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28 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 email of 21 June 2022 responding to my initial scrutiny views. This is my final decision on initial scrutiny.

**General comment**

You allocated all of your appeal points to ground two in your appeal letter, but you did not number each of your appeal points. As explained in my initial scrutiny letter, I therefore identified and numbered your arguments as points 2.1(a)-(e) and 2.2(a)-(d). I also explained why I did not consider each one to be a valid appeal point and invited you to submit further clarification and/or evidence to me in relation to your appeal points. Having considered your further submissions, I set out my final decision in respect of each point below.

With regard to your list of FEmISA’s expected actions by NICE “to protect women with symptomatic fibroids expects”, I respond to each demand at the relevant points below. I can assure you that I have considered the points raised by FEmISA very carefully. With regard to the request that “NICE should show clearly the lack of any long-term safety and efficacy data and encourage all side effects and adverse events to be reported” I note, as I expect you know, that patient safety (including matters such as reporting of suspected side effects and adverse events) primarily rest with the MHRA.

***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 have considered your further comments in your email (under the heading “Patient Choice and CCG/ICS Violet Lists”) under this ground 2.1(a).

You say:

“CCGs and soon ICSs restrict patient access to effective NICE approved treatment by rationing and Violet Lists e.g. bariatric surgery, IVF and many treatment for women including hysterectomy.  In your letter you state -

*“ 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”*

How will NICE act to ensure that women are not given the cheaper Relugolix instead of effective long-term hospital treatment for symptomatic fibroids?”

Relatedly you appear to argue that NICE should state “That Relugolix–estradiol–norethisterone acetate is not an alternative to hospital treatments for fibroids i.e. UFE/UAE, hysterectomy, myomectomy, MRfUS, and there is no evidence that it is superior to any other treatment”.

I remain unpersuaded that point 2.1(a) is a valid appeal point, for the same reasons explained in my initial scrutiny letter. Having considered your further arguments, which I understand relate to hypothetical future restrictive commissioning policies and/or clinical decision-making in this area following publication of the FAD, I still see no arguable point under ground 2 that the recommendation is unreasonable in the light of the evidence submitted to NICE.

Nor can I see any arguable point under ground 1. NICE has no statutory remit or authority when carrying out an appraisal of one technology to “ensure” that clinicians recommend and/or commissioners fund other treatments for patients.

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

I have considered your further comments in your email (under the heading “Long-Term Use”) under this ground 2.1(b). You say:

“Nowhere in the SPC does it say that this medicine is  for ‘long-term use’ and the studies only show 24 week use in the SPC.   NICE does not define ‘long-term’ and this term is potentially misleading and imprecise. The SPC does not give an upper limit for use, as with many GNRH agonists of 6 months, but nor does it state anywhere it is suitable for long-term use.

In your letter you state – “*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.*”

This statement is very concerning and shows no regard for patient safety and a complete lack of understanding of medicines and pharmacology and the regulations.   Safety has to be proven not assumed.  It is astonishing that NICE thinks because no upper limit is given on the duration of use of a medicine that it is automatically acceptable to be used long-term and what does long-term mean?”

Relatedly, I note that you expect that NICE should:

“Remove the term – ‘long-term’ since i) the SPC and MHRA does not support this; ii) there is no clinical evidence on safety and efficacy long term; iii) that ‘long-term’ is not defined and as FEmISA has stated some women particularly with darker skins could need treatment for 20 years or more.  NICE is extending the medicine’s use outside the SPC without evidence or the powers to do so.”

On reflection I agree that this is a valid appeal point insofar as it relates to whether it was reasonable for the committee to conclude, based on the evidence submitted to it, that Relugolix “can be used long term” and whether this conclusion is either inaccurate or so unclear as to mean that the recommendation cannot reasonably be justified from the evidence that was presented to the Committee.

For the reasons explained in my initial scrutiny letter I do not agree that there is a valid appeal point that the Committee are prevented from considering “long term use” at all solely because the summary of product characteristics (“SmPC”) for Relugolix (which does not provide a maximum duration of therapy) does not state expressly that the technology “can be used long term”. Indeed it is not uncommon for the SmPC for a medicine that is used in clinical practice over a prolonged duration, including durations beyond those of the registration clinical trials, not to specifically state that the medicine is “suitable for long-term use”.

Put another way, I note that NICE does not normally make recommendations regarding the use of a drug outside the terms of its marketing authorisation, as published in the manufacturer's SmPC (see para 6.1.12 of the 2013 Methods Guide) and I consider there is no arguable point under ground 2 or otherwise that it has done so in this appraisal.

***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 have considered your further comments in your email (under the heading “Efficacy”) under this ground 2.1(c). You say:

“The studies do not show that the medicine is effective against all symptoms. It is clear from your comments that there is little understanding of the symptoms or effect on women.”

Relatedly, you say NICE “should make it clear that the efficacy to treat all symptoms has not been determined.”

I remain unpersuaded this is a valid appeal point under ground 2 for the reasons in my previous letter. I note that you have not provided further clarification and/or evidence to me in your response letter so there is nothing to which I can respond in final scrutiny.

***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 remain unpersuaded this is a valid appeal point under ground 2 for the reasons in my previous letter. I note that you have not provided further clarification and/or evidence to me in your response letter so there is nothing to which I can respond in final scrutiny.

***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 remain unpersuaded this is a valid appeal point under ground 2 for the reasons in my previous letter. I note that you have not provided further clarification and/or evidence to me in your response letter so there is nothing to which I can respond in final scrutiny.

***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 have considered your further comments in your email (under the heading “Safety and Efficacy”) under this ground 2.2(a). You say:

“Both the evidence in the 350 page dossier produced by NICE and the Summary of Product Characteristics (SPC) produced by MHRA only show safety and efficacy data for only 24  and in one study 52 weeks.  The SPC states –

“*Efficacy and safety over 24 weeks The efficacy and safety of Ryeqo once daily was assessed in two replicate, 24-week, multinational, randomised, double-blind, placebo-controlled studies in patients aged 18 – 50 with heavy menstrual bleeding associated with uterine fibroids. Patients were required to have uterine fibroids confirmed by ultrasound and menstrual blood loss (MBL) volume of ≥ 80 mL, as assessed by the alkaline hematin method. Both studies had 3 treatment arms: Women were randomised to receive relugolix 40 mg + estradiol 1 mg and norethisterone acetate 0.5 mg (E2/NETA) (Ryeqo) for 24 weeks, or placebo for 24 weeks, or relugolix 40 mg for 12 weeks followed by relugolix 40 mg co-administered with E2/NETA for 12 weeks. The median age of women was 42 years, and mean body mass index was 31.7 kg/m2 . Approximately 49.4% of women were Black, 44.7% were White, and 5.9% were of other races*.”

The two studies in the NICE dossier only show data for 24 and 52 weeks.

In your letter you state… “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”.

It is particularly concerning that NICE gives no regard to that fact that some women, particularly Afro-Caribbean women and those with darker skins will suffer fibroid symptoms requiring treatment for many years and seeks to suggest that this medicine is suitable for long-term use with no long-term safety, efficacy or fertility data.”

On reflection I agree that this is a valid appeal point insofar as it relates to whether it was reasonable for the committee to conclude, based on the evidence submitted to it, that Relugolix “can be used long term” and whether this conclusion is either inaccurate or so unclear as to mean that the recommendations cannot reasonably be justified from the evidence that was presented to the Committee.

Given that they consider the same aspect of the FAD (relating to “long term use”) I will refer points 2.1(b) and this 2.2(a) together for consideration by the panel as one appeal point 2.1(b).

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

I have considered your further comments in your email (under the heading “Fertility”) under this ground 2.2(b). You say:

“There is no evidence that it ‘preserves fertility’ or what the effect of the medicine is on fertility, particularly long-term, so this statement is untrue.  The Summary of Product Characteristics for Relugolix states –

“Fertility Ryeqo inhibits ovulation and often causes amenorrhoea. Ovulation and menstrual bleeding will return rapidly after discontinuing treatment (see section 5.1).”  and

“Effects on ovulatory function In a single cohort study in healthy premenopausal women, administration of Ryeqo once daily for 84 days substantially suppressed follicular growth throughout the 84-day treatment period (mean dominant follicle size of approximately 6 mm) and ovulation was inhibited in 100% of women as assessed by the Hoogland-Skouby score. After discontinuation of treatment, all women assessed (66 of 67) returned to ovulation within 43 days (mean 23.5 days).”

So the statement on fertility can only be substantiated for 84 days, after which the effect on fertility is unknown.  The studies submitted in the NICE dossier did not include any studies on fertility, so the information in the SPC is the only information and it does not substantiate any claim that fertility is maintained.”

On reflection I agree that this is a valid appeal point insofar as it relates to whether it was reasonable for the committee to conclude, based on the evidence submitted to it, that Relugolix “preserved fertility” and whether this conclusion is either inaccurate or so unclear as to mean that the recommendation cannot reasonably be justified from the evidence that was presented to the Committee.

***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 have considered your further comments in your email (under the heading “3.2. “Treatment pathway and comparator”) under this ground 2.2(c).

I note your original point was:

“*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.*

In your response you repeat the above and say “*This has not been addressed and it reflects poorly on NICE’s knowledge and expertise*” and that “the Section on “Treatment pathway and comparator” is rewritten and corrected, as it reflects poorly on NICE.”

I remain unpersuaded this is a valid appeal point under ground 2 for the reasons in my previous letter. As you have not identified the alleged factual inaccuracies or otherwise provided further clarification and/or evidence in your response letter there is nothing to which I can respond in final scrutiny.

***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 remain unpersuaded this is a valid appeal point under ground 2 for the reasons in my previous letter. I note that you have not provided further clarification and/or evidence to me in your response letter so there is nothing to which I can respond in final scrutiny.

Conclusion

Therefore the valid appeal points are your points 2.1(b) (to cover both your above points 2.1(b) and 2.2(a) in one appeal point) and 2.2(b).

These will be the only two appeal points for the panel to consider. There are no other appellants.

NICE will be in contact with you regarding the administration of the appeal, which will be held orally.

Yours sincerely

Dr Mark Chakravarty

Lead Non-executive Director for Appeals

National Institute for Health and Care Excellence