SMC2678

# relugolix film-coated tablets (Orgovyx®)

## Accord-UK Ltd

06 September 2024

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 Therapeutics Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

**ADVICE**: following a full submission

**relugolix (Orgovyx®)** is accepted for use within NHSScotland.

**Indication under review:**

- for the treatment of adult patients with advanced hormone-sensitive prostate cancer
- for the treatment of high-risk localised and locally advanced hormone dependent prostate cancer in combination with radiotherapy
- as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced hormone dependent prostate cancer.

In an open-label, randomised phase III study, there was a significantly higher sustained castration rate in patients with advanced hormone-sensitive prostate cancer treated with relugolix compared with a gonadotrophin releasing hormone (GnRH) agonist for 48 weeks.

**Chair**
**Scottish Medicines Consortium**

# 1. Clinical Context

## 1.1. Medicine background

Relugolix is a non-peptide gonadotrophin releasing hormone (GnRH) antagonist that binds to GnRH receptors in the anterior pituitary gland, thereby decreasing the release of luteinising hormone (LH) and follicle-stimulating hormone (FSH). This in turn reduces the production of testosterone from the testes. The FSH and LH levels decline rapidly after starting relugolix and testosterone levels are suppressed to below physiologic concentrations. Following treatment discontinuation, pituitary and gonadal hormone concentrations return to physiologic concentrations.[1, 2]

Relugolix is the first oral GnRH antagonist and the first oral androgen deprivation therapy (ADT) to be licensed in the UK. The recommended dose is relugolix 120 mg orally once daily (following a loading dose of 360 mg, three tablets, on day 1).[2]

## 1.2. Disease background

Prostate cancer is the most common cancer in men. Disease is characterised as localised, locally advanced or metastatic. Both localised and locally advanced disease can be treated with curative intent with radical therapy. The level of risk of progression in localised or locally advanced disease is determined by Gleeson score, the prostate-specific antigen (PSA) level and the clinical stage of the tumour and is categorised as low, intermediate or high. Hormone-sensitive prostate cancer refers to disease that has not been treated with ADT or that is continuing to respond to it. In these patients, prostate cancer can be controlled by keeping the testosterone level as low as would be expected following castration. This can be achieved by orchiectomy or taking GnRH agonists or antagonists.[1, 3]

## 1.3. Treatment pathway and relevant comparators

Guidelines recommend medical castration with ADT in combination with radical radiotherapy for the treatment of patients with prostate cancer if they have intermediate- or high-risk localised disease; neo-adjuvant plus adjuvant ADT plus radical radiotherapy with or without docetaxel for locally advanced disease; and, ADT plus hormonal therapy or docetaxel for hormone-sensitive metastatic disease.[4-6]

The relevant comparators include available GnRH agonists (leuprorelin, triptorelin and goserelin) and the GnRH antagonist (degarelix). The GnRH agonists are associated with an initial rise in testosterone levels which can lead to a flare in symptoms. This flare is not experienced by patients treated with GnRH antagonists. Depending on the stage of disease, level of risk and patient characteristics, ADT may be used in combination with radiotherapy, docetaxel or hormonal therapy according to current guidelines.[4-6]

# 2. Summary of Clinical Evidence

## 2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of relugolix for the treatment of prostate cancer comes from the HERO study. Details are summarised in Table 2.1.

**Table 2.1. Overview of relevant study[1, 7]**

| Criteria | HERO |
|---|---|
| Study design | An international, open-label, randomised, phase III study |
| Eligible patients | • Male aged ≥18 years with histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate.<br>• Requiring ≥1 year of continuous ADT for the management of androgen-sensitive advanced prostate cancer with one of the following clinical disease state presentations:<br>- evidence of biochemical relapse (a rising PSA) or clinical relapse following local primary intervention with curative intent, and not a candidate for salvage surgery<br>- newly diagnosed androgen-sensitive metastatic disease<br>- advanced localised disease unlikely to be cured by local primary intervention with either surgery or radiation with curative intent<br>• Serum PSA concentration >2.0 nanograms/mL at screening or >0.2 nanograms/mL post radical prostatectomy or >2.0 nanograms/mL above the post interventional nadir post radiation therapy, cryotherapy, or high frequency ultrasound<br>• ECOG performance status, 0 or 1 |
| Treatments | Relugolix orally 360 mg loading dose on day 1 followed by 120 mg daily or leuprorelin 22.5 mg (11.25 mg in Japan, Taiwan and China) every 12 weeks by subcutaneous or intramuscular injection for 48 weeks. Patients in the leuprorelin group could take an anti-androgen for the first 4 weeks or longer for initial flare response. Patients with disease progression during study treatment and testosterone levels ≤50 nanograms/dL could receive radiotherapy. Patients with confirmed PSA progression were allowed to receive enzalutamide or docetaxel during the study. |
| Randomisation | Patients were randomised in a ratio of 2:1 to study treatment with stratification for geographic region (North and South America, Europe and Asia-Pacific), presence of metastatic disease and age (≤75 years or >75 years). |
| Primary outcome | Sustained castration rate, defined as achieving and maintaining serum testosterone suppression at castrate levels (<50 nanograms/dL) by day 29 to week 48 of treatment. |
| Secondary outcomes | • Castration rate (testosterone <50 nanograms/dL) on day 4<br>• Castration rate (testosterone <50 nanograms/dL) on day 15<br>• Proportion of patients with PSA response on day 15, confirmed at day 29<br>• Profound castration rate (testosterone <20 nanograms/dL) on day 15<br>• FSH level at the end of week 24<br>• Castration resistance-free survival (defined by disease progression despite testosterone <50 nanograms/dL) during 48-week treatment period in patients with metastatic disease at final analysis<br>• Castration resistance-free survival during 48-week treatment period in all patients at final analysis.<br>• Time to testosterone recovery to 280 nanograms/dL at the 90-day follow-up in approximately 150 patients who completed 48 weeks of treatment |

| | |
|---|---|
| | and participated in the testosterone recovery follow-up |
| Statistical analysis | A hierarchical statistical testing strategy was applied to the primary and key secondary outcomes in the study with no formal testing of outcomes after the first non-significant outcome in the hierarchy. The testing order was as listed above and varied slightly between regulatory authorities. All outcomes were analysed in the primary mITT population, with the exception of castration resistance-free survival which was analysed in the final mITT population. |

ADT = androgen deprivation therapy; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; mITT = modified intention to treat; PSA = prostate-specific antigen

The study randomised more than 1,000 patients and included two analyses: a primary and a final analysis. The primary analysis (data cut-off 10 December 2019) was performed in the primary modified intention-to-treat (mITT) population, which included all randomised patients who received at least one dose of study medicine (622 patients in the relugolix group and 308 patients in the leuprorelin group). The final analysis (data cut-off 23 September 2020) was performed in the mITT final analysis population after additional patients with metastatic disease and patients from China and Taiwan had been enrolled (717 patients in the relugolix group and 357 patients in the leuprorelin group, which included a subset of the mITT final analysis population who had metastatic prostate cancer).

At the primary analysis (data cut-off 10 December 2019), the primary outcome of sustained castration rate was achieved by 97% of patients in the relugolix and 89% of patients in the leuprorelin group. The difference between groups met the pre-specified criteria for non-inferiority (lower boundary of the 95% confidence interval [CI] >-10%) and for superiority (lower boundary of the 95% CI > 0%, p<0.001). Subgroup analysis of the primary outcome found consistently high sustained castration rates with relugolix, including patients with metastatic disease. Key secondary outcomes analysed at the primary analysis significantly favoured relugolix over leuprorelin. Detailed results are presented in table 2.2.

**Table 2.2: Results of primary and key secondary outcomes in primary mITT population of the HERO study (data cut-off 10 December 2019)[1, 7]**

| | **Relugolix (n=622)** | **Leuprorelin (n=308)** | **Difference (95% CI), p-value** |
|---|---|---|---|
| **Primary outcome** | | | |
| Sustained castration rate (testosterone <50 nanograms/dL from day 29 to week 48) | 97% | 89% | 7.9% (4.1% to 12%), p<0.001 |
| **Key secondary outcomes** | | | |
| Castration rate (testosterone <50 nanograms/dL) on day 4 | 56% | 0 | 56% (NE, NE), p<0.001 |
| Castration rate (testosterone <50 nanograms /dL) on day 15 | 99% | 12% | 87% (83% to 90%), p<0.001 |
| Proportion of patients with PSA | 79% | 20% | p<0.001 |

| | | | |
|---|---|---|---|
| response on day 15, confirmed at day 29 | | | |
| Profound castration rate (testosterone <20 nanograms /dL) on day 15 | 78% | 1.0% | 77% (74% to 81%), p<0.001 |
| FSH level at the end of Week 24, IU/L | 1.72 | 5.95 | p<0.001 |

CI = confidence interval; FSH = follicle-stimulating hormone; mITT = modified intention to treat; NE = not estimable; PSA = prostate-specific antigen

The key secondary outcome of castration resistance-free survival (CRFS) was only assessed at the final analysis, firstly in patients with metastatic disease and then in all patients. Median CRFS was not estimable in either treatment group and since there was no statistical difference between treatment groups in patients with metastatic disease, further formal statistical testing was not performed. The cumulative probability of testosterone recovery (defined as >280 nanograms/mL at the 90-day follow-up visit in the subpopulation) found this was higher with relugolix (54%) compared with leuprorelin (3.2%).[1, 7]

### 2.2. Health-related quality of life outcomes

Health-Related Quality of Life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQC30) and 25-item prostate cancer module (EORTC QLQ-PR25) sexual activity and hormonal-treatment-related symptom subdomains and the generic EuroQol 5-Dimension 5-Level Scale (EQ-5D-5L) questionnaires. These were analysed as additional secondary outcomes and were not included in the hierarchical statistical testing. The descriptive results found no notable differences between the treatment groups.[1, 7]

### 2.3. Supportive studies

C27003 was a supportive, open-label, phase II study in 103 patients with intermediate-risk, localised prostate cancer requiring (neo)adjuvant ADT for 6 months plus external beam radiation therapy (EBRT). Eligible patients were randomised to receive relugolix (320 mg orally as a loading dose then 120 mg daily to week 24, n=65) or degarelix (240 mg subcutaneously on day 1, then 80 mg every 4 weeks to week 24, n=38). The primary outcome of effective castration rate (defined as testosterone <50 nanograms/dL between weeks 4 and 24 of treatment) was achieved by 95% of patients in the relugolix group and 89% of patients in the degarelix group. Results were descriptive only. [1, 8]

### 2.4. Indirect evidence to support clinical and cost-effectiveness comparisons

In the absence of direct evidence comparing relugolix with GnRH agonists, other than leuprorelin, and with degarelix in a relevant patient population, the submitting company presented two indirect treatment comparisons. One assessed efficacy in terms of testosterone suppression and the other assessed safety in terms of major adverse cardiovascular event (MACE). The results of the NMA on testosterone suppression were used indirectly in the economics to support an assumption of comparable efficacy between the GnRH agonist and antagonists. Results have only been used directly to inform the economic base case for relugolix versus leuprorelin and for degarelix versus leuprorelin for MACE in the subgroup of patients with metastatic hormone-sensitive prostate cancer.

**Table 2.3: Summary of indirect treatment comparison**

| Criteria | Overview |
|---|---|
| Design | One hierarchical random effects NMA compared the efficacy of relugolix and a second random effects NMA compared the safety of relugolix with GnRH agonists and degarelix for the treatment of HSPC. |
| Population | Patients with HSPC aged ≥18 years |
| Comparators | NMA of testosterone suppression versus leuprorelin (common comparator), degarelix, triptorelin, goserelin.<br>NMA of MACE versus degarelix, and either leuprorelin or a mix of GnRH agonists (common node). |
| Studies included | NMA of testosterone suppression included five studies ( HERO, [7] CS21, [9] Heyns et al, [10] Silva et al, [11] Tanaka et al [12]).<br>NMA of MACE included three studies ( HERO, [7] CS21, [9, 13] Margel et al [14]). |
| Outcomes | Proportion of patients who achieve testosterone suppression to castrate levels (<50 nanograms/dL).<br>Proportion of patients who experience a MACE based on definitions which differed across studies. |
| Results | NMA of testosterone suppression suggested relugolix was more effective than goserelin and leuprorelin, and there was no evidence of a difference between relugolix compared with degarelix or triptorelin. There was no evidence of a difference between the GnRH agonists and the point estimates were similar across these results.<br>NMA of MACE suggested that there was no clear evidence of a difference between relugolix compared with degarelix or leuprorelin. |

HSPC = hormone-sensitive prostate cancer; MACE = major adverse cardiovascular events; NMA = network meta-analysis.

## 3. Summary of Safety Evidence

At the primary safety analysis of HERO (data cut-off 10 December 2019), the median duration of treatment in each group was 48 weeks. Any treatment-emergent adverse event (AE) was reported by 93% (578/622) of patients in the relugolix group and 94% (288/308) in the leuprorelin group and these were considered treatment-related in 74% and 69% respectively. In the relugolix and leuprorelin groups respectively, patients reporting a grade 3 or higher AE were 18% versus 20%, patients with a reported serious AE were 12% versus 15%, the proportion of AEs that led to dose interruptions were 2.7% versus 0% and patients discontinuing therapy due to an AE was 3.5% versus 0.3%.[1, 7]

The most frequently reported AE was hot flush (54% versus 52%) and this and other treatment-emergent AEs were reported with a similar incidence in the relugolix and leuprorelin groups with the exception of constipation, diarrhoea, arthralgia, hypertension and MACE. There was a higher incidence of constipation (12% versus 9.7%), diarrhoea (12% versus 6.8%) and arthralgia (12% versus 9.1%) in the relugolix group and a higher incidence of hypertension (7.9% versus 12%) in the leuprorelin group.[1, 7]

The incidence of MACE (recorded as one of the following AEs: non-fatal myocardial infarction, non-fatal stroke, and death from any cause) was 2.9% in the relugolix group versus 6.2% in the leuprorelin group; Kaplan–Meier estimated hazard ratio 0.46 (95% CI 0.24 to 0.88).[1, 7]

In a post hoc analysis, patients were assessed according to a broad post hoc assessment of risk factors for cardiovascular and cerebrovascular events. Assessment of risk included: life-style related risk factors (smoking status, alcohol use and body mass index > 30); any cerebrovascular or cardiovascular risk factors and any history of MACE. In patients reported to have a medical history of MACE, the incidence of MACE during HERO was 3.6% (3/84) in the relugolix group and 18% (8/45) in the leuprorelin group; in patients without a medical history of MACE, the incidence was 2.8% (15/538) versus 4.2% (11/263) respectively.[1]

## 4. Summary of Clinical Effectiveness Considerations

### 4.1. Key strengths

- Relugolix is the first oral GnRH antagonist to be licensed for the treatment of prostate cancer. It would provide the first orally administered formulation of ADT for these patients. As a GnRH antagonist, relugolix does not result in an initial testosterone flare avoiding the need for additional anti-androgen therapy.[1, 2]
- Key evidence from the phase III study HERO has shown that relugolix is at least as effective as the GnRH agonist, leuprorelin, which is a relevant comparator. The primary outcome of sustained castration rate was achieved by significantly more patients receiving relugolix than leuprorelin. This was supported by significant improvements in the key secondary outcomes at the time of the primary analysis.[1, 7]
- The treatment effect on testosterone suppression was observed earlier with relugolix at days 4 and 15 of the HERO study compared with leuprorelin.[1, 7]
- During the 48-week treatment period of HERO, the incidence of MACE appeared to be lower in the relugolix group compared with the leuprorelin group.[1, 7]

### 4.2. Key uncertainties

- The key evidence from HERO primarily assessed the efficacy of relugolix versus leuprorelin in terms of the surrogate outcome of castration rate based on testosterone levels over 48 weeks and other biochemical measures. Although these are acceptable outcomes for patients with hormone-sensitive advanced prostate cancer, they may be of less clinical relevance to patients than the key secondary outcome of CRFS, which was not significantly different between groups. There was also no notable difference between groups in quality of life assessments.[1, 7]
- During HERO, MACE was not assessed as a study outcome but was recorded from events reported in the safety data and events were not adjudicated. Although the rate of MACE was lower in the relugolix group compared with the leuprorelin group (2.9% versus 6.2%), this outcome was not included in the statistical plan or hierarchical testing; the results should be considered descriptive only. Further analysis according to previous history of cardiovascular disease was performed post hoc and should be interpreted with caution. In addition, patients

with a recent history of MACE or uncontrolled cardiovascular disease were excluded from HERO, which may affect the generalisability of results to clinical practice.[1, 7]

- The regulators considered that there was insufficient evidence to draw definitive conclusions regarding the rate of MACE with relugolix versus leuprorelin[1, 2] The New Drugs Committee agreed that there was uncertainty in the relative treatment effect of relugolix compared with leuprorelin in the incidence of MACE in HERO.
- HERO was an open-label study. However, measurements of testosterone, PSA and FSH were performed at a central laboratory in a blinded manner to minimise potential bias. Quality of life and safety outcomes, which were assessed by the investigator, may be prone to bias.[1, 7]
- HERO enrolled patients with advanced hormone-sensitive prostate cancer and did not specifically assess the efficacy of relugolix in combination with radiotherapy or as neo-adjuvant treatment prior to radiotherapy in patients with high-risk localised and locally advanced hormone dependent prostate cancer. The efficacy of relugolix in combination with radiotherapy is based on a therapeutic class effect and indirect data of non-inferiority in terms of testosterone suppression with GnRH agonists and antagonists, not specific to relugolix. In addition, a small subset of patients did receive radiotherapy with study treatment during the study period and results were similar.[2, 7, 15]
- In HERO, the leuprorelin dose was higher than the recommended dose for prostate cancer in the UK, which may affect the generalisability of the study results to clinical practice.[7]
- There are no direct data comparing relugolix with GnRH agonists, other than leuprorelin, or with degarelix in a patient population reflecting the marketing authorisation. The company performed NMAs which supported an assumption of equivalent efficacy of GnRH agonists allowing the HERO results to be used as a proxy for this therapeutic class. The only NMA result applied directly in the economic analysis was for the relative risk of MACE when relugolix was compared with degarelix. The NMA results are limited by heterogeneity (including the baseline level of risk of MACE and definitions of MACE), small number of studies and were sensitive to the inclusion of Margel et al.[14] Notably the NMA did not include the PRONOUNCE study which compared degarelix with leuprorelin using MACE as a primary outcome.[17] Despite these limitations, the conclusions of no evidence of a difference between treatments in the incidence of MACE seems reasonable and is in line with PRONOUNCE and a published indirect comparison.[17, 18]

### 4.3. Clinical expert input

Clinical experts consulted by SMC considered that relugolix is a therapeutic advancement offering an oral ADT.

### 4.4. Service implications

As an orally administered medicine, relugolix may reduce the burden of parenteral ADT.

## 5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Groups.

- We received patient group submissions from: Prostate Cancer UK, Prostate Scotland and Tackle Prostate Cancer. All three organisations are registered charities.
- Prostate Cancer UK has received less than 1% pharmaceutical company funding in the past two years, with none from the submitting company. Prostate Scotland has not received any funding from pharmaceutical companies in the past two years. Tackle Prostate Cancer has received 18% pharmaceutical company funding in the past two years, with none from the submitting company.
- A diagnosis of advanced hormone-sensitive prostate cancer is a time of deep emotional and psychological distress for patients and their families and carers. Some patients will initially be asymptomatic whilst others may experience or develop symptoms, often bone pain. Men with advanced prostate cancer who have bone metastases, including in the spine, may develop spinal cord compression. These men require urgent treatment to prevent permanent nerve damage and potential paralysis. This can be a debilitating and life-changing problem.
- Currently patients have a few treatment options available to them. Treatments such as leuprorelin and goserelin are administered by injection and can cause problems at the injection site.
- Relugolix is an oral treatment and so has benefits for patients since they do not need to travel to a GP or hospital setting for injection. Some patients are unable to have injections due to anxiety or physical reactions to the administration and would benefit greatly from an oral treatment. As would those who live at a distance from their hospital or GP practice.

## 6. Summary of Comparative Health Economic Evidence

### 6.1. Economic case

The submitting company provided an economic case, summarised in Table 6.1.

**Table 6.1 Description of economic analysis**

| Criteria | Overview |
|---|---|
| Analysis type | Cost-utility analysis. |
| Time horizon | Lifetime time horizon (26 years). |
| Population | The cost-effectiveness of relugolix was evaluated in patients with advanced hormone-sensitive prostate cancer. It was assumed that the cost-effectiveness of relugolix in this population was generalisable to the high-risk localised setting. |
| Comparators | Blended GnRH agonists comprising goserelin (4%), leuprorelin (64%) and triptorelin (31%). Degarelix was considered an additional comparator in a subgroup analysis of patients with spinal metastasis (conducted in the metastatic hormone-sensitive prostate cancer subpopulation). |
| Model | A Markov cohort model was used. The model included a set of health states for non- |

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| description | metastatic hormone-sensitive prostate cancer (including locally advanced and biochemical relapse), and facilitated transitions for metastasis and PSA progression, with health states of metastatic hormone-sensitive prostate cancer, non-metastatic castration resistant prostate cancer and metastatic castration resistant prostate cancer, with death possible in all states. The model further comprised two sub-models for patients with prior MACE and those with no prior MACE.<br><br>Initial treatments are given indefinitely throughout the non-metastatic hormone-sensitive prostate cancer health states, subject to discontinuation in the locally advanced and biochemical relapse health states, and the metastatic hormone-sensitive prostate cancer health state. Patients that experience PSA progression and become castration resistant continue to receive initial treatments, with additional subsequent treatments of androgen receptor inhibitors or chemotherapy. |
| Clinical data | Baseline demographic characteristics, initial health state proportions, castration rates, time to PSA progression, and non-MACE adverse events (grade 3 and above with an incidence of at least 10%) were from HERO.[7]<br><br>Data for time to distant metastasis for both non-metastatic hormone-sensitive and castration resistant health states were drawn from literature.[19, 20] Survival data for metastatic health states were drawn from literature.[21, 22] Survival data for non-metastatic health states used general population survival. Treatment discontinuation in the locally advanced and biochemical relapse health states were sourced from submitting company analyses.<br><br>MACE data used in the model were primarily drawn from HERO and a real-world evidence study by Brady et al.[23] The submitting company noted it used literature due to HERO excluding patients with MACE during the six months prior to enrolment, and as patients in clinical trials are generally healthier than those in typical clinical practice, the risk of MACE among patients in HERO may not be representative of that among patients with advanced hormone-sensitive prostate cancer seen in typical clinical practice.<br><br>Relative risk results from the NMA of testosterone suppression were used indirectly to support an assumption that different GnRH agonist formulations had equivalent clinical efficacy. Relative risk results from the MACE NMA were applied in the model in the spinal metastases subgroup analysis (conducted in the metastatic hormone-sensitive prostate cancer subpopulation). |
| Extrapolation | Time to PSA progression, time to distant metastases and metastatic survival were extrapolated. These extrapolations were not treatment dependent. The key area of difference and driver of the treatment effect between relugolix and the comparators was MACE.<br><br>MACE was extrapolated in the model using an annual probability of MACE for GnRH agonists without prior MACE of 10.08% from HERO and Brady et al, a relative risk of MACE given prior MACE of 2.62 (95% CI 1.27 to 5.45) from HERO, and a relative risk reduction (relugolix versus leuprorelin) of 0.38 (95% CI 0.18 to 0.79) from HERO.<br><br>In the spinal metastases subgroup analysis (conducted in the metastatic hormone-sensitive prostate cancer subpopulation), the economic model used relative risk reductions from the MACE NMA for relugolix versus leuprorelin (0.42 (95% credible intervals 0.19 to 1.23)) and degarelix versus leuprorelin (0.33 (95% credible intervals 0.15 to 0.74)). |

| | |
|---|---|
| Quality of life | Utility values were from EQ-5D-5L data collected from HERO. Utility values were adjusted for age related declines. Given the initial utility generated utility values exceeded the UK general population, utility values in the model were adjusted to ensure utilities in each health state were not higher than those in the general population.[24] A chronic disutility of -0.09 for non-fatal MACE was applied to the prior MACE states. Disutilities associated with non-MACE adverse events were also included. |
| Costs and resource use | Costs included medicine acquisition, administration, subsequent treatments, MACE and non-MACE adverse events, end of life costs, and healthcare resource utilisation. |
| PAS | PAS discounts are in place for comparators apalutamide, degarelix, enzalutamide, darolutamide, abiraterone, radium-223, and cabazitaxel. These were included in the results used for decision-making by using estimates of the comparator PAS price. |

### 6.2. Results

The base case results are presented in Tables 6.2.1 and 6.2.2. The results use list prices for all medicines.

**Table 6.2.1: Base Case Result (list prices)**

| | **ICER (£/QALY)** |
|---|---|
| Relugolix versus GnRH agonists | 10,226 |

Abbreviations: GnRH= gonadotrophin releasing hormone; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

**Table 6.2.2: Subgroup analysis in spinal metastases (conducted in the metastatic hormone-sensitive prostate cancer subpopulation) (list prices)**

| | **ICER (£/QALY)** |
|---|---|
| Relugolix versus degarelix | 61,597 (SW) |

Abbreviations: ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years; SW = South-West quadrant (the comparison between relugolix and degarelix results in a cost-outcome pairing sitting in the South-West quadrant of the cost-effectiveness plane. This means that relugolix was estimated as resulting in lower total costs and worse health outcomes than degarelix. When this is the case, a larger incremental cost-effectiveness ratio (ICER) indicates higher savings relative to the projected health loss.

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

### 6.3. Sensitivity analyses

Scenario analysis results are shown in the table below. The results were most sensitive to the exclusion of MACE from the model.

**Table 6.3: Scenario analyses against the blended GnRH agonist comparator (list prices)**

| | **Parameter** | **Base case** | **Scenario** | **ICER (£/QALY)** |
|---|---|---|---|---|
| | ***Base case*** | - | - | **10,226** |
| 1a | Carry over period of MACE | 6.8 months | 0 months | 10,914 |
| 1b | | | 12 months | 10,117 |
| 2 | Initial ADT treatment continuation after castrate resistance | Yes | No | 9,183 |

| | | | | |
|---|---|---|---|---|
| 3 | Impact of MACE | RR of MACE | No MACE impact | Dominated |
| 4 | Comparison against the cheapest GnRH agonist | Blended GnRH agonist comparator | Use of Triptorelin (cheapest GnRH agonist) | 10,619 |
| 5a | MACE Relative risk reduction hazard ratio (relugolix versus leuprorelin) from HERO | 0.38 | Upper bound 0.79 | 11,934 |
| 5b | | | Lower bound 0.19 | 9,824 |
| 6a | Utility values (Relugolix, BR off-treatment) | Base case * | Lower bound * | 28,609 |
| 6b | | | Upper bound * | 6,995 |

Abbreviations: ADT = androgen deprivation therapy; BR = biochemical relapse; GnRH = gonadotrophin releasing hormone; ICER = incremental cost-effectiveness ratio; LYG = life years gained; MACE = major cardiovascular events; RR =relative risk; QALY = quality-adjusted life years. Notes. ( * ) Utility values are shown prior to adjustment for general population. Dominated: The assessed medicine was estimated as having higher costs and lower outcomes than the comparator.

### 6.4. Key strengths

- The company presented a comprehensive model structure for modelling disease progression for patients receiving treatment for advanced HSPC.
- The selection of included health state resource use costs was appropriate.
- A comprehensive selection of parameters was considered in one-way deterministic scenario analysis.

### 6.5. Key uncertainties

- There was uncertainty in the MACE improvements for relugolix applied in the economic model. Firstly, MACE was not a study outcome in HERO, and the results indicating a risk reduction with relugolix compared with leuprorelin should be considered descriptive only. Secondly, several assumptions were made when extrapolating MACE outcomes in the model. Several of these could be explored in scenario analyses with a limited impact on economic results (Scenarios 1 and 5). However, the primary sources of MACE clinical data, HERO and the Brady et al study, had differing MACE definitions with Brady et al being more expansive. This required an assumption that the treatment effects on MACE in HERO could be extrapolated to the components of MACE in Brady et al that were not included in the HERO definition. The submitting company viewed the underlying MACE events as similar to support this, but detailed scenario analysis was not presented. Thirdly, the MACE NMA results suggested there was no evidence of a difference in terms of MACE or CV-related events between relugolix versus either of the other comparators. These issues generated uncertainty in MACE being the principal driver of the treatment effect for relugolix in the economic evaluation. The impact of excluding MACE completely from the economic model had the most substantial impact in scenario analysis, leading to relugolix being dominated by the blended GnRH agonists (Scenario 3).
- The spinal metastases subgroup analysis (conducted in the metastatic hormone-sensitive prostate cancer subpopulation) was subject to uncertainty. Firstly, the applied MACE NMA

hazard ratios for treatments were derived from the broader hormone-sensitive prostate cancer population of the NMA, with no restriction for patients with metastatic prostate cancer. Secondly, although the submitting company highlighted degarelix is prescribed to patients with spinal metastases, due to no formal analysis in spinal metastases, a broader metastatic subpopulation was used as a proxy. SMC clinical experts indicated this proxy was reasonable, but one noted that degarelix would be specifically used in those with signs or perceived high risk of spinal cord compression and would have a poorer prognosis. Given these uncertainties, the results of the subgroup analysis should be interpreted with caution.

- The population in the economic evaluation was patients with advanced hormone-sensitive prostate cancer, which is narrower than the licensed indication. The company assumed the results of this population would generalise to the high-risk localised and locally advanced setting when used before or with radiotherapy included in the full licensed indication. Without additional economic analysis, this assumption is challenging to explore.
- There was uncertainty in the utility values. Firstly, the utility values derived from the HERO study were high and required adjustment to ensure these were not exceeding the general population. Secondly, comparative health state utility values that aligned with health states in the economic model were unavailable. Thirdly, HERO was an open-label study, which many have biased health-related quality of life outcomes. A conservative utility scenario was available to potentially understand the impact of these uncertainties (Scenario 6a).
- The dosing used in the economic model for leuprorelin was the licensed UK dose of 11.25 mg every 3 months. However, dosing of leuprorelin in HERO was based on global licensing, 22.5 mg every 3 months (with 11.25 mg every 3 months in Japan, Taiwan and China). Considering costing under the global 22.5 mg dosing would have less relevance and increase costs in the comparator arm. However, given the dose differences there remains potential uncertainty regarding efficacy differences between these two doses.

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

## 7. Conclusion

After considering all the available evidence, the Committee accepted relugolix for use in NHSScotland.

## 8. Guidelines and Protocols

The European Association of Urology (EAU), the European Association of Nuclear Medicine (EANM), the European Society for Radiotherapy & Oncology (ESTRO), the European Society of Urogenital Radiology (ESUR), the International Society of Urological Pathology (ISUP) and the International Society of Geriatric Oncology (SIOG) published guidelines on prostate cancer in April 2024.[6]

The National Institute for Health and Care Excellence (NICE) published guideline 131: Prostate cancer: diagnosis and management in May 2019 and this was updated in December 2021.[4]

The European Society for Medical Oncology (ESMO) published: Prostate cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up in June 2020.[5]

# 9. Additional Information

## 9.1. Product availability date

January 2023

**Table 9.1 List price of medicine under review**

| Medicine | Dose regimen | Cost per year (£) |
|---|---|---|
| **relugolix** | **120 mg orally daily (following 360 mg loading dose)** | **Year 1: £1,067**<br>**Year 2 onwards: £1,061** |

*Costs from eMC Dictionary of Medicines and Devices Browser on 15 July 2024. Costs do not take any patient access schemes into consideration.*

# 10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 4,772 patients eligible for treatment with relugolix in year 1 and 5,011 patients by year 5 in each year.

The estimated uptake rate was 10% in year 1 and 25% in year 5 with a discontinuation rate of 0% applied each year. This resulted in 477 patients estimated to receive treatment in year 1 rising to 1,253 patients in year 5.

The gross medicines budget impact was estimated to be £508k in year 1 rising to £1m in year 5. As other medicines were assumed to be displaced the net medicines budget impact was estimated to be £16k in year 1 falling to £5k in year 5. The uptake rate is uncertain and may be underestimated based on SMC clinical experts' responses.

These estimates do not take account of any patient access schemes applied to displaced medicines.

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This assessment is based on data submitted by the applicant company up to and including 16 August 2024.

**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:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

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.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the

operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

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.