. There was no significant difference for the sixth secondary outcome, change in primary uterine fibroid volume.[2,3]

Table 1: Primary and key secondary outcomes of LIBERTY-1 and LIBERTY-2.[2,3]

	LIBERTY-1		**LIBERTY-2**	
	Relugolix CT	**Placebo**	**Relugolix CT**	**Placebo**
	N=128	N=128	N=126	N=129
Primary outcome	94 (73%)	24 (19%)	89 (71%)	19 (15%)
difference (95% CI)	55% (44%, 65%) p<0.001		56% (46%, 66%) p<0.001	
Amenorrhoea over last 35 days	67 (52%)	7 (5.5%)	63 (50%)	4 (3.1%)
difference (95% CI)	47% (37%, 56%) p<0.001		47% (38%, 57%), p<0.001	
Change in MBL at week 24	-84%	-23%	-84%	-15%
difference (95% CI)	61% (-74%, -49%) p<0.001		-69% (-84%, -54%) p<0.001	
Change in BPD at week 24	-45	-16	-52	-18
difference (95% CI)	-29 (-36, -21) p<0.001		-33 (-41, -26) p<0.001	
Increase in Hb of >2g/dL at week 24 in those with anaemia	15/30 (50%)	5/23 (22%)	19/31 (61%)	2/37 (5.4%)
difference (95% CI)	28% (4%, 53%) p=0.04		56% (37%, 75%) p<0.001	
NRS≤1 at week 24 in those with pain at baseline (NRS>4)	25/58 (43%)	7/69 (10%)	32/68 (47%)	14/82 (17%)
difference (95% CI)	33% (18%, 48%) p<0.001		30% (16% to 44%) p<0.001	

CI = confidence interval; Relugolix CT = relugolix combination therapy (relugolix, estradiol and norethisterone acetate); MBL = menstrual blood loss volume; BPD = bleeding and pelvic discomfort scale score as measured by Uterine Fibroid Symptom and Health-Related Quality of Life (UFS-QoL) questions 1, 2 and 5; Hb = haemoglobin; NRS = numerical rating scale for uterine fibroid associated pain.

Patients who completed LIBERTY-1 and -2 were able to enter the open-label LIBERTY-3 study where all patients received relugolix CT one tablet daily for 28 weeks. The primary outcome was the same as the preceding studies. Analyses were conducted in all patients who received at least one dose of study treatment in this extension study. Of the 610 patients who completed LIBERTY-1 and -2, there were 477 (78%) who enrolled in LIBERTY-3 and the primary outcome was achieved by 88% (143/163), 80% (119/149) and 76% (124/164) of patients who had received relugolix CT, delayed relugolix CT and placebo in the preceding studies.[2]

Patients who were responders (as defined previously) at week 48 in LIBERTY-3 could enrol in a double-blind phase 3 withdrawal study (MVT-601-035). They were randomised at week 52 to once daily relugolix CT (n=115) or placebo (n=113) for one year. Patients who had heavy menstrual bleeding (defined as MBL >80mL) had their blinded treatment discontinued and were offered open-label relugolix CT. The primary outcome was the proportion of patients who maintained MBL volume <80mL though week 76 (that is the first 24 weeks of the withdrawal study). This was achieved by significantly more patients in the relugolix CT group compared with placebo: 78% versus 15%, with a difference of 64% (95% confidence interval [CI]: 53% to 74%), p<0.001.[2]

A double-blind phase 3 study (TAK-385/CCT-002) recruited Japanese pre-menopausal women with uterine fibroids and regular heavy menstrual bleeding defined by a score of at least 120 on the pictorial blood loss assessment chart (PBAC) for one cycle during the run-in period. They were randomised equally to 12 weeks' double-blind double-dummy treatment with relugolix 40mg monotherapy orally once daily or leuprorelin 1.88mg or 3.75mg injection every 4 weeks (with higher dose for patients with heavy weight or enlarged uterus). The use of sex hormone preparations was prohibited. The primary outcome was the proportion of patients with a total PBAC less than 10 for weeks 6 to 12, calculated as the sum of the daily scores over the 6-week period. This was assessed in the full analysis set, which comprised randomised patients who received at least one dose of study drug. The primary analysis was non-inferiority at -15% margin. Relugolix was shown to be non-inferior to leuprorelin, with the primary outcome achieved by 82% (111/135) and 83% (118/142) of patients in the respective groups, with a difference of -0.9% (95% CI: -15% to 8.35%).[4]

Within the submission, there was an indirect treatment comparison (ITC) of relugolix CT versus leuprorelin, which was assumed to be representative of GnRH agonists. This used data from the LIBERTY-1 and -2 studies and the PEARL-1 and -2 studies of leuprorelin versus placebo and ulipristal, respectively.[2,3,5,6] There was a Bucher comparison of relugolix CT versus ulipristal and then an extension to leuprorelin via a direct comparison of this with ulipristal. The comparison suggested a treatment benefit in percent change from baseline in MBL with relugolix CT versus leuprorelin, which was applied to the economic analysis.

Summary of evidence on comparative safety

In the LIBERTY studies, the pattern of adverse events with relugolix CT was consistent with that expected for a GnRH antagonist, with frequently reported treatment-related adverse events, such as hot flushes, due to the low estradiol levels. However, these symptoms were lower with relugolix CT than with delayed relugolix CT, where patients received relugolix monotherapy for the initial 12 weeks. In pooled data from LIBERTY-1 and -2 within the relugolix CT, delayed relugolix CT and placebo groups vasomotor symptoms were reported as adverse events by 11%, 37% and 6.6% of patients, respectively.[2]

Effects on bone mineral density (BMD) were of special interest. Pooled data from LIBERTY-1 and -2 within the relugolix CT, delayed relugolix CT and placebo groups found loss of BMD adverse events in 0.8%, 2.3% and 1.2% of patients, respectively. Including treatment in LIBERTY-3, the rates were 0.8%, 3.9% and 1.3% in the respective groups. Dual X-ray absorptiometry (DXA) of lumbar spine indicated significantly less BMD loss with relugolix CT compared with delayed relugolix CT at week 12: -0.5% versus -2.0% in LIBERTY-1 and -0.8% versus -1.9% in LIBERTY-2. The differences between relugolix CT and placebo were small at week 12: −0.5% versus 0.2% in LIBERTY-1 and -0.8% versus 0.5% in LIBERTY-2 and at week 24: −0.4% versus 0.1% and -0.1% versus 0.3% in the respective studies. In LIBERTY-3 the reduction in lumbar spine BMD in the group that had received relugolix CT from baseline of the parent studies was -0.7% and -0.8% at week 36 and 52, respectively. A comparison of BMD changes in LIBERTY-1, -2 and -3 with a cohort of women with uterine fibroids in a prospective observational study (MVT-601-034) indicated that in those aged >35 years there was no meaningful differences. During LIBERTY-1 and -2, some patients, who had normal BMD at baseline, had clinically relevant reductions in BMD (>3% to 8%) and it was not possible to define criteria to identify them at treatment initiation. It is recommended in the summary of product characteristics (SPC) that a DXA scan be performed after the initial 52 weeks of treatment to verify there is not an unwanted degree of BMD loss.[1,2]

Pooled data from the LIBERTY-1 and -2 studies indicated that within the respective relugolix CT, delayed relugolix CT and placebo groups the rates of adverse events were 61% (155/254), 72% (186/258) and 63% (160/256), which were treatment-related in 36%, 56% and 26% of patients. Adverse events led to treatment discontinuation in 3.9%, 12% and 4.3% of patients and serious adverse events were reported by 3.1%, 1.9% and 2.3% of patients, respectively.[2]

Summary of clinical effectiveness issues

Uterine fibroids are benign smooth muscle tumours in the uterus that are hormone-sensitive, requiring oestrogen for growth, although this is also influenced by other hormones such as progesterone and local growth factors. The prevalence of uterine fibroids increases with age up to the menopause. Many patients do not have symptoms. Those with symptoms typically have heavy menstrual bleeding, which may lead to iron deficiency anaemia, and they may experience pelvic pain, irregular bleeding or gastrointestinal upset (constipation, bloating or diarrhoea). Uterine fibroids may be associated with infertility or problems during pregnancy.[2]

Initial treatment options for patients with uterine fibroids and heavy menstrual bleeding may include tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs), levonorgestrel-releasing intra-uterine system and hormonal contraceptives.[2,7] After these, the progesterone antagonist, ulipristal, is an option. This was restricted due to hepatic adverse events to intermittent treatment of pre-menopausal patients with moderate to severe symptoms of uterine fibroids when uterine fibroid embolisation and/or surgical treatment options are not suitable or have failed.[8] Other subsequent treatment options include uterine artery embolisation or surgeries, such as hysterectomy or myomectomy. Pre-treatment with a GnRH agonist before hysterectomy and myomectomy can be considered if uterine fibroids are causing an enlarged or distorted uterus.[2,8] Their use is limited to three to six months as they reduce estrogen to castration levels, which can cause menopausal symptoms and a loss of BMD. However, in practice, hormone replacement therapy (HRT) can be combined with GnRH agonists to reduce menopausal symptoms and effects on BMD thereby allowing longer duration of treatment.[2]

In the LIBERTY-1 and -2 studies relugolix CT, compared with placebo, significantly reduced MBL volume and was associated with benefits on the bleeding and pelvic discomfort scale and on assessments of pain associated with uterine fibroids. Benefits in MBL volume were maintained in patients who continued treatment in the LIBERTY-3 study and in patients who remained on relugolix CT in the randomised withdrawal study.[2,3]

There are no direct comparative data for relugolix CT versus GnRH agonists, which have been used off-label for long-term treatment in combination with HRT. The Japanese non-inferiority study of relugolix monotherapy versus leuprorelin provides some evidence of comparable efficacy.[4] The company also provided an ITC of relugolix CT versus leuprorelin, which had some limitations. There was heterogeneity across the included populations, for example the LIBERTY studies of relugolix CT recruited patients not scheduled for surgery in the next 6 months, whereas the PEARL studies of leuprorelin only included patients scheduled for surgery.[2,3,5,6] It is possible that there was a higher proportion of treatment-naïve patients in the LIBERTY studies. The studies had different methods of assessing MBL volume, with the LIBERTY studies using the quantitative alkaline hematin method and the PEARL studies using a semi-quantitative method, PBAC, with a conversion to estimate MBL volume. This conversion may have introduced uncertainty into the estimates of MBL with leuprorelin and subsequent estimates of between treatment differences. Overall, there is uncertainty around suggested treatment differences between relugolix CT versus leuprorelin.

The company has clarified that relugolix CT is positioned for patients with uterine fibroids who have failed or are unsuitable for conventional therapies (first line treatments), such as tranexamic acid, hormonal contraceptives and intrauterine delivery systems. However, it is not clear how many patients within the LIBERTY-1 and -2 studies met these criteria and there were no subgroup analyses in this cohort. In the relugolix CT, delayed relugolix CT and placebo groups the proportion of patients who had previous surgery for uterine fibroids were 16%, 11% and 10% in LIBERTY-1; 8.8%, 12% and 8.5% in LIBERTY-2. The proportions of patients who reported a history of uterine fibroid-specific treatment (medicine) were 7.0%, 4.5% and 8.7% in LIBERTY-1; 4.8%, 9.5% and 2.3% in LIBERTY-2.[9,10] However, the company noted that the disease duration of uterine fibroids at

baseline was more than three years since diagnosis in 53% of patients in LIBERTY-1 and 54% of patients in LIBERTY-2 during. Therefore, it is likely that they may have received treatment to alleviate their symptoms.

There is a lack of long-term data beyond two years. Also, the LIBERTY-1 and -2 studies excluded patients with increased risk of adverse events due to BMD loss. That is, patients with a BMD z-score < -2.0 at spine, total hip, or femoral neck and those who had a history of or currently had osteoporosis, or other metabolic bone disease, hyperparathyroidism, hyperprolactinemia, hyperthyroidism, anorexia nervosa or fractures.[2,3] Therefore, there are no data on adverse events linked to BMD loss in patients at higher risk of these.

The introduction of relugolix CT would provide the first GnRH analogue licensed for long-term treatment of heavy menstrual bleeding associated with uterine fibroids. In contrast to parenterally administered GnRH agonists currently used off-label in combination with oral HRT, it is orally administered as a single tablet that also contains HRT (estradiol and norethisterone).

Clinical experts consulted by SMC noted that relugolix CT may be more convenient than a parenteral GnRH agonist with oral HRT, but it offers less flexibility to adjust HRT. They considered that relugolix CT would be used in place of these medicines.

Summary of comparative health economic evidence

A cost-utility analysis was presented evaluating the use of relugolix CT within a restricted subset of the licensed population, namely premenopausal patients with moderate to severe symptoms associated with uterine fibroids who have failed or are unsuitable for conventional hormonal therapy including contraceptives. Comparisons were provided against six short and long-acting formulations of GnRH agonists (leuprorelin acetate, goserelin and triptorelin); the submitting company stated that ulipristal has a restricted usage and is rarely used.

An eight-state cohort-level Markov model was used to represent the pathway from treatment initiation to best-supportive care, followed by pre-surgical waiting time (as a tunnel state), surgery and post-surgery. A separate menopause health state was used to represent the timepoint when treatment and surgery would no longer be required (at an age of 51 years), with patients no longer eligible for surgery within 5 years of menopause. Patients could move to an absorbing state of death at any point. A one-month cycle length was used, and a lifetime time horizon (60 years) applied.

The primary sources of evidence for relugolix CT were the LIBERTY-1 and -2 trials, complemented by the LIBERTY-3 extension study.[2,3] Effectiveness of relugolix CT was based primarily on MBL data and withdrawal rates from the pooled trials. The ITC described previously was used to estimate relative effectiveness of GnRH agonists: these were all assumed to have equivalent effectiveness based on a systematic review.[11] Effectiveness data for the best supportive care (BSC) state were derived from the placebo arms of LIBERTY 1 and 2. Extrapolation of MBL data from the available clinical data was conducted using a last-observation carried forward (LOCF) approach, implying that the treatment effect for each was maintained until discontinuation or surgery.

Utilities were applied separately for the treatment-related health states and surgical health states. For treatment states, although EQ-5D data were collected in the LIBERTY-1 and -2 studies, the submitting company stated that these data were insufficiently sensitive to change in MBL due to collection at only one time-point post-baseline, as well as having a short recall period. Instead, the submitting company used a complex approach of using mapping to EQ-5D from condition-specific data using the uterine fibroid health and symptom-related quality of life (UFS-QoL) questionnaire,[12] followed by the use of a second ordinary least squares (OLS) regression using MBL volume and baseline age as explanatory variables. No details were provided into the model selection process for this approach, other than that a similar approach had been used in a previous published cost-effectiveness analysis.[13] Surgical health states used age-banded population norms,[14] with a significant number of disutilities applied to reflect quality of life implications associated with surgery and surgical adverse effects. The key utilities are summarised below:

Table 2: Key utility values (disutilities not shown)

Treatment-specific utilities	**Mapped EQ-5D utility estimate**
Baseline	0.731
Relugolix CT, week 52 onwards	0.81
GnRH agonists, week 12 onwards	0.797
BSC, week 24 onwards	0.758
Surgery/post-surgery baseline estimates (age-specific population norms)	**EQ-5D utility weight**
35-44 (first 3 years of model)	0.911
45-54	0.847
55-64	0.799
65-74	0.779
75+	0.726

EQ-5D: EuroQoL EQ-5D-3L questionnaire, CT: combination therapy, BSC: best supportive care

Medicines acquisition and administration costs were included according to doses stipulated in the marketing authorisations, and monitoring assumptions applied on a treatment-specific basis (with reduced overall requirements for relugolix CT versus the GnRH agonists). BSC treated patients were assumed to receive NSAIDs and iron supplementation. Treatment duration with relugolix CT was assumed to align with the rates observed in the LIBERTY 1, 2 and 3 studies, followed by a constant discontinuation rate until menopause; however, a post hoc review of reasons for discontinuation was used to select only reasons for discontinuation that were judged to be applicable in the real world. Discontinuation data for GnRH agonists were initially derived from the PEARL II study, followed by the estimated average proportions of patients on treatment at 1, 5 and 10 years provided by clinical experts consulted by the company. Surgical costs were based upon NHS reference costs for a range of potential surgical procedures, including hysterectomy and myomectomy, and costs of adverse effects of treatment and surgery were included.

The main base case results were presented against individual short and long-acting GnRH agonists, and are summarised below. These resulted in a small Quality Adjusted Life Year (QALY) gain for relugolix CT alongside a small additional cost. The QALY gains likely result from the slight utility benefit estimated for patients receiving relugolix CT, alongside the delayed time until treatment

withdrawal and transition to BSC/surgery. Relatively low incremental costs are on the one hand due to increased treatment duration, offset by savings from delay or avoidance of surgery.

Table 3: Base-case results (relugolix CT vs comparator)

Treatment	**ICER relugolix CT vs. comparator (£/QALY)**
Relugolix CT	
Goserelin monthly	10,597.77
Triptorelin 3-monthly	10,290.50
Triptorelin monthly	10,279.33
Leuprorelin monthly	9,877.09
Leuprorelin 3-monthly	9,452.51
Goserelin 3-monthly	9,145.25

QALY: Quality-adjusted life year, ICER: incremental-cost-effectiveness ratio, CT: combination therapy

Key scenario and sensitivity analyses are presented below, with scenarios presented for the lowest cost monthly and three monthly GnRH agonists, and only for the lowest cost GnRH agonist (goserelin) for sensitivity analyses. Note that only the intercept term from the utility function is shown from the one-way sensitivity analysis, however the model was also noticeably sensitive (to a lesser extent) to numerous other parameters associated with utilities. Cumulatively, this highlights a high degree of uncertainty with the estimates of QALY gains from the model.

Table 4: Key scenario and sensitivity analyses

	Variable/structural assumption	**Base-case scenario**	**Other scenarios considered**	**Comparator**	**ICER vs. relugolix CT**
	Base-case			**Goserelin monthly**	**£10,648**
				Triptorelin 3-monthly	**£10,340**
1.	Utility function – intercept term	As base case	20% reduction	Goserelin monthly	£45,150
2.	MBL volume input for utility algorithm	MBL volume for GnRH agonists derived from ITC	Mean MBL in the GnRH agonist arms assumed the same as relugolix CT for the utility algorithm	Goserelin monthly	£12,337
				Triptorelin 3-monthly	£11,980
3.	Inclusion of surgery health states	Included	Excluded	Goserelin monthly	£15,564
				Triptorelin 3-monthly	£15,282

4.	Referral to surgery upon discontinuation of treatment	No referrals within 5 years of menopause	Referrals possible up until menopause (51 years of age)	Goserelin monthly	£11,491
				Triptorelin 3-monthly	£11,175
5.	Waiting time before surgery	15 months	6 months	Goserelin monthly	£13,963
				Triptorelin 3-monthly	£13,547
6.	GnRH agonist treatment duration and inclusion of add-back therapy	Cap on % remaining on treatment at multiple periods based on KOL opinion; add-back therapy included	Fixed maximum duration of 6 months as per SPC, add-back therapy costs and effect on AEs excluded	Goserelin monthly	£15,547
				Triptorelin 3-monthly	£15,508
7.	GnRH agonist treatment duration (including add-back)	Cap on % remaining on treatment at multiple periods based on KOL opinion	Fixed maximum duration of 12 months; PEARL II withdrawal rates applied throughout	Goserelin monthly	£13,228
				Triptorelin 3-monthly	£13,175

ICER: incremental cost-effectiveness ratio, CT: combination therapy, MBL: menstrual blood loss, AE: adverse events, KOL: key opinion leader

The key limitations are as follows:

- In structural terms, the model imparts benefits upon relugolix CT which have not been demonstrated in either direct clinical evidence or indirect comparative evidence, as well as being potentially unlikely due to the very similar mechanism of action of relugolix CT (a GnRH antagonist) to GnRH agonists. There may be face validity concerns with the model outputs given the potential similarities between relugolix CT and comparators; however, a simpler cost-comparison was provided upon request which provides reassurance regarding the relative costs and benefits of relugolix CT versus available comparators. It may also be reasonable to assume a small utility benefit due to oral administration versus currently available parenteral treatments, which was not captured in the economic analysis.
- The approach to estimating utilities is potentially over-complicated, involving both mapping from a condition-specific measure to EQ-5D, before adjusting for MBL volume and age. This approach introduces significant uncertainty into the utility estimates, particularly when EQ-5D data were collected within the LIBERTY trials. In addition, the assumption of a difference in

MBL volume in the analysis, when no significant difference was demonstrated in the ITC, confers a quality of life benefit for relugolix CT.

- Similarly, numerous disutilities are applied in the surgical and pre- and post-surgical health states. Whilst many of the dimensions considered are reasonable in isolation, the use of multiple sources which in turn use different measurement and valuation methods results in a high likelihood that the overall disutility estimates include a degree of double-counting (for example, an aggregate 'loss of uterus' disutility is applied alongside several specific disutilities associated with hysterectomies).

Despite these limitations, the economic case was considered to have been demonstrated.

Summary of patient and carer involvement

No patient group submission was received.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) guideline 88 (NG88), heavy menstrual bleeding: assessment and management was published in March 2018 and updated in May 2021. It recommends a levonorgestrel-releasing intra-uterine system for patients with heavy menstrual bleeding and uterine fibroids less than 3 cm in diameter, which are not causing distortion of the uterine cavity. If a woman declines this or it is not suitable, the following pharmacological treatments can be considered: tranexamic acid, non-steroidal anti-inflammatory drugs (NSAIDs), combined hormonal contraceptives and cyclical oral progesterone (this is an off-label use for NSAIDs and some oral contraceptives). If treatment is unsuccessful, the woman declines pharmacological treatment or symptoms are severe, consider referral to specialist care for further investigation and treatment options, including surgery. For patients with uterine fibroids greater than 3cm in diameter the guideline initially recommends referral to specialist care for further investigation and treatment options. The size, location and number of fibroids, and the severity of the symptoms should be taken into account when considering treatments. These may include medicines such as tranexamic acid, NSAIDs, levonorgestrel-releasing intra-uterine system, combined hormonal contraceptives, cyclical oral progesterone and ulipristal acetate. (Ulipristal acetate should only be considered for intermittent treatment of moderate to severe symptoms of uterine fibroids in premenopausal patients if surgery and uterine artery embolisation for fibroids are not suitable or have failed or the woman declines these. The risks and possible benefits of intermittent treatment with ulipristal acetate should be discussed with the woman). Other treatment options include uterine artery embolisation or surgeries, such as hysterectomy or myomectomy. The guideline notes that pre-treatment with a GnRH analogue before hysterectomy and myomectomy should be considered if uterine fibroids are causing an enlarged or distorted uterus.[7]

Additional information: comparators

In practice, relugolix CT may be used in place of parenteral GnRH agonists used off-label for long-term treatment in combination with HRT.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost/year (£)
Relugolix 40mg, estradiol 1mg, norethisterone acetate 0.5mg (Ryeqo®)	One tablet daily	936

Costs from BNF online on 11 March 2022.

Additional information: budget impact

The submitting company estimated that there would be 180 patients treated with relugolix CT in year 1 and 495 patients in year 5.

SMC is unable to publish the budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget.

*Other data were also assessed but remain confidential.**

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This assessment is based on data submitted by the applicant company up to and including 13 April 2022.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy*

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for

comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.