1st May 2024

Dr Mark Chakravarty

Lead Non-executive Director NICE Appeals – Technology Appraisals and Highly Specialised Technologies

National Institute for Health and Care Excellence 2nd Floor

2 Redman Place London E20 1JQ

Dear Dr Chakravarty,

# Letter of Support for the Appeal from Tuberous Sclerosis against the Final Appraisal Determination – Fenfluramine for treating seizures associated with Lennox–Gastaut syndrome in people 2 years and over

We are fully in support of the appeal by the Tuberous Sclerosis Appeal.

Tuberous Sclerosis provided evidence of the devastating unmet need. Lennox– Gastaut like Dravet is a very severe epilepsy diagnosis with severe impacts, but devastating impacts when best care is denied for the patient, their families and health,education, and social care providers. SUDEP Action has worked with families with lived experience and seen the incredible benefits of best care for the person and the family, and the devastation and impacts of the very worst, including most recently the high profile inquiry into the life and death of Clive Treacey [Vulnerable man Clive](https://www.bbc.co.uk/news/uk-england-nottinghamshire-59598728) [Treacey 'failed in life and death' - BBC News](https://www.bbc.co.uk/news/uk-england-nottinghamshire-59598728); [NHS England-funded project is lasting](https://sudep.org/article/nhs-england-funded-project-lasting-legacy-clive) [legacy to Clive | SUDEP Action](https://sudep.org/article/nhs-england-funded-project-lasting-legacy-clive). The recommendations include access to effective medicine as the costs to him and his family and to the whole system escalated when his seizures (he had Lennox-Gestaut) were most out of control. The importance of patients accessing a last resort individualised medication plan which is effective in reducing seizures cannot be overstated because of the heterogeneity of epilepsy and of Lennox-Gestaut. Whilst, like with fenfluramine treatment for Dravet, fenfluramine will not work for all in need, but the benefits of reduced seizures can be transformative for many and save money not just in the NHS but across education and social care.

With the needs that have been shared already including the evidence Para 3.2 in the final guidance from clinical experts that “stated that the NG217 treatment pathway for

LGSbroadly reflective of clinical practice in the NHS. But, they noted that the choice of treatment regime is highly individualised and based on effectiveness, adverse effects, sedative effects, and drug–drug interactions”. Needs and inequalities have worsened very significantly for people with epilepsy and their families before and since the pandemic. Given the context of severe need, It is unfair to use the Fenfluramine versus SC because from a costs point of view as this works against an individual’s access to a last resort medication which could be transformative for that individual, their family and the NHS and care settings that they use. The treatment of issues of uncertainty does not appear to be proportionate to the impacts on this highly vulnerable population with protected characteristics.

We support an appeal and hope that NICE will take more time to understand the need for flexibility for people with Lennox-Gestaut with view to approving a last resort medication to decrease the risk of seizures and a range of harms. The concern for the future, in the absence of flexibility, is a NICE approach to new medicines for people with epilepsy that will be set a precedent and be a major barrier to improving care and reducing economic and non -economic burdens on families and the whole system.

Specific points of support for the Appeal

# Ground 1a: In making the assessment that preceded the recommendation, NICE has failed to act fairly

**1a.1 The committee compares Fenfluramine versus not having Fenfluramine – usual standard of care and refusal to base its recommendations on a comparison with cannabidiol plus clobazam**

Lennox–Gastaut like Dravet is a very severe epilepsy diagnosis with severe impacts, but devastating impacts when best care is denied for the patient, their families and health, education, and social care providers. SUDEP Action has worked with families with lived experience and seen the incredible benefits of best care for the person and the family, and the devastation and impacts of the very worst, including most recently the high profile inquiry into the life and death of Clive Treacey Vulnerable man Clive Treacey 'failed in life and death' - BBC News; NHS England-funded project is lasting legacy to Clive | SUDEP Action. The recommendations include access to effective medicine as the costs to him and his family and to the whole system escalated when his seizures (he had Lennox-Gestaut) were most out of control. The importance of patients accessing a last resort individualised medication plan which is effective in

reducing seizures cannot be overstated because of the heterogeneity of epilepsy and of Lennox-Gestaut. It is unfair to use the Fenfluramine versus SC because from a costs point of view this works against an individual’s access to a last resort medication which could be transformative for that individual, their family and the NHS and care settings that they use. This was recognised in the appraisal of access by patients with Dravet to Fenfluramine which was approved after a finding: “The drug is effective in reducing the number of seizures and may be more effective than cannabidiol plus clobazam. The Dravet recommendation recognised the importance that whilst the add on would not work for everyone, it’s value was as an add on to highly individualised person-centred treatment because of the heterogenous nature of the condition and recognised the wider benefits of this…. There were some uncertainties around the assumptions in the model. However, the committee considered that the most plausible ICER for fenfluramine compared with cannabidiol was likely to be within the range normally considered an effective use of NHS resources”

The first draft report for Fenfluramine and people with Lennox Gestaut stated: “Evidence from a clinical trial show that people who have fenfluramine have fewer drop seizures per month than people who have standard care. There is no evidence directly comparing fenfluramine with cannabidiol plus clobazam. But, an indirect comparison suggested that fenfluramine may be more effective than cannabidiol plus clobazam in reducing the number of drop seizures” (January 31st draft). It was really surprising to read that this evidence-based statement in January was materially changed in the final guidance. The report does not state what clinical opinion was sought, if any, on this significant change to the wording of the finding: “Evidence from a clinical trial show that people who have fenfluramine have fewer drop seizures per month than people who have standard care without cannabidiol plus clobazam.

There is no evidence directly comparing fenfluramine with cannabidiol plus clobazam. The results of an indirect comparison comparing fenfluramine with cannabidiol plus clobazam are uncertain” (Final Guidance) Despite the accepted evidence of the severity of impact of Lennox-Gestaut, the treatment of issues of uncertainty does not appear to be proportionate to the impacts on this highly vulnerable population with protected characteristics. In particular the final guidance refers to uncertainties about the long-term. For people with Lennox-Gestaut there is an urgent timeliness issue regarding the need for new medications. All new medicines will have uncertainties about the long-term. SUDEP Action and the families we work with value the flexible approach taken by NICE previously, recognising not just the seriously disadvantages to the epilepsy patient population

but also serious disadvantages because of built in barriers to evidence because of the heterogeneous nature of the population. Para 3.2 in the final guidance includes the evidence from clinical experts that “stated that the NG217 treatment pathway for LGS is broadly reflective of clinical practice in the NHS. But, they noted that the choice of treatment regime is highly individualised and based on effectiveness, adverse effects, sedative effects, and drug–drug interactions”. We are appealing to ask that NICE take time with clinicians and patient groups and the company to understand the need for flexibility for people with Lennox-Gestaut with view to approving a last resort medication to decrease the risk of seizures and a range of harms. The serious concern for the future, in the absence of flexibility, is a NICE approach to new medicines for people with epilepsy that will be set a precedent and be a major barrier to improving care and reducing economic and non -economic burdens on families and the whole system. Ground 1b: In making the assessment that preceded the recommendation, NICE has exceeded its powers 1b.1 The Institute has exceeded its powers by making recommendations that are incompatible with the Human Rights Act 1998 People with Lennox-Gestaut have protected characteristics. This is relevant with regard to positive obligations under the Human Rights Act 1998 with regard to Article 2 Right to Life and Article 8 respect for private family life and equality obligations under the statute. Whilst these obligations are relative, not absolute, they require a positive concern and weighting. SUDEP Action welcomes the committee’s recognition that LGS is a severe epilepsy including considering the carer burden for economic modelling. However, the concern of the committee in accepting this severity is not matched by their approach to the decision. The committee is inflexible when adjudicating on outstanding uncertainties. SUDEP Action would expect that proportionality, given the committee’s acceptance of the impact of LGS, would lead to acceptance of the evidence of clinical benefit of fenfluramine in comparison with cannabidiol plus clobazam and use of that comparator in cost analysis as well as recognising wider economic and non- economic benefits of approving the medication. This is in marked contrast to the previous NICE technology appraisals on the use of the drug in Dravet and indeed the flexibilities shown in relation to cannabidiol. The need for flexibility, especially in light of the urgent need for new epilepsy medications, in the Dravet appraisal and indeed in relation to appraisals for cannabidiol does not appear to be present in the appraisal for Lennox Gestaut and we ask that this be reconsidered (as per 1.1a).

# 1b.2 The Institute has exceeded its powers by making recommendations that are incompatible with the public sector equality duty People with LG are people with protected characteristics under the Equality Act. They suffer

particular disadvantages and they and their carers are a highly vulnerable population. The impact and value of new epilepsy medications cannot be overstated, most especially at a time when there is reduced access to epilepsy medications.

SUDEP Action is alongside patients and carers and bereaved carers who experience agonising daily battles with severe impacts. The health inequalities of this population are well established and are included in the five conditions for targeted reduction in health inequalities CORE20PLUS5. The draft final determination fails to give consideration to the importance of this new epilepsy medication as a last resort that can reduce disadvantage of this patient population and their carers. The severity of the impact of the condition whilst acknowledged, which we welcome, is not reflected in the approach to the decision.

# Ground 2: The recommendation is unreasonable in the light of the evidence submitted to NICE 2.a The Appraisal Committee’s refusal to consider the use of Fenfluramine was based on an error and therefore cannot reasonably be justified in the light of the evidence submitted

SUDEP Action refers to the evidence on the change of wording on the finding of clinical effectiveness and comparisons in ground 1.1.(a) above. The change of wording is fundamentally different, and it is difficult to understand how an evidence- based finding from January that fenfluramine may be more effective than cannabidiol plus clobazam could be so materially altered between then and the final draft. The committee has acknowledged the challenges of robust data collection in people with LGS (3.3, 3.5), but the impact of not adequately taking account of this in the decision not to approve the medicine for a highly disadvantaged patient population, is severe and not proportionate. Additionally, additional requests to compare with individual or specific combinations of antiseizure medications were not required beyond a comparison with cannabidiol plus clobazam in other appraisals (3.3). The final guidance has not taken on board the refractory nature of LGS and the heterogeneity of the treatment population and what this means with regard to what is possible regarding robust comparisons and the equalities impacts of this inflexible approach. There is an omission in the final determination to explain the change in the substance of the finding in the final guidance. It does not appear that clinical opinion was sought on this. There are other matters where in the final guidance clinical representations appear to be missed e.g. The committee wanted to factor in waning (loss of efficacy over time), but we cannot find where this was supported by evidence provided or by the clinicians.

Yours sincerely,

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Director of Policy and Influencing, SUDEP Action