Dr Mark Chakravarty

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

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Dear Dr Chakravarty,

# Re: Final Appraisal Determination – Fenfluramine for treating Lennox-Gastaut seizures in people aged 2 and over [ID1651]

Tuberous Sclerosis Association (TSA) would like to appeal against the Final Appraisal Determination for the above-mentioned technology appraisal on the following grounds:

Ground one: In making the assessment that preceded the recommendation, NICE has either:

* failed to act fairly
* exceeded its powers

Ground two: The recommendation is unreasonable in the light of the evidence submitted to NICE

The TSA is supported by the following patient advocacy groups in this appeal:

1. UK Rare Epilepsies Together (UKRET) (Appendix 1)
2. SUDEP Action (Appendix 2)
3. Young Epilepsy (Appendix 3)
4. Epilepsy Society (Appendix 4)

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

The TSA is the only patient group that attended the first committee meeting with a patient representative – a parent with a young child with primary diagnosis of TSC and secondary diagnosis of LGS. The patient representative also attended the second committee meeting. However, there was no formal representation from other patient groups that may have primary or secondary diagnosis of LGS and most importantly, a patient who could share their experience of the treatment under consideration.

It has come to light that there may have been a breakdown or miscommunication between NICE and patient groups. As the only patient advocacy group (PAG) engaged during the appraisal process, we believe that NICE acted unfairly by failing in its duty to ensure fair representation of LGS patients resulting in important evidence around impact of the condition and quality of life of both patients and caregivers not being considered appropriately by the Committee, especially before and after treatment. In our view, not hearing from a patient for whom fenfluramine has made a significant positive difference to their quality of life, is a serious omission in the appraisal process. Over the last one week, the TSA, the only registered PAG stakeholder of this appraisal, has, therefore, been in discussion with other patient support groups representing rare epilepsy

conditions with secondary diagnosis of LGS and urge the panel to understand the scale of the condition by liaising with these groups. We enclose letters of support (Appendix 1-4) from a number of stakeholders and request that these organisations are given an opportunity to formally share their experiences of living with LGS and consider vital evidence to help inform the

decision-making process.

In the final draft guidance, NICE has stated that there are uncertainties about various aspects of fenfluramine. If this was the case, surely NICE should be enabling more discussion from patients and clinicians to help inform a more inclusive assessment. It is also not clear why NICE was not able to work with the company to resolve any uncertainties throughout the process. Even if NICE thinks the treatment has limited clinical efficacy in patients who would otherwise have no treatment, this must be of tangible benefit.

# Ground 1a (2) 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 (feedback received from SUDEP Action)

Lennox-Gaustet, like Dravet Syndrome, 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](https://sudep.org/article/nhs-england-funded-project-lasting-legacy-clive) [News; NHS England-funded project is lasting 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 LGS) 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 LGS.

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

*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 LGS, 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 LGS 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 they 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. However,

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 (1): In making the assessment that preceded the recommendation, NICE has failed to fully explore health inequalities

Tuberous Sclerosis Complex (TSC) is a rare genetic condition. Every month around 10 babies are born with TSC in the UK. TSC causes growths to develop in different organs around the body, such as the brain, lungs, kidneys, eyes, heart and skin. These growths are sometimes referred to as benign (non-cancerous) tumours. When they cause problems, it is mainly because of their size and where they are growing in the body.

Eight out of ten people with TSC have epilepsy that typically starts in infancy and is difficult to control using epilepsy medication. Different types of epilepsy - called the 'epilepsy syndrome' - can occur in children with TSC. The two most common epilepsy syndromes are: (1) West syndrome: this is diagnosed on the basis of infantile spasms, the age at onset of spasms (under

12 months of age) and a typical EEG appearance - called hypsarrhythmia. (2) LGS: this is diagnosed on the basis of different seizure types that occur in a child (particularly tonic, tonic- clonic and partial seizures), the age at onset of the different types of seizures (between 1 and 6 years of age) and a typical EEG appearance (called slow spike and slow wave activity). It is important to understand that a child with TSC may start with West syndrome in the first year of life and then evolve (change) into Lennox-Gastaut syndrome in the second or third year of life.

When a TSC diagnosis is made, the whole family is affected both physically and mentally. A secondary diagnosis of LGS can have even deeper impact on families’ quality of life and on their ability to cope with the disease and support the child's ability to reach an acceptable level of well- being. Families and carers have reported the experience of losing control and feelings of despair and helplessness. They have shared their day-to-day struggles with their children’s behaviour including what it’s like to manage the rage, anger and mood swings. It not only affects their relationship with their child who has TSC/LGS but also their relationship with each other and the wider family circle including siblings who feel left-out and neglected as the parents focus on the needs of their child with the condition. In many instances, parents have had to give up work to become full time carers. There are additional costs for home improvements associated with TSC: the TSA Support Line receives regular calls from parents wishing to access our small family grants to purchase fridges to store medication or batches of ketogenic food, replace washing machines, tumble dryers, beds and bedding urgently needed to cope with the impact of urinary and faecal incontinence, and invest in improvements to make back gardens secure and safe for children with no sense of danger to play in.

The committee has acknowledged and concluded that Lennox-Gastaut seizures severely affect the quality of life of people with the condition, their families and carers. The committee also

concluded that LGS is a heterogenous condition and there is an unmet need for treatments that reduce the number of drop seizures without markedly increasing adverse events. As mentioned in 1.1a, without formal representation from a dedicated LGS PAG, key perspectives and evidence of the impact of the condition was not considered by the committee. Moreover, considering a large unmet need, not approving fenfluramine for use raises large inequality concerns, as LGS community already have limited treatment options available for patients.

We also do not believe, from a patient advocacy perspective, that the reasons why the committee made its decision are clear and unambiguous or addressed the difference between NICE’s decision to approve the same drug for one condition (Dravet Syndrome) but not another with similar aetiology.

Whilst we accept there is a balance to be struck to meet the communication needs of all stakeholders involved with this process, it is not easy to explain this point to the LGS patient community, other than NICE does not believe fenfluramine represents value for money for the NHS and the taxpayer.

# Ground 1b (2) NICE has exceeded its powers by making recommendations that are incompatible with the Human Rights Act 1998

People with LGS have protected characteristics. This is relevant with regards to positive obligations under the Human Rights Act 1998 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 have fed back to the TSA that they welcome 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 and the TSA 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).

# Ground 1b (3) NICE has exceeded its powers by making recommendations that are incompatible with the public sector equality duty (feedback received from SUDEP Action)

People with LGS are people with protected characteristics under the Equality Act. They suffer disadvantages, and together with 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 consider 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

**Ground 2.1** Despite the Appraisal Committee recognising and acknowledging a large unmet need within the LGS patient committee, along with the fact that fenfluramine is already recommended as an add‑on to other antiseizure medicines for treating seizures associated with Dravet syndrome in people aged 2 years and older, it is unfair that patients with LGS with similar aetiology will not have access to a new treatment option.

LGS can be difficult to treat with anti-epileptic medicines, with most children and adults with LGS requiring a combination of medicines and other therapies. When we asked people living with LGS and their families and carers to share the aspects of living with the condition that are not met by currently available treatments, families said that their child’s seizures, epilepsy and behaviour problems are the areas that need addressing urgently. These areas impact the most on their day-to-day lives and they would welcome help and support in addressing these unmet needs.

TSC patients, including those with LGS, often try between 15 and 20 anti-epileptic drugs. Most of them state that there tends to be a “honeymoon period” where the prescribed drug works for a short duration, then it stops working and they move to next medication so it is vital that they are

given access to fenfluramine which may provide better seizure control, therefore, better quality of life.

In general, this patient group has previously had poor access to care because of the variety and severity of their problems. The availability of a new effective treatment and the effectiveness of that treatment will vastly improve their health outcome; especially for those who are least able to advocate for themselves (or whose families are less able to articulate their needs).

# Ground 2.2: 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 (feedback received from SUDEP Action)

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.

Moreover, 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 regards 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.

**Conclusion**

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The TSA is strongly of the opinion that, fenfluramine should be offered as a potential treatment option to patients with LGS. It wishes this appeal to proceed to an oral hearing. The TSA would urge that NICE and drug sponsor work together to recognise patient subgroups that we believe clearly benefit from fenfluramine. The TSA would also like to thank the committee for the opportunity to bring these points to your attention. Please do not hesitate to contact us in case you have any questions.

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Joint Chief Executive