National Institute for Health and Care Excellence

Health Technology Evaluation

Relugolix for treating hormone-sensitive prostate cancer [ID6187]

Response to stakeholder organisation comments on the draft remit and draft scope

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Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness of an evaluation and proposed evaluation route	Tackle Prostate Cancer	This appraisal for an oral form of hormone therapy (ADT) is certainly appropriate to many patients already on injection treatment but finding this difficult. There is no oral form of ADT currently available in the UK. The single technology appraisal route is appropriate for this evaluation. There is only one technology involved: that of ADT for hormone sensitive prostate cancer. As I understand it the marketing authorization for Relugolix is 'for the treatment of adult patients with hormone sensitive prostate cancer'. This would appear to be a broad authorization with no specific inclusions or exclusions.	Thank you for your comment. No action required.
	Prostate Cancer UK	Prostate cancer UK welcomes the development of alternative hormone therapies for use within the metastatic hormone sensitive setting. We believe there is a need for further detail about how this treatment will be used, for example, will it be used with Novel Hormone Agents (NHAs) or as a monotherapy? In this indication most patients will either have docetaxel plus	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
		ADT or an NHA plus ADT. Patients who are particularly unwell or have many co-morbidities will be given ADT monotherapy. We believe that the single technology appraisal route is appropriate in this instance.	
	Ipsen Ltd	N/A	No action needed.
	Accord	Relugolix represents the first oral gonadotrophin-releasing hormone (GnRH) antagonist for advanced hormone-sensitive prostate cancer. Gonadotrophin-releasing hormone is also known as luteinising hormone-releasing hormone (LHRH). Accord believes that relugolix is appropriate for appraisal via the proportionate approach, specifically using a cost comparison analysis, as outlined later in the response.	Thank you for your comment. A cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. The comparators in this case have NICE guidance in place only for patients with advanced hormone sensitive prostate cancer with spinal metastases, which is a

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			smaller population than the anticipated licensed population. Given that NICE is committed to appraising new technologies according to the licensed population, the criteria for a cost-comparison appraisal are not fully met. Refer to sections 4.2.18 to 4.2.21 of NICE's health technology evaluation manual for more information.
Wording	Tackle Prostate Cancer	No comment	No action needed.
	Prostate Cancer UK	We believe the wording is appropriate.	Thank you for your comment. No action required.
	Ipsen Ltd	N/A	No action needed.
	Accord	Accord considers that the proposed wording of the draft remit does not fully reflect the proposed indication. Accord recommends that the indication wording is revised to **"Advanced hormone-sensitive prostate cancer"** as	The population in the scope is kept broad. If the marketing authorisation is

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		per the approved indication. This approval followed a favourable opinion by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA; procedure EMEA/H/C/005353/0000 in February 2022) and by MHRA (PLGB 55917/0001 in June 2022.	narrower, the appraisal committee will consider that population in the appraisal. No action required.
Timing Issues	Tackle Prostate Cancer	There is no particular urgency for this evaluation to the NHS but for patients currently experiencing difficulties with other forms of ADT a swift decision would be appreciated.	Thank you for your comment. No action required.
	Prostate Cancer UK	The timing of this appraisal appears appropriate.	Thank you for your comment. No action required.
	Ipsen Ltd	N/A	No action needed.
	Accord	- Current standard of care with GnRH agonists has known limitations, including requirement for subcutaneous administration, an initial surge in testosterone with risk of clinical flare, increased risk of cardiovascular events, and slow recovery of testosterone after discontinuation of treatment. There have also been reports of medication errors (MEs) leading to lack of efficacy (LoE) associated with leuprorelin-containing depot medicinal products, albeit with different reporting rates per formulation (European Medicines Agency,EMA/397961/2020) (European Medicines Agency 2020). - The only other GnRH antagonist, degarelix, is associated with a high frequency of injection site reactions (Klotz et al. 2008). In England, it is also limited to patients with spinal metastases (TA404) (National Institute for Health and Care Excellence 2016). Relugolix would have lower resource use than its comparators which all require subcutaneous administration by a nurse, whereas relugolix is orally	Thank you for your comment. No action required.

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		administered. Therefore, relugolix fulfils an unmet need for an improved, oral treatment option for advanced hormone-sensitive prostate cancer, that can be delivered in a timely manner.	
Additional comments on the draft remit	Tackle Prostate Cancer	No comments	No action needed.
	Prostate Cancer UK	No comments	No action needed.
	Ipsen Ltd	The final title of this appraisal does not specify the population defined by the license, i.e. for “advanced hormone-sensitive” prostate cancer patients.	The population in the scope is kept broad. If the marketing authorisation is narrower, the appraisal committee will consider that population in the appraisal. No action required.
	Accord	None.	No action needed.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Tackle Prostate Cancer	This is helpful and accurate	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Prostate Cancer UK	No comments	No action needed.
	Ipsen Ltd	N/A	No action needed.
	Accord	No comments	No action needed.
Population	Tackle Prostate Cancer	It is appropriate to offer this new formulation of ADT to all patients for whom ADT therapy is appropriate. It may enable patients to have a choice of therapies that are equally effective as treatments for prostate cancer but can be given by the orally rather than by subcutaneous injection.	Thank you for your comment. No action required.
	Prostate Cancer UK	We consider the defined population appropriate However, we have some questions about the population chosen: • 90% of men from the HERO trial had cardiovascular (CV) risk factors. Can those with and without CV effects equally benefit/is there anything about the overall health of these patients that would warrant further investigation or analysis? Data by Gleason score may be helpful here. • Also, is relugolix particularly useful for patients with CV problems and how can this potential benefit be examined in context of usefulness for men over vs under 75? • Patient selection included patients who had been on ADT for a year; does this risk exaggerating the effect of relugolix in individuals with stable disease, relative to those cancers that quickly spread? • Around 71% of patients in both trial arms were under 75, and therefore differences (benefits) seen from use of relugolix apply to this age group, Therefore, it would be good to know what percentage of people should be expected to benefit from this drug after working out average age of patients with advanced disease.	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	Ipsen Ltd	As mentioned above, the population should reflect the license and be updated to “people with advanced hormone-sensitive prostate cancer”.	The population in the scope is kept broad. If the marketing authorisation is narrower, the appraisal committee will consider that population in the appraisal. No action required.
	Accord	Consistent with our comments on the remit, the population of interest should be amended **to “People with advanced hormone-sensitive prostate cancer”**	The population in the scope is kept broad. If the marketing authorisation is narrower, the appraisal committee will consider that population in the appraisal. No action required.
Subgroups	Tackle Prostate Cancer	From the patient’s perspective I suggest there are three main potential subgroups: • Patients already established on long term ADT injections but for whom an oral therapy would be a more preferable route of administration. Such patients may also have added treatments such as novel hormonal agents. In such patients the ADT usage would represent the use of an equally effective ADT in a formulation more acceptable to the patient or clinician. • Patients newly diagnosed with aggressive prostate cancer for whom ADT will be a single and long term therapy until such time as ADT becomes less effective.	Thank you for your comment. Some potential subgroups have been added to the final scope.

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		• Patients newly diagnosed with aggressive prostate cancer for whom surgery or radiotherapy maybe appropriate but in whom added ADT is deemed clinically necessary before during and after that radical therapy. Such patients may only need ADT for a relatively short period of time (often up to two years) after which ADT is discontinued. These patients are often in a younger age group and for whom a rapid return of testosterone levels after cessation of ADT is highly desirable.	
	Prostate Cancer UK	n/a	No action needed.
	Ipsen Ltd	N/A	No action needed.
	Accord	The current licence covers several advanced prostate cancer subgroups (locally advanced, metastatic and biochemical recurrence). Subgroup analysis of the HERO study indicated that the primary endpoint of testosterone suppression (sustained castration rate) did not vary by subgroup (Shore et al. 2020). Therefore, relugolix is not anticipated to differ in its clinical or cost effectiveness in any subgroup within the proposed population.	Thank you for your comment. No action required.
Comparators	Tackle Prostate Cancer	The major comparator has to be that of formulations of ADT in current usage. It is my understanding that the current major forms of ADT already approved by NICE (GnRH agonists, GnRH antagonists) are equally effective. The Important factor here is whether Relugolix is equally effective as the injectable alternatives. The HERO trial suggests that Relugolix is as equally effective and possibly more effective than the comparator used: i.e. injectable leuprolide. Previous NICE appraisals relating to combinations of ADT and a second agent such as chemotherapy or novel hormonal agents did not specify the drug used for ADT in relevant trials. I must therefore assume that NICE also believe that all current formulations of ADT used are equally effective.	Thank you for your comment. Combination treatments have been removed from the comparator list in the final scope.

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		It would seem irrelevant and inappropriate to try and compare monotherapy with Relugolix with combination therapies - one is not comparing like with like.	
	Prostate Cancer UK	We consider the comparators to be sufficient. However, we feel it should be noted that degarelix should be the main comparator in this instance as it is the only other commercially available GnRH antagonist. We believe relugolix will fit into the same parts of the pathway. We would also ask for more data in comparison to degarelix efficacy, the HERO trial only looked at it in comparison with leuprolide.	Thank you for your comment. The comparators in the final scope have been updated. The appraisal committee will discuss the current treatment pathway during the development of this appraisal.
	Ipsen Ltd	Ipsen would question the inclusion of the docetaxel/apalutamide/enzalutamide/darolutamide as comparators.	Thank you for your comment. These treatments have been removed from the comparator list.
	Accord	Below we outline the appropriateness of each group of comparators listed in the draft scope. **Androgen Deprivation Therapies (ADTs)** As described in the background section of the scope, androgen deprivation therapy (ADT) is the foundation therapy for the treatment of advanced hormone-sensitive prostate cancer. Accord would like to highlight that when there is progression, ADT remains the backbone treatment to which other treatment options may be added.	Thank you for your comment. Combination treatments and bicalutamide have been removed from the comparator list in the final scope. Thank you for your comment. A cost-

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		Relugolix is the only oral option for use within the ADT backbone. 1. GnRH agonists, such as leuprolide, goserelin, triptorelin, are the most established and commonly used ADTs, and as such are appropriate comparators. They are considered clinically equivalent, and are all used for people with advanced hormone-sensitive prostate cancer. 2. Degarelix is only a comparator within the subgroup of people with spinal metastases (TA404). As Accord wishes to pursue a cost comparison route, our assumption is that if relugolix is cost-effective/cost saving vs. the GnRH analogues then it will also be cost-effective/cost saving against degarelix in the spinal metastases subgroup (National Institute for Health and Care Excellence 2016). 3. Orchidectomy is not a relevant comparator as it is offered to a clinically distinct subgroup, that is, people with metastatic prostate cancer as an alternative to continuous GnRH agonists. However, orchidectomy is rarely used in clinical practice within the NHS (NICE technology appraisal 721). **Monotherapy with bicalutamide** Bicalutamide monotherapy is not considered a relevant comparator as it is limited to a small subgroup of patients for whom preservation of sexual function is important and those who are willing to accept the adverse effects of treatment, such as reduced overall survival and liver problems. Exclusion of bicalutamide as a comparator was accepted by committee in the degarelix appraisal TA404. **Therapies used in combination with androgen deprivation therapy** Combination therapies listed in the scope (e.g. docetaxel, apalutamide, enzalutamide, darolutamide) are not relevant comparators for relugolix as each option is for use in combination with ADT. The NICE Clinical Guideline for Prostate Cancer: diagnosis and management (NG131) does not	comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. The comparators in this case have NICE guidance in place only for patients with advanced hormone sensitive prostate cancer with spinal metastases, which is a smaller population than the anticipated licensed population. Given that NICE is committed to appraising new technologies according to the licensed population, the criteria for a cost-comparison appraisal are not fully met. Refer to sections

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		differentiate between different forms of ADT for prostate cancer and any ADT can be used as monotherapy or in combination. Relugolix could replace other ADTs within these combinations.	4.2.18 to 4.2.21 of NICE's health technology evaluation manual for more information.
Outcomes	Tackle Prostate Cancer	These seem acceptable. Patient preference for choice of an oral therapy over the potential disadvantages of an injectable therapy are important quality of life issues that should be considered.	Thank you for your comment. No action required.
	Prostate Cancer UK	We believe the outcomes listed to be appropriate and will capture the most important health benefits. We would welcome clinical guidance on whether testosterone suppression is a suitable surrogate for progression free or overall survival in this instance.	Thank you for your comment. No action required.
	Ipsen Ltd	N/A	No action needed.
	Accord	The majority of outcomes listed in the scope are appropriate. In addition to those listed, major cardiovascular events (MACE) should be considered an outcome of interest due to the risks of cardiovascular side effects in men commencing ADT. Men with prostate cancer have a higher risk of cardiovascular (CV) and thromboembolic events and this risk increases with the use of GnRH receptor agonists (Crawford et al. 2017; Keating et al. 2010; Plummer et al. 2017). There is also evidence that the risk of major CV events is higher in men treated with GnRH agonists compared with GnRH antagonists or bilateral orchidectomy (Bosco et al. 2015; Gandaglia et al. 2014), particularly in men with pre-existing cardiovascular disease (Levine et al. 2010; Margel et al. 2019). In support of these findings, results (pre-specified safety analysis) from the HERO trial showed the incidence of (MACE) was 2.9% (95%CI: 1.7-4.5) in	The outcomes listed within the scope are not intended to be exhaustive. Data on additional outcomes, including major cardiovascular events and testosterone recovery can be included within the appraisal submission.

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		the relugolix group and 6.2% (95%CI: 3.8-9.5) in the leuprolide group. Relugolix achieved a 54% lower risk of MACE than leuprolide (hazard ratio, 0.46; 95% CI, 0.24 to 0.88) (Shore et al. 2020). Additionally, testosterone recovery could be considered an outcome of interest as current ADT options are only available as injectable depot formulations, with testosterone suppression persisting months (up to two years) following discontinuation of treatment, prolonging safety concerns and symptoms associated with therapy (Nascimento et al. 2019). Testosterone deficiency is associated with metabolically adverse changes in body composition, increased insulin resistance, impaired bone health and hypogonadal symptoms, this inability to stop treatment rapidly with depot formulations is a major disadvantage.	
Equality	Tackle Prostate Cancer	No comment	No action needed.
	Prostate Cancer UK	We consider the draft remit to be sufficient with regards to the equality aims. This drug may be beneficial for those who have co-morbidities, would have long distances to travel for injection (as with the administration of leuprolide), or disability, compared to other options. However, Black men are not represented in the trial as patient subgroups are only broken down by North and South America, Europe and Asia Pacific rather than by ethnicity. Baseline risk for Black men with cardiovascular risk factors and diagnosis of advanced prostate cancer may lead to different outcomes.	Thank you for your comment. No action required.
	Ipsen Ltd	N/A	No action needed.

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	Accord	Accord does not believe that there are equality considerations that are likely to impact the recommendations and their appropriateness.	Thank you for your comment. No action required.
Other considerations	Tackle Prostate Cancer	Where many similar drug treatments are available with equal effect on a disease process, patient preference, availability of treatment and ease of treatment are important factors. Cost is always an important consideration and a cost comparison study will need to be undertaken.	Thank you for your comment. It has been decided this topic will be routed as a single technology appraisal. A cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. The comparators in this case have NICE guidance in place only for patients with advanced hormone sensitive prostate cancer with spinal metastases, which is a smaller population than the anticipated licensed

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			population. Given that NICE is committed to appraising new technologies according to the licensed population, the criteria for a cost-comparison appraisal are not fully met. Refer to sections 4.2.18 to 4.2.21 of NICE's health technology evaluation manual for more information.
	Prostate Cancer UK	It should be considered that hormone therapies are also used across the pathway in combination with radiotherapy for non-metastatic disease as well.	Thank you for your comment. No action required.
	Ipsen Ltd	N/A	No action needed.
	Accord	Not applicable.	No action needed.
Questions for consultation	Tackle Prostate Cancer	No comments	No action needed.
	Prostate Cancer UK	n/a	No action needed.
	Ipsen Ltd	N/A	No action needed.

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	Accord	**Question 1: Where do you consider relugolix will fit into the existing care pathway for hormone-sensitive prostate cancer?** As described earlier in the document, relugolix is indicated for the treatment of advanced hormone-sensitive prostate cancer and therefore would be considered by clinicians as an alternative to other ADTs, such as GnRH agonists and antagonists, including leuprolide, goserelin, triptorelin and degarelix.	Thank you for your comment. No action required.
		Question 2: Do you expect relugolix to be used as an alternative to other androgen deprivation therapies? Would it also be used in combination with nonsteroidal androgen receptor antagonist such as apalutamide, enzalutamide and/or darolutamide? Relugolix is expected to be used as an alternative to GnRH agonists and antagonists, such as leuprolide, goserelin, triptorelin and degarelix. It will be an additional option within the ADT range where the others are all injectable. As mentioned, relugolix could also be used in combination with nonsteroidal androgen receptor antagonists such as apalutamide, enzalutamide, or darolutamide at the discretion of the prescribing clinician, as all the combinations are used with an unspecified ADT.	Thank you for your comment. No action required.
		Question 3: Are the outcomes listed in the scope appropriate? As described in the outcomes section of this response, the outcomes listed are appropriate, with the addition of MACE and testosterone recovery as additional outcomes of interest.	Thank you for your comment. No action required.
		Question 4: Do you consider relugolix to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?	Thank you for your comment. No action required.

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		As mentioned previously, ADT is recommended for the treatment of patients with advanced hormone-sensitive prostate cancer. However, there are known issues with current ADTs, and the unmet needs of current treatments are as follows: - There have been reports of medication errors (MEs) leading to lack of efficacy (LoE) associated with leuprorelin-containing depot medicinal products, albeit with different reporting rates per formulation (European Medicines Agency,EMA/397961/2020) (European Medicines Agency 2020). - Available ADTs for advanced prostate cancer are injectables which require NHS nurse administration in primary and/or secondary care settings. - The associated injection-site adverse events can lead to treatment discontinuation (Crawford et al. 2019). - Testosterone surge, along with the consequent disease flare, is a complication of treatment initiation with an GnRH agonist for prostate cancer (Pokuri et al. 2015). - Lowering the risk and rate of MACE in people with advanced prostate cancer treated with ADT is an important clinical and economic unmet need (Berger et al. 2019; Leong et al. 2020). - Patients can wait for months to recover testosterone upon treatment discontinuation (Bong et al. 2008; Crawford et al. 2019; Dearnaley et al. 2020). Despite these limitations, the majority of patients are treated with a GnRH agonist, as the alternative, degarelix, is restricted to use in a smaller subgroup of patients with spinal metastases (NICE TA 404). Relugolix can address these needs in the following ways:	

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		Oral administration Relugolix is a once daily oral treatment option, which eliminates the need for NHS nurse administration and associated injection-site reaction and pain of currently available ADTs (Crawford et al. 2019). **Testosterone surge** Relugolix is a GnRH antagonist that leads to a rapid reduction of testosterone levels upon initiation of treatment, by blocking the production of follicle stimulating hormone (FSH), luteinising hormone (LH), then testosterone. In contrast to GnRH agonists, relugolix is not associated with initial testosterone surge that can result in bone pain, urinary issues, spinal cord compression, and tumour progression in patients (Rosario et al. 2016). Use of relugolix, therefore, does not require bicalutamide administration within the first 4-weeks to counteract the surge associated with the agonists. **Risk and rate of MACE** As stated previously, relugolix has a comparable safety profile to leuprolide, but with a lower risk of MACE (secondary endpoint). Relugolix achieved a 54% lower risk of MACE versus leuprolide (hazard ratio, 0.46; 95% CI, 0.24 to 0.88) (Shore et al. 2020) with an incidence of 2.9% (n=18/622; 95%CI: 1.7-4.5) in the relugolix group and 6.2% (n=19/308; 95%CI: 3.8-9.5) in the leuprolide group Shore, 2020 #97}. **Testosterone recovery** Relugolix results in rapid testosterone recovery after treatment has ceased, helping to relieve the burden of extended testosterone deprivation on patients (such as loss of bone mineral density, cognitive dysfunction, and loss of sexual function) (Nascimento et al. 2019).	

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		Question 5: Do you consider that the use of relugolix can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation? **Please identify the nature of the data which you understand to be available to enable the committee to take account of these benefits.** No **Question 6: NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:** • **could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which the treatment will be licensed;** • **could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;** • **could have any adverse impact on people with a particular disability or disabilities.** **Please tell us what evidence should be obtained to enable the committee to identify and consider such impacts.?**	Thank you for your comment. No action required. Thank you for your comment. No action required.

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		Accord does not believe that there are equality considerations that are likely to impact the recommendations and their appropriateness. **Question 7: Would it be appropriate to use the cost-comparison methodology for this topic?** Accord believes it would be appropriate to use cost comparison methodology for this topic as there is direct and indirect evidence available demonstrates comparable efficacy and safety of relugolix relative to other ADTs (See Q 8). As mentioned previously, the appropriate comparators for relugolix are ADTs, and in particular the GnRH agonists and degarelix. Both of these comparators were appraised by NICE in advanced hormone-sensitive prostate cancer in TA404. The NICE Clinical Guideline for Prostate Cancer: diagnosis and management (NG131) as well as International guidelines such as ESMO and EAU do not differentiate between different forms of ADT for prostate cancer. Relugolix is similar in its clinical efficacy to leuprolide, as discussed in Question 8 below. In addition, Accord is committed to working with NHS England and NICE to ensure a similar cost to currently recommended technologies. In summary, there is a strong case that relugolix "is likely to provide similar or greater health benefits at similar or lower cost than technologies already recommended in technology appraisal guidance and used in clinical practice."	Thank you for your comment. A cost-comparison case can be made if a health technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication. The comparators in this case have NICE guidance in place only for patients with advanced hormone sensitive prostate cancer with spinal metastases, which is a

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			smaller population than the anticipated licensed population. Given that NICE is committed to appraising new technologies according to the licensed population, the criteria for a cost-comparison appraisal are not fully met. Refer to sections 4.2.18 to 4.2.21 of NICE's health technology evaluation manual for more information.
		Question 8: Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators? The efficacy and safety for relugolix has been demonstrated in the phase 3 HERO trial in men with advanced prostate cancer requiring at least 1 year of continuous ADT (Shore et al. 2020). Evidence from the HERO trial demonstrated non-inferiority of relugolix compared to leuprolide as assessed by the cumulative probability of sustained testosterone suppression (sustained castration rate). The proportion of patients who achieved	Thank you for your comment. No action required.

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		sustained testosterone suppression was 96.7% (95% CI, 94.9-97.9) in the relugolix treatment group compared with 88.8% (95% CI, 84.6-91.8) in the leuprolide group. The difference in the EMA primary endpoint result between the relugolix and leuprolide arms (7.9%; 95% CI, 4.1-11.8), was greater than the noninferiority margin of −10 percentage points and greater than the superiority threshold of zero percentage points, demonstrating both noninferiority and statistical superiority to leuprolide, respectively (Shore et al. 2020). In support of the clinical comparison of relugolix with GnRH agonists, NICE acknowledged in TA404 that it is plausible to assume equivalent clinical efficacy between GnRH agonists. Degarelix is a relevant comparator within the subgroup of patients with spinal metastases. Relugolix was shown to be clinically equivalent to degarelix (and other ADTs) in a published network meta-analysis (NMA) by Motlagh et al, (Sari Motlagh et al. 2022). In a cost-comparison approach, we would anticipate that if relugolix were cost neutral or saving vs. GnRH agonists then it would be cost-saving vs. degarelix. Relugolix would have lower resource use than its comparators, which all require subcutaneous administration by a nurse, whereas relugolix is orally administered. **Question 9: Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?** Yes, cumulative probability of sustained testosterone suppression (sustained castration rate) is considered clinically relevant in this setting. **Question 10: Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?**	Thank you for your comment. No action required.

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		No, we are not aware	Thank you for your comment. No action required.
Additional comments on the draft scope	Tackle Prostate Cancer	Relugolix is the first oral formulation of an effective ADT for use in prostate cancer. As such this could therefore be described as a 'step change' in current treatments. In addition to the convenience of being an oral therapy the HERO trial would suggest it has a faster onset of reduction in testosterone levels at the beginning of therapy and this is reflected as a faster recovery off testosterone levels at cessation of treatment. This may be a strong factor in choice of treatment for younger men for whom only a short period of ADT is indicated. Early and more reliable return of testosterone levels and thus potential sexual function etc could be an important factor in decision making by this group. There are also potential advantages with Relugolix related to potential adverse events involving the cardiovascular system.	Thank you for your comment. No action required.
	Prostate Cancer UK	Potential benefits: • Less clinical time needed as relugolix is in tablet form rather than injection (compared to leuprolide use in the HERO trial which requires injections every 3 months). Treatment adherence with oral relugolix was more than 99% in the trial. • Uptake may increase in patients already on ADT due to lack of travel required, time off work etc. This is a particular benefit to those unwell with other co-morbidities, disabled, unable to travel, live far away, etc. • 54% lower risk of major adverse cardiovascular events in comparison to leuprolide	Thank you for your comment. No action required.

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		• Relugolix achieved a superior suppression of testosterone levels to that of leuprolide Potential disadvantages: • As an oral application, this can be taken at home daily; there may be a potential issue with regards to compliance to this medication regimen compared to less regular injection, in real world setting. However, it's important to note that in trial context, there was no difference in treatment adherence observed when using oral therapy vs injectable leuprolide.	
	Ipsen Ltd	N/A	No action needed.
	Accord	No comments	No action needed.

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

- Astellas