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7 June 2022

Dear xxxxxxxxxxxxxxxxxx

**Re: Final Appraisal Document — Relugolix–estradiol–norethisterone acetate for treating moderate to severe symptoms of uterine fibroids [ID3842]**

Thank you for your letter of 23 May 2022, lodging an appeal against the above Final Appraisal Document (FAD). I refer in this letter to relugolix–estradiol–norethisterone acetate as “Relugolix”.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

* 1(a) NICE has failed to act fairly, or
* 1(b) NICE has exceeded powers;
* (2) the recommendation is unreasonable in the light of the evidence submitted to NICE.

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I will make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

I assess each of your points in turn. For the purposes of this letter and efficient management of the appeal I have identified and numbered what I understand to be your individual appeal points below, bearing in mind the requirements under NICE’s Guide to the technology appraisal and highly specialised technologies appeal process [[PMG18]](https://www.nice.org.uk/process/pmg18/chapter/making-an-appeal#what-must-the-appeal-letter-contain) (the “**appeals process guide**”) that each appeal point be numbered and a 1‑sentence description provided.

Before considering each of your appeal points I set out two preliminary matters of clarification.

First, the recommendation of Relugolix in the draft FAD is not a disinvestment decision in respect of any other treatment option for moderate to severe symptoms of uterine fibroids. The committee recognised that in clinical practice, treatment is determined based on factors including patient preferred treatment choice and noted that treatment for symptomatic uterine fibroids is generally aligned with NICE guideline [[NG88]](https://www.nice.org.uk/guidance/NG88) on assessment and management of heavy menstrual bleeding. This guideline is explicit about the importance of patient preference. As you will know, the NICE guideline supports a range of surgical and non-surgical treatment options for patients with fibroids of 3 cm or more in diameter (who are likely to be those patients for whom this FAD is relevant) (see recommendations 1.5.7 to 1.5.17) and includes uterine artery embolisation (“UAE”) and surgical procedures as first-line treatment options (given that “*pharmacological treatment is not always the best option for fibroids that are substantially greater than 3 cm in diameter because of their physical effect on the uterine cavity*” and “*some women may prefer not to have pharmacological treatment”*).

Patient preference is therefore preserved in the NICE guideline, and the draft FAD on Relugolix does not undermine this.

Rather, the legal effect of a recommendation for use of Relugolix ‘as an option’ within the terms of the FAD is set out at paragraph 4.3 of the FAD. In short, there would be a duty on commissioners to comply with the FAD meaning that, where deemed appropriate by the clinician and agreed by the patient, treatment with Relugolix could not be denied solely for lack of funding.

What the FAD does not mean is that commissioners should refuse funding for other effective treatments. The role of technology appraisal guidance (as set out in the FAD) is to make available new choices for patients and to broaden rather than narrow the range of treatment options available.

Secondly, I note that the aspects of the final draft guidance you appeal against are primarily contained in the statement (at paragraphs 1 and 3.12 of the draft FAD) that “there are likely additional benefits” of Relugolix not captured in the economic model, including that it “is an effective non-surgical treatment”, “can be used long term, which could mean improved and sustained symptom relief” and “preserves the uterus and ferity”. In light of this non-exhaustive list of “likely additional benefits” not captured in the economic model, the committee concluded that the economic model likely underestimates the utility values informing the QALY gains. While this was relevant for the committee’s recommendation, it is important to understand that the committee’s discussion of these factors was an economic conversation regarding the limitations of the economic model and was in that sense distinct from its evaluation of the clinical trials and expert clinical and patient evidence. I have this specific context in mind when considering the validity of your appeal points.

***Ground 2:******the recommendation is unreasonable in the light of the evidence submitted to NICE***

***Appeal point 2.1: Efficacy***

Your appeal letter groups your points under the headings of Efficacy and Safety.

With regard to Efficacy, you state as follows:

*“2.1 Efficacy*

*The NICE appraisal document states – Relugolix “*is an effective non-surgical treatment*”. There was no evidence submitted or considered that it is as effective as hospital treatment for symptomatic fibroids e.g. uterine artery/fibroid embolisation [UAE/UFE], myomectomy, hysterectomy, MR guided focused ultrasound and endometrial ablation for fibroids <3cm, which are proven long-term treatments for symptomatic fibroids. (Both hysterectomy and myomectomy have never been formally reviewed for safety or efficacy and there is a paucity of evidence on morbidity and mortality for myomectomy.)*

*There is serious concern that women will be denied access to these effective hospital treatments by CCGs/ICSs as this medicine is so much cheaper.*

*The only clinical evidence submitted was for treatment duration of 1 year, so efficacy beyond this is not established.*

*As per FEmISA’s submission, fibroids cause a large number of symptoms and the medicine has only been shown to be effective at reducing some symptoms for the maximum of 1 year.*

*There were no comparative studies between Relugolix and other GNRH agonists, even though superiority was claimed that side-effects were fewer and less severe.*

*GNRH agonists should not be administered to women immediately before UAE/UFE, as the reduced blood supply to the fibroids compromises the outcome.”*

I refer to this appeal point relating to efficacy as point 2.1. I address your points as appeal points 2.1(a)-2.1(e) below.

***2.1(a)* The recommendation is unreasonable because *“the NICE appraisal document states Relugolix ‘is an effective non-surgical treatment’* [and] *there was no evidence submitted or considered that it is as effective as hospital treatment for symptomatic fibroids... There is serious concern that women will be denied access to these effective hospital treatments by CCGs/ICSs as this medicine is so much cheaper.”***

I do not regard this as a valid appeal point. That is because a vital aspect in any appraisal is identifying the appropriate comparator (drawing on current NHS clinical practice or management as assessed in accordance with NICE’s processes) against which the relevant technology will be assessed. The project documents available on NICE’s website show that the question of most appropriate comparator for the purposes of the appraisal was analysed and resolved in the usual way in this appraisal. Options were discussed in the draft scope on which NICE invited comment and on which there was opportunity to comment throughout. Neither the draft scope as consulted on nor the final scope included the “hospital treatments” listed in your appeal as potential comparators. Therefore it was not for the committee to consider these treatments.

Following the committee’s consideration of the comparators within scope and conclusion that GnRH agonists were the most appropriate comparator, it was appropriate for the committee to consider the effectiveness of Relugolix against that of GnRH agonists. There was no requirement for the committee to assess effectiveness against the hospital treatments that you list.

In light of the above, I am not persuaded that the absence of evidence that Relugolix is as effective as the treatments you list could have any bearing on the committee’s conclusions or support an argument of unreasonableness. I am not minded to refer this point to an appeal panel.

With regard to your comment that there is serious concern that women will be denied access to these effective hospital treatments by CCGs/ICSs as Relugolix is so much cheaper, I refer to my preliminary points at the top of this letter which I trust clarify the legal effect and intention of the FAD in broadening (not restricting) treatment options available.

***2.1(b)* The recommendation is unreasonable because *“the only clinical evidence submitted was for treatment duration of 1 year”***

Under this appeal point I consider all of your concerns arising from the duration of treatment in the clinical evidence, namely: (1) that “the only clinical evidence submitted was for treatment duration of 1 year so efficacy beyond this is not established*”*;(2) your related complaint (under your heading “Safety”) against the committee’s statement that a likely additional benefit of Relugolix is that it “can be used long term, which could mean improved and sustained symptom relief”; and (3) your statement that “safety beyond 12 months has not been established and other GNRH agonists can normally only be given for a maximum duration of 6 months”.

On careful consideration, I do not regard these arguments as constituting a valid appeal point.

I note the committee considered clinical trial data covering treatment periods of varying length, from relatively short treatment periods in the LIBERTY 1 and LIBERTY 2 trials to 52 weeks / 1 year in the long term extension study LIBERTY 3 and 104 weeks / 2 years in the ongoing LIBERTY withdrawal study.

I am satisfied from the committee papers and the FAD that the committee understood the duration of treatment relevant to the trial data presented to it and had this in mind when assessing clinical effectiveness of Relugolix and concluding that Relugolix is likely to be equally as effective as GnRH agonists.

The comment that Relugolix “can be used long term” does not cast doubt on the recommendations. That is because the committee’s use of the term “long term” must be understood by reference to the clinical context and currently available treatment options in the care pathway where Relugolix is positioned. In this regard the committee discussed three classes of drug in particular:

1. GnRH antagonists (such as Relugolix);
2. GnRH agonists (such as Goserelin acetate); and
3. Ulipristal acetate, a selective progesterone receptor modulator.

As you will know, GnRH antagonists and GnRH agonists fall within the umbrella term “GnHR analogues” but work by different, distinct mechanisms of action. As set out in the FAD, the license for GnRH agonists in the indications relevant to this appraisal is for a limited treatment duration (< 6 months). This restriction is imposed by a licensing decision relating to the risk/benefit arising from the distinct mechanism of action of GnHR agonists. Ulipristal acetate, a selective progesterone receptor modulator, is a different class of drug again, which is only licensed for intermittent treatment when uterine fibroid embolisation or surgery are unsuitable or unsuccessful. It is in light of these restrictions on comparator licenses, as determined by the MHRA (not NICE) that paragraph 3.1 of the FAD notes “there are limited long-term treatment options”.

By contrast, the SmPC for Relugolix does not provide a maximum duration of therapy. Therefore it is accurate to note that Relugolix “can be used long term”. I see no potential unreasonableness arising from the committee considering this was a likely additional benefit not captured in the economic model.

For the above reasons I am not minded to refer this point to an appeal panel.

***2.1(c)* The recommendation is unreasonable because *“fibroids cause a large number of symptoms and the medicine has only been shown to be effective at reducing some symptoms for the maximum of 1 year”***

I do not regard this as a valid appeal point. See my response above in respect of the duration of treatment. With regard to the range of symptoms, paragraph 3.1 of the FAD shows that the committee were aware that there are a range of symptoms, noting that “Symptoms are broadly classed into prolonged and heavy menstrual bleeding, pelvic pain and pressure, and reproductive dysfunction”. Similarly paragraph 3.2 notes that the aim of treatment can vary and the committee papers show that the clinical trials studied a breadth of symptoms. (I note that while volume and percentage menstrual blood loss was a primary end point, the clinical trial data for Relugolix showed benefits in a range of secondary end points including pain, distress from bleeding and pelvic discomfort and anaemia and uterine volume.) Nonetheless, paragraph 3.2 of the FAD notes that the clinical experts explained that control of menstrual blood loss volume is a clinically important outcome because it reduces the risk of anaemia and improves quality of life. While the committee were aware of the range of symptoms, paragraph 3.6 of the FAD sets out why the committee concluded menstrual blood loss volume is a relevant outcome measure of treatment effectiveness.

In my view the FAD is well reasoned on this point and I am not persuaded that the committee’s conclusion could amount to unreasonableness. I am not minded to refer this point to an appeal panel.

***2.1(d)* The recommendation is unreasonable because *“there were no comparative studies between Relugolix and other GNRH agonists, even though superiority was claimed that side-effects were fewer and less severe”***

I do not regard this as a valid appeal point.

First, for the avoidance of doubt, it is important to clarify that Relugolix is not a GnRH agonist as potentially suggested by your letter. It is a GnRH antagonist and therefore acts in a different way and has a different profile of side effects from GnRH agonists.

The FAD shows that the committee understood that there was no evidence directly comparing Relugolix with the GnRH agonists. Paragraphs 3.5 and 3.7 of the FAD in particular explain how the committee compared Relugolix against GnRH agonists and the reasons why it concluded Relugolix is likely to be equally as effective as GnRH agonists.

In my view the FAD is again well reasoned on this point and I am not persuaded that the committee’s conclusion could amount to unreasonableness. I am not minded to refer this point to an appeal panel.

I am unsure what you mean by “superiority was claimed” or where you say it is stated that side-effects of Relugolix are fewer and less severe than those of GnRH agonists. I note the committee “cautiously accepted that the treatment effect for [Relugolix] was not any worse than for GnRH agonists” and that “[Relugolix] is likely to be as equally effective as GnRH agonists” (paragraph 3.7 of the FAD), so superiority was not claimed in that regard.

With regard to side effects, I have identified no statement that the side effects of Relugolix are fewer and less severe. Rather there is discussion of the side effects of various treatments, including GnRH agonists, and a detailed explanation of why the committee concluded Relugolix is generally well tolerated at paragraph 3.9.

In the absence of further details, I can see no basis for an argument that the recommendations in the FAD cannot reasonably be justified from the evidence presented to the committee. I am presently not minded to refer this point to an appeal panel.

***2.1(e)* The recommendation is unreasonable because *“GNRH agonists should not be administered to women immediately before UAE/UFE, as the reduced blood supply to the fibroids compromises the outcome.”***

I am unclear whether this is an appeal point but for the avoidance of doubt Relugolix is not a GnRH agonist. If you are referring to Relugolix then I note the above restriction is not included in the SmPC and clinical use and management in the treatment pathway would in any event be managed by clinicians. From the information in your appeal letter I am not currently satisfied that this is a valid appeal point.

**Appeal point 2.2: Safety**

With regard to Safety, your appeal letter states:

“*Safety* – “can be used long term, which could mean improved and sustained symptom relief” *The only clinical evidence on Relugolix submitted had a treatment duration of 1 year. The safety beyond 12 months has not been established. Other GNRH agonists can normally only be given for a maximum duration of 6 months.*

“preserves the uterus and fertility” *– There was no evidence submitted on the effect of Relugolix on fertility. It is unknown. There was also no mention that Afro-Caribbean women and other women with darker skins suffer from fibroids much younger than others and will require treatment at an early age, sometimes in their 20s and 30s. The effect of Relugolix on fertility is even more important to them than older women.*

*3.2. “*Treatment pathway and comparator*” – The information summary is incorrect. Women seek treatment from the symptoms of fibroids and they may also be a cause of infertility. The commonest symptom is heavy menstrual bleeding, but there are many other including severe pain. Anaemia can be the outcome of poor or inadequate management of heavy menstrual bleeding symptoms.*

*There are so many factual inaccuracies in this section that they are not all commented upon here, but this section needs rewriting. It appears that RCOG was not a stakeholder and did not have a gynaecologist on the committee reviewing the evidence. If this is the case it is a serious flaw and is possibly why the information is incorrect. RCGP also does not appear to be a stakeholder.*

*“3.3.* GnRH agonists are the most relevant comparators for relugolix–estradiol–norethisterone acetate” ……… “The ERG agreed that it was justifiable to exclude GnRH antagonists as comparators.” *– It is not clear why the ERG agreed and how it can be justified.”*

I refer to this appeal point as point 2.2. I address your points as appeal points 2.2(a)-2.2(d) below.

***2.2(a):* The recommendation is unreasonable because the FAD states that Relugolix *“can be used long term, which could mean improved and sustained symptom relief”***

I am not currently minded to refer this as a valid appeal point for the reasons in my response to appeal point 2.1(b) above.

***2.2(b):* The recommendation is unreasonable because the FAD states that Relugolix *“preserves the uterus and fertility”***

I understand your appeal point to be that it was unreasonable for the committee to state that a “likely additional benefit” of Relugolix not captured in the economic model is that it preserves the uterus and fertility, because there was no specific evidence submitted on the effect of Relugolix on fertility.

I do not regard this as a valid appeal point. That is because in reading the FAD and accompanying committee papers it is clear that the conversation around uterus and fertility preservation is framed by the negative and irreversible effect on the uterus and fertility of some surgical treatments such as hysterectomy. (See e.g. page 34 of Company Submission- “There are many reasons why women may wish to decline surgery, including the desire to preserve fertility...”). Comments around pharmacological treatments “preserving fertility” were clearly intended and should be taken in the context of fertility and surgical options as understood in the medical community.

Considering the committee’s comments in their context within the FAD as a whole I can see no arguable point that the recommendation is unreasonable in the light of the evidence submitted to NICE. I am not presently minded to refer this point to an appeal panel.

Given the above I consider your criticism that the FAD does not refer to the impact of treatments that negatively impact fertility on Afro-Caribbean women and other women with darker skins who may suffer from fibroids at a younger age, falls away.

***2.2(c)* The recommendation is unreasonable because *“RCOG was not a stakeholder and did not have a gynaecologist on the committee reviewing the evidence… RCGP also does not appear to be a stakeholder … the information summary is incorrect.”***

I do not regard your comments in respect of the above subheading as comprising a valid appeal point. That is because:

1. The Royal College of Obstetricians and Gynaecologists (RCOG) and the Royal College of General Practitioners (RCGP) were both included as formal consultees in the final stakeholder list for the appraisal. It is not within NICE’s powers to require them to comment;
2. The committee was constituted in line with NICE’s processes; and
3. Comments were provided from gynaecologists (see the committee papers).

In addition you allege that “*the information summary is incorrect. Women seek treatment from the symptoms of fibroids and they may also be a cause of infertility. The commonest symptom is heavy menstrual bleeding, but there are many other including severe pain. Anaemia can be the outcome of poor or inadequate management of heavy menstrual bleeding symptoms. There are so many factual inaccuracies in this section that they are not all commented upon here, but this section needs rewriting.”*

I note that you have submitted your appeal letter to NICE’s programme team as being your request for factual changes, and I have provided my initial views where you have pointed to specific aspects of the FAD that you consider inaccurate. I note that section 3.2 of the FAD you refer to relates to treatment pathway and comparator. However it seems to me that you have not specified any additional factual inaccuracies relating to the treatment pathway or comparator. Therefore, I cannot assess either their accuracy or whether any inaccuracies are sufficiently significant as to support an argument that they render the committee’s recommendation unreasonable.

***2.2(d)* The recommendation is unreasonable because it was unreasonable to conclude that *“GnRH agonists are the most relevant comparators for relugolix–estradiol–norethisterone acetate...The ERG agreed that it was justifiable to exclude GnRH antagonists as comparators.”***

I understand that you consider it was unreasonable for the committee to conclude that GnRH agonists are the most relevant comparators for Relugolix and that it is not clear why the ERG agreed that it was justifiable to exclude GnRH antagonists as comparators and how it can be justified.

On careful consideration, I do not regard this as a valid appeal point.

I acknowledge that the NICE final scope lists GnRH analogues as relevant comparators, which include both agonists and antagonists, so it was open to the committee to include GnRH antagonists as comparators. Paragraph 3.3 of the FAD shows the committee considered the potential comparators and explains the reasons why the committee concluded that GnRH agonists are the most relevant comparators for Relugolix in detail.

Within the appraisal, goserelin acetate (Zoladex) and ulipristal acetate (Esmya) were considered as separate classes of medicine to GnHR antagonists.

I note that the ERG questioned the company about this decision in the committee papers, and the company explained that “*Four GnRH antagonists have been identified as part of the SLR (relugolix, elagolix, linzagolix and cetrorelix). Among these four identified compounds, relugolix is the first and only GnRH antagonist with an approved licensed indication for UF in EU/UK. Elagolix is licensed for use in the USA but does not have an approval for use within Europe. Linzagolix is currently under review by the European regulatory authorities but, as of the time of this appraisal, does not have an approval for use in Europe. Cetrorelix is indicated and used for fertility purposes only. Therefore, in Gedeon Richter’s view, no other GnRH antagonists are relevant comparators for relugolix CT in this appraisal.”*

During the appraisal and consultation on the draft FAD no comments were raised by any patient or clinical expert or other consultee or commentator to suggest that GnRH antagonists are a significant current therapy routinely used in the NHS or any concern regarding an omission in the comparators.

In my view the FAD is well reasoned with regard to the comparator (see paragraph 2.2) there is nothing in your appeal point that persuaded me that the committee’s conclusion that the GnRH agonists are the most relevant comparators could amount to unreasonableness. I am not minded to refer this point to an appeal panel.

Conclusion

The above sets out above my initial views on all of your appeal points. I am not currently minded to refer your appeal to the Appeal Panel. There are no other appellants.

You are entitled to submit further clarification and/or evidence to me in relation to your appeal points within the next 10 working days, **no later than 21 June 2022**, and I will then give a final decision on the points (if any) to put before an appeal panel.

If your appeal letter and/or responses to scrutiny contain confidential information please ensure you have provided a version with this information redacted by 29 June 2022.

Yours sincerely

Dr Mark Chakravarty

Lead Non-executive Director for Appeals

National Institute for Health and Care Excellence