**From:** xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
**Sent:** 21 June 2022 10:39
**To:** xxxxxxxxxxxxxxxxxx
**Cc:** xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx xxxxxxxxxxxxxxxxxxxxxxxxxxxxx
**Subject:** [EXTERNAL]:RE: Initial scrutiny: Relugolix-estradiol-norethisterone acetate for treating moderate to severe symptoms of uterine fibroids [ID3842]
**Importance:** High

Dear Dr Chakravarty and xxxxxxxx,

It is very concerning that NICE does not take the issues of patient safety, efficacy and maintenance of fertility seriously and makes unsubstantiated claims that Relugolix–estradiol–norethisterone acetate has patient benefits which are not evidence based or backed up by any clinical studies or by the MHRA.

The Summary of Product Characteristics (SPC)  which is the legal text required by MHRA accompanying the Product license/Marketing Authorisation of any medicine can be found here and must be the basis upon which any medicine is used - <https://mhraproducts4853.blob.core.windows.net/docs/daeaec9a015f1b9cba077751dd60eb695532a66d>

NICE seeks to go  outside the SPC from MHRA and make claims that have no evidence base.  This is potentially dangerous for patients and irresponsible.

**Long-Term Use**

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?

**Safety and Efficacy**

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.

**Efficacy**

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.

**Fertility**

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.

**Patient Choice and CCG/ICS Violet Lists**

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?

***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.*

This has not been addressed and it reflects poorly on NICE’s knowledge and expertise.

It is notable that whoever wrote the letter signed by Dr Mark Chakravarty appears to have little clinical, pharmaceutical or regulatory knowledge and does not address any of the serious points FEmISA has raised on behalf of patients.  It is not acceptable to compromise patient safety by assuming that because MHRA does not give an upper limit for duration of use for this medicine it is acceptable to use it ‘long-term’, particularly when this is not defined.   Neither it is acceptable to state that is does not effect fertility when there is no evidence of this.  Nor that is it effective at controlling fibroid symptoms when there is no evidence to show this for all common symptoms , only some.

There can be no confidence in this appraisal document and recommendations. NICE staff do not have sufficient understanding of the disease – symptomatic fibroids, the effect on patients, patient pathways or the risks to patients and seek to extend the use of the medicine beyond the marketing authorisation issued by MHRA with no evidence base.  This is unsafe for patients and there has been little regard for their welfare, which should be the first consideration.  It is obvious that FEmISA’s concerns have not been properly considered or addressed so we will need to take our concerns and the opaque way this appraisal is conducted further and make them public.  NICE has no scrutiny and it is clear this compromises standards.

To protect women with symptomatic fibroids FEmISA expects –

1.  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

2.  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.

3.  It should make it clear that the efficacy to treat all symptoms has not been determined

4. The effect on fertility longer than 84 days is unknown and should be reported to MHRA

5. 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

6. The Section on “Treatment pathway and comparator” is rewritten and corrected, as it reflects poorly on NICE

Kindest regards,

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For FEmISA – Fibroid Embolisation – Information, Support and Advice

A voluntary, independent patient support group

[www.femisa.org.uk](http://www.femisa.org.uk)

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