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cc. The Right Honourable Sajid Javid, MP
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Concerns about the latest NICE draft guidance on Inclisiran

Introduction:

We are concerned about your draft final guidance recommending the novel anti-cholesterol drug inclisiran (Leqvio and made by Novartis) for people with primary hypercholesterolaemia or mixed dyslipidaemia who have already had a cardiovascular event such as a heart attack or stroke.

We would ask for this decision to be over-turned immediately until there is enough data to support any hard outcome benefit of Inclisiran, namely the prevention of heart attacks, strokes or death.

Our main concerns are addressed in six key areas:

1. Inclisiran is an investigational drug in the UK

Inclisiran gained approval by the European Medicines Agency in Dec 2020, however, the drug remains unapproved in the UK (which is not part of the European Union) since 31 Jan 2020 and other major nations. The novel PCSK-9 inhibitor has not been approved by the US Food and Drug Administration.

We would recommend however, that a full appraisal of the Inclisiran trial data and marketing license be obtained by UK's Medicines and Healthcare products Regulatory Agency prior to rolling out the drug to patients in the NHS.

2. Lack of transparency in NICE decision making process

The decision for NICE follows an agreement on a population-level commercial deal between NHS England and NHS Improvement and Novartis which will make inclisiran available with a discount to its list price.

The full details to the pricing agreement have been kept confidential and not available for independent scrutiny. This lack of transparency should be of concern to the British public, prescribing doctors and taxpayers who fund NICE.

3. No long-term data on effectiveness or safety

To date, the trials are short term, only 18 months. NICE's daft guidelines acknowledge this issue. "The committee was concerned that there was a lack of long-term data on cardiovascular outcomes from the clinical trials that compared Inclisiran with placebo. However, it noted that ongoing clinical trials would provide more data on these outcomes."

We propose that more long-term data on safety and efficacy is accumulated before recommending Inclisiran, even as an adjunct to statin therapy.

4. Decision based on a surrogate marker (LDL-C)

Inclisiran, the novel PSCK-9 inhibitor is effective at lowering Low Density Lipoprotein cholesterol (LDL-C), however, mounting evidence demonstrates that it is a weak surrogate marker of cardiovascular disease.

The push to lower cholesterol with statins to prevent heart disease has been largely influenced over the years by meta-analyses performed by the Cholesterol Treatment Trialists Collaboration at Oxford University researchers.

The CTT suggests that there is a linear relationship between LDL-C reduction by statins and the reduction in risk of cardiovascular disease. The individual patient data, upon which they make these claims, is not accessible to third parties for independent scrutiny.

NICE justifies its decision to be guided by the CTT in its recommendations "The clinical experts stated that the CTT meta-analyses were appropriate and that a similar relationship between LDL-C lowering and a reduction in cardiovascular event risk as seen with statin use could be expected with Inclisiran."

However, it should be noted that statins have pleotrophic effects - anti-inflammatory and anti-thrombotic - that may be responsible for the benefits seen in secondary prevention patients.

Further, there is conflicting evidence that LDL-C is a causal factor in heart disease. A 2020 recent study published by Danish researchers, for example, demonstrated that LDL-C the lowest risk of all-cause mortality was found at an LDL-C concentration of 3.6 mmol/L (140 mg/dL).

In comparison the **highest** association with all-cause mortality was actually at LDL-C levels of less than 1.8mmol (70mg/dL).

Notably, NICE recommendations suggest that people with LDL-C concentrations persistently 2.6 mmol/l or more, despite maximum tolerated lipid-lowering therapy, should be on Inclisiran. This has no independent scientific basis.

Although the NICE recommendation is specific to patients with either previous cardiovascular disease or FH such a well-publicised recommendation feeds into a false narrative that the lower the LDL-C the better when it comes to overall health and/or managing cardiovascular disease. It's instructive to note that there is also no difference in levels of LDL-C in patients with FH who develop

premature heart disease versus the one's that don't suggesting that LDL-C is not the main driving factor for the development of coronary artery disease in these patients.

Furthermore, an independent peer reviewed systematic review of drug trials carried out by three cardiologists in 2020 published in BMJ Evidence Based Medicine revealed that there was no clear relationship with reduction in LDL in both high risk and low risk patients in reducing cardiovascular events.

5. No evidence for cardiovascular benefit with Inclisiran lowering LDL-C

Low Density Lipoprotein cholesterol (LDL-C) has been the primary outcome of the clinical trials. While we agree that Inclisiran demonstrates effective reduction in LDL-C, we find that the clinical data to support the benefit of cholesterol lowering is absent.

An analysis by the European Medicines Agency (EMA) found there was a "**lack of cardiovascular outcome data**" in the regulatory documents sent to the drug agency.

It also found that "the number and percentage of deaths **was comparable** between the placebo and the Inclisiran group, but numbers are too small for clear conclusions."

"In addition, **no definite data** on cardiovascular morbidity and mortality are currently available," the report stated.

NICE's own guidelines state, "there is also no long-term evidence on whether inclisiran reduces cardiovascular events. This means the clinical evidence and the cost-effectiveness estimates are very uncertain".

Given that Inclisiran has not proven to reliably reduce major cardiovascular events, cardiovascular morbidity, or mortality, we believe a decision to recommend this drug based is premature.

Two studies, ORION-4 in secondary prevention and ORION-17 in primary prevention are currently underway.

6 Loss of professional confidence

The lack of transparency in the decision-making process may undermine professional and public confidence in NICE and its decision-making processes. This could be critically damaging to professional confidence in the delivery of evidence-based healthcare in the UK

In light of our concerns, we urge you to withdraw the current guidance on Inclisiran for people with primary hypercholesterolaemia or mixed dyslipidaemia who have already had a cardiovascular event such as a heart attack or stroke until further important clinical data with clear cardiovascular benefits are made available.

Your Sincerely,

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