NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Committee Papers

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NICE National Institute for Health and Care Excellence

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Contents:

The following documents are made available to consultees and commentators:

1. **Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)**

2. **Comments on the Appraisal Consultation Document from GW Research Ltd / Jazz Pharmaceuticals**

3. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   a. Tuberous Sclerosis Association
   b. Young Epilepsy

4. **Evidence Review Group critique of company comments on the ACD**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

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Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Single Technology Appraisal

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Type of stakeholder:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and Social Care and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal document (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health and Social Care, Social Services and Public Safety for Northern Ireland).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1	Company	GW Research Ltd / Jazz Pharmaceuticals	**<u>Summary – company's updated base case</u>** • Based on the feedback from the NICE Committee in the ACD, the company has made changes to its base case. • As outlined in more detail in Comment 4 below, we have updated our base case to incorporate many of the Committee's preferred assumptions (as stated in the e-mail from the NICE TA team dated 03/11/2022) as follows: o Using a 6.61 day cut-off for the proportion of people who are seizure-free over 7 days o Using the health state utilities from the company's vignette o Assuming a cumulative 1.8 carers o Adjusting for institutionalisation using the ERG's approach* o Including cost and benefits for TAND aspects for people aged 2 to 6 years, using the utility benefit from the company's base case. * Note that this includes an updated calculation for institutionalisation as communicated to the NICE Technical Team on 22/11/2022 (see Comment 9 below for more detail) • The company maintains that the average dose of cannabidiol (12 mg/kg/day – as accepted by NICE for the DS and LGS appraisals) used in our cost-effectiveness analysis is reasonable and justified, based on robust evidence, feedback from clinical experts and as observed in real-world prescribing data from 118 patients in Germany since 2019 (please see Comment 6 below for more detail). • As per section 5.5.1 of NICE's PMG9, the company has updated healthcare resource use costs in the economic model to include the latest NHS reference costs (from the National Schedule of NHS Costs - Year 2020-21) • The company's updated base case ICER incorporating all the above changes is **£11,833** per QALY. The application of a disease severity QALY modifier (to appropriately reflect the severity	Comment noted. Please see individual responses to specific comments below.

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			of TSC-associated epilepsy – see Comment 2 below) would reduce the company's revised base case ICER to **£9,861** per QALY.	
2	Company	GW Research Ltd / Jazz Pharmaceuticals	**Severity of the disease** • The NICE Committee has recognised the severity of TSC-associated epilepsy and that it "severely affects the quality of life of patients, carers and their families". • TSC-associated epilepsy is a rare (orphan), devastating and life-threatening form of epilepsy that presents early in childhood and is associated with refractory seizures and poor outcomes. In addition to the high seizure burden, the associated cognitive and behavioural difficulties known as TSC-associated neuropsychiatric disorders (TAND) prevent children from achieving independence in adult life. Mortality rates for people with TSC are higher than in the general population, with uncontrolled epilepsy among the most common causes of death in TSC as a result of status epilepticus or Sudden Unexpected Death in Epilepsy (SUDEP). • The Committee's recognition of the severity of the disease also reflects the brave and comprehensive testimony of the parent/patient expert at the Committee meeting on 15th September 2022. The patient expert outlined the stark reality of living day to day with a child with TSC-associated epilepsy and the profound impact on the quality of life of both the patient and the family as a result of the seizures and TAND. • The company further notes from the ACD that "half of people with tuberous sclerosis complex have associated learning difficulties, which is a protected characteristic under the Equality Act 2010". • We note that the NICE methods guidance was updated in February 2022 in order to support patients with severe diseases. This updated 2022 guidance introduced new criteria to reflect, in exceptional circumstances, the severity of disease within decision making. The company is aware that this submission is being assessed under the old methods guidance (the invitation to participate was sent to us on 18th January 2022, just two weeks before the new guidance was introduced on 1st February 2022). However, given the subsequent long delays in the appraisal process, we consider it appropriate to include the severity of TSC-associated epilepsy and the impact of this on the economic analysis. As detailed in our submission, cannabidiol in a patient population with TSC-associated seizures satisfies the criteria laid out by NICE under the new methods for a severity of disease modifier. Given the severe impact of TSC-associated epilepsy, a QALY weight of 1.2 (applicable for the absolute loss of between 12 to 18 QALYs) should be applied in the context of decision making. • The application of a disease severity QALY modifier (to appropriately reflect the	Comment noted. This topic is subject to the methods and processes pre-2022, therefore the severity modifier is not applicable. However, the committee considered the severity of the disease in its decision making. See FAD section 3.19.

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			severity of TSC-associated epilepsy) reduces the company's revised base case ICER (of £11,833) to £9,861 per QALY. Of note, using *all* the NICE Committee's preferred assumptions (as stated in the e-mail from the NICE TA team dated 03/11/2022, that is: using a 6.61 day cut-off for the proportion of people who are seizure-free over 7 days; using an average dose of 15 mg/kg/day; using the health state utilities from the company's vignette; assuming a cumulative 1.8 carers; adjusting for institutionalisation using the ERG's approach (with an updated calculation as outlined in Comment 9 below); including cost and benefits for TAND aspects for people aged 2 to 6 years using the utility benefit from the company's base case), the ICER is £22,401 per QALY (and with the severity modifier applied, it is £18,668 per QALY), which is well within the Committee's stated 'acceptable ICER' range.	
3	Company	GW Research Ltd / Jazz Pharmaceuticals	**Additional benefits of cannabidiol not captured in the current model / economic analysis** There are additional benefits of cannabidiol that are not captured in the current model/economic analysis. For example, the cost-effectiveness estimates do not include the value of: • A beneficial impact on the mortality related to Sudden Unexpected Death in Epilepsy (SUDEP) that is associated with effective seizure control • The broader impact on TAND (not captured in the very conservative assumptions used in the current model) • Improving the quality of life of the wider family, including siblings and other family members • Increasing caregiver productivity and the associated societal benefits of the parent(s)/primary caregiver(s) not needing to give up work to care for a patient with TSC-associated epilepsy • Reducing the duration/severity of seizures (the model only captures seizure frequency) • The long-term impact of improved seizure control on comorbidities and injuries	Comment noted. At the second meeting, the committee agreed that there are additional benefits of cannabidiol not captured in the modelling and considered these in its decision making. See FAD section 3.19.
4	Company	GW Research Ltd / Jazz Pharmaceuticals	**NICE's preferred assumptions** The company noted the preferred assumptions from the NICE Committee. In order to avoid any further delays in patients with TSC-associated epilepsy and their families having access to a much-needed treatment for this severe condition, we have adopted the majority of these assumptions in our revised company base case. However, we reiterate below why we consider that they are extremely conservative and/or may lead to the ICER being over-estimated:	Comments noted. The committee considered these comments in the second committee meeting. See FAD section 3.12 to 3.17.

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			• **Impact of cannabidiol on TAND aspects** The Committee has recognised *some* of the potential impact of cannabidiol on TAND, since aspects of TAND can have a huge impact on the lives of patients with TSC-associated epilepsy and their caregivers. As noted in the ACD: "patient experts highlighted the significant quality-of-life impact from TAND for patients and families. Severe learning difficulties occur in around 30% of people and may impede speech. Impaired movement may also limit all aspects of daily living. Poor behaviour including anger, mood swings, aggression and a lack of perception of risk often makes daily activities impossible and people may need round the clock care. People with the condition also have disrupted sleep, which can impact on the mental health of the entire family". Even though the Committee's preferred base case only includes a very conservative assumption on TAND, we consider that it is important to include it in the analysis and that there is potential *additional benefit* from the impact of cannabidiol on TAND that it is not possible to capture in the economic model. • **6.61 versus 6.5 cut-off for people seizure-free over 7 days** We note that the NICE Committee considered that "the proportion of people who are seizure-free over 7 days in the model is uncertain but a 6.61 day cut-off is most appropriate for decision making". Although we accept that NICE's preference was to use the ERG's very conservative approach, we maintain that there were robust methodological reasons for choosing the 6.5 cut-off and that this better reflected the trial outcomes in the model. • **1.8 carers** We note that the Committee considered that "The effect on carers' quality of life should be modelled and the ERG's assumption using 1.8 carers is most appropriate". Whilst the significant impact of TSC-associated epilepsy on caregiver quality of life has been recognised by NICE, in our submission and in our responses to the ERG report, the company included utilities for *two* caregivers. This reflects the impact of TSC-associated epilepsy on the quality of life of the wider family. We acknowledge that not every patient will have two primary caregivers (although many will need more than two). However, the company is aware that there are often many other people contributing to the care of the patient (for example, siblings, grandparents, aunts, uncles, family friends). Each family carer has the burden, worry and psychological distress of caring for a patient at risk of injury and even death from	

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			their seizures. Thus, it would be expected that incorporating the full and cumulative effect of TSC-associated epilepsy on the lives of *all* family members would result in a further reduction of the ICER. • **Institutionalisation*** We note that the NICE Committee concluded that it is appropriate to include a reduction in carer disutility associated with institutionalisation of a patient. However, we also note that the Committee considered that "the increase in carer quality of life in the company and ERG's analyses were not supported by data and other scenarios would be equally plausible...Given the lack of evidence to support the size of this reduction, it considered the ERG's approach preferable". Based on this, although we accept that NICE's preference was to use the ERG's very conservative approach, the company's approach is equally valid. We also refer back to the patient expert's comments: "the patient expert agreed that although carers had more free time if a person with TSC was institutionalised, concerns and guilt would remain, especially about exposure to abuse". * Note that the company's base case includes an updated calculation for institutionalisation (see Comment 9 below for more detail) • **Different values of the seizure-free health states for carers** The ERG adjusted the caregiver utility for the seizure-free health state to that of an average adult aged 45. The company accepted this adjustment from the ERG at the Technical Engagement stage of the appraisal process and it is reflected in the company's revised base case. With regard to the scenarios using different values, we note from the ACD that the NICE Committee concluded that "Scenarios varying the seizure-free utility value for carers had minimal impact on the ICER".	
5	Company	GW Research Ltd / Jazz Pharmaceuticals	**<u>NICE process for handling uncertainty</u>** The company noted that the NICE Committee has changed the standard threshold for the ICER: *"…the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)"* We would like to make the following observations on this: • TSC-associated epilepsy is a severe and orphan disease • As presented in the Committee meeting on 15th September 2022, both the previous company base case (before the updates outlined in Comment 4 above) and the	Comment noted. The committee considered the company's response to consultation during the second committee meeting. When taking the uncertainties, uncaptured benefits and severity of the disease into account, it agreed that cannabidiol is considered an appropriate use of NHS resources and recommended it for use in people with seizures

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			ERG base case ICERs were substantially under £20,000 per QALY gained compared with usual-care (ERG base case ICER was £16,928; previous Company base case ICER was £14,594) • The ACD document makes reference on numerous occasions to the ERG's 'conservative' assumptions being the Committee's preferred option. In this context, it is difficult to understand why, when all these 'conservative' assumptions have been used in the Committee's preferred base case, the acceptable ICER threshold is then set much lower than for other rare (orphan) and severe diseases • The threshold is also not in line with previous appraisals of cannabidiol in severe epilepsies – in TA614 (Dravet syndrome) and TA615 (Lennox-Gastaut syndrome), the accepted ICERs were £32,471 and £33,721, respectively. This was because the Committee recognised the additional benefits of cannabidiol that could not be captured in the economic model. Based on the above, the Committee's 'acceptable ICER' threshold appears unreasonable considering that many elements of the Committee's preferred base case remove uncertainty or are noted in the ACD as being 'conservative'.	caused by tuberous sclerosis complex. See FAD section 3,22.
6	Company	GW Research Ltd / Jazz Pharmaceuticals	**<u>Dose of cannabidiol in clinical practice</u>** The company maintains that the average dose of cannabidiol (12 mg/kg/day – as accepted by NICE for the DS and LGS appraisals) used in our cost-effectiveness analysis for cannabidiol in TSC-associated epilepsy is reasonable and justified, based on robust evidence, feedback from clinical experts and as observed in real-world data from 118 patients with TSC. <u>*Evidence base*</u> In the company's submission, and in our responses to the ERG report and technical engagement, the *average* dose of cannabidiol used in the cost-effectiveness analysis base case is 12 mg/kg/day reflecting that, *across a cohort* of UK patients with TSC-associated epilepsy in clinical practice, there will be a spectrum of doses ranging from ≤ 10 mg/kg/day to the maximum of 25 mg/kg/day. We have provided a large body of evidence in support of this (please refer to the ID1416 Committee Papers for more detailed information, which is not reproduced here). In particular, we have provided recent and robust real-world data from a large cohort in Germany that demonstrates that lower doses of cannabidiol are used in clinical practice. As noted in the ACD, data from 118 patients in Germany indicate that the median	Comment noted. The committee agreed that the average dose of cannabidiol in clinical practice was likely to be around 12 mg/kg/day. However, it was concerned that the dose in the clinical trial was not reflective of that in the cost-effectiveness analyses and agreed that some adjustment for loss of benefit compared to the trial results should be included in the modelling. So, it preferred an average dose of 15 mg/kg/day. See FAD section 3.11.

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			cannabidiol dose in the real world was 12.2 mg/kg/day in children and 7.8 mg/kg/day in adults. *NICE Committee's view on cannabidiol dose (from the ACD)* The company noted that the NICE Committee: • "Agreed that the dose of cannabidiol that would be used in clinical practice is unknown, but an average dose of 15 mg/kg/day should be used for decision making". • "Decided that the ERG's scenario using an *average* dose of 15 mg/kg/day for cannabidiol is appropriate" This was even though the clinical expert at the Committee meeting contradicted the ERG's scenario, stating: 15 mg/kg/day is likely to be the *maximum* dose of cannabidiol used in clinical practice as a trade-off between efficacy and side effects. However, many people would have a dose closer to the company's modelled estimate of 12 mg/kg/day. *Fenfluramine appraisal (Dravet syndrome)* In the ACD, it is stated that the Committee noted that a 15 mg/kg/day average dose for cannabidiol was 'accepted' in NICE's technology appraisal guidance on fenfluramine for treating seizures associated with Dravet syndrome. We would like to draw attention to some key aspects of the fenfluramine appraisal that are of relevance (information taken from NICE TA808, where appropriate): • In the pre-consultation version of the fenfluramine model, the fenfluramine manufacturer used a dosage of *12 mg/kg/day* for cannabidiol, which was in line with the dosage accepted in NICE's technology appraisal guidance on cannabidiol in DS/LGS. However, the fenfluramine manufacturer then changed its mind, arguing that the typical maintenance dosage of cannabidiol used in the UK was likely to be higher, and increased this to a dosage of 15 mg/kg/day in its updated model (note: this change was not requested by either the ERG or the NICE technical team). This large increase in the average dose of cannabidiol used in the fenfluramine model is perhaps not unexpected, given that demonstrating the possible cost-effectiveness of fenfluramine relied on a comparison with the cost of cannabidiol. Of note, the 'typical' dose of fenfluramine was not increased similarly in the updated model. • The fenfluramine manufacturer aimed to justify the large increase in the average dose of cannabidiol with information including the following: o Evidence from a study on slow titration of cannabidiol add-on in drug-	

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			resistant epilepsies (D'Onofrio *et al*., 2020), which was conducted in France. This looked at slow titrations to improve safety without affecting the efficacy of cannabidiol. For all indications (not just DS), the study showed that dosages increased from 10 mg/kg/day to 15.5 mg/kg/day from month 1 to month 6. The study included only 5 patients with TSC. o Evidence from a study of 6 people with Dravet syndrome in 1 centre in the UK, which reported an average cannabidiol dose of 13.3 mg/kg/day (Desai *et al*., 2021). Of note, the same study reported an average cannabidiol dose of 9.3 mg/kg/day for 9 patients with LGS. No patients with TSC were included. o Testimony from the fenfluramine manufacturer's clinical experts (who remain anonymous) that the average dose of cannabidiol in the UK could be 15 mg/kg/day or higher. • The following are quoted directly from TA808: o "The clinical experts said that there was no reason to expect that patients in the UK would be treated differently to patients in Europe". o "The committee noted that, while it would prefer not to disconnect the effects from the drug from the amount of drug given, it considered this to be an exceptional situation. It noted that treatments to reduce seizures are not used in the same way as other treatments that aim to reach the maximum tolerable dose. And it heard from clinical experts that the dose used would be a balance between seizure reductions and adverse effects of treatment". o "In this case, the committee concluded that it was reasonable to *use the real-world evidence presented by the company* to determine the dosages of both treatments in the model". *Dosing evidence for cannabidiol in the current appraisal compared with the fenfluramine appraisal* In the current appraisal of cannabidiol in TSC-associated epilepsy, the clinical expert present at the NICE Committee meeting on 15th September 2022 (Dr Sam Amin, who is highly experienced in managing patients with TSC-associated epilepsy) stated that "many people would have a dose closer to the company's modelled estimate of 12 mg/kg/day". In addition, the company has provided robust real-world cannabidiol dosing evidence from Germany, indicating that the observed median dose in clinical practice in 118 patients with TSC was 12.21 mg/kg/day in children and 7.77 mg/kg/day in adults.	

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			This testimony and evidence is stronger and more appropriate than the sources cited by the manufacturer in the fenfluramine DS submission for the following reasons: • The D'Onofrio study included only 5 patients specifically with TSC-associated epilepsy. • The Desai study included no patients with TSC at all, and was largely anecdotal. • Regarding the testimony about cannabidiol dosing from clinical experts provided by the manufacturer at the fenfluramine appraisal, the ERG noted that the company chose not to share any details about who these "highly-respected UK experts" were. Thus, it remains unclear if these anonymous experts had any experience of using cannabidiol in clinical practice and thus whether they were qualified to comment on its dosing. • The real-world German data provided for the current appraisal: o Are based on a significantly larger dataset – a cohort of 118 patients with TSC-associated epilepsy (identified within a national dataset covering approximately 64 million patients) o Are more recent, allowing time for clinical experts to become familiar with the usage/dosage of cannabidiol in TSC-associated epilepsy. *Conclusions* Overall, it is reasonable to expect that the NICE Committee would not base its decision regarding the appropriate cannabidiol dose for the economic analysis in this current appraisal solely on relatively weak sources of evidence/anonymous clinician testimony from a prior appraisal for a competitor product in a different indication. It is also reasonable to expect that the NICE Committee would apply the same general principles it adopted in the fenfluramine appraisal (as outlined above) to the current appraisal, specifically: • Accepting clinical expert testimony. • Acknowledging that patients in the UK would not be treated differently to patients in Europe. • Recognising that treatments to reduce seizures are not used in the same way as other treatments that aim to reach the maximum tolerable dose: the dose used would be a balance between seizure reductions and adverse effects of treatment. • Using the real-world evidence presented by the company to determine the dosage in the model.	

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			Based on the above: • The real-world evidence from Germany represents the best available evidence on which to determine the dose of cannabidiol in TSC-associated epilepsy • A clinical expert highly experienced in managing patients with TSC-associated epilepsy confirmed at the Committee meeting on 15th September 2022 that 15 mg/kg/day is likely to be the *maximum* dose of cannabidiol used in clinical practice and that many people would have a dose closer to 12 mg/kg/day. • The company retains 12 mg/kg/day as the average dose in its base case.	
7	Company	GW Research Ltd / Jazz Pharmaceuticals	**HCRU estimates** The company noted from the ACD that the NICE Committee considered that "healthcare resource use is likely overestimated in the company's model". The ERG provided a scenario that reduced the hospitalisation rates used in the model by an arbitrary 50%. The Committee noted that "the hospitalisation rates used in the ERG's scenario *were not underpinned by evidence*, so the true resource use for people with tuberous sclerosis complex was unknown". However, despite this cited lack of evidence, the Committee concluded that healthcare resource use is likely overestimated in the company's model and considered the ERG's scenario (with a 50% reduction in admissions) in its decision making. We note from the e-mail from the NICE TA team (dated 03/11/2022) that the ERG's scenario of reducing hospitalisation rates by 50% "informed the Committee's decision-making process" but was not a "strictly preferred assumption". Even though this was not one of the Committee's preferred assumptions, the company would like to make the following points: • For the TA614 and TA615 appraisals of cannabidiol in DS and LGS, in the absence of published evidence on resource use (both DS and LGS are orphan diseases, so this is not unexpected), some of the HCRU estimates were informed by *interviews with clinicians*. For the current appraisal, we took on board NICE's feedback from TA614 and TA615 – i.e. to use a more robust method for estimating HCRU – and have used a *two-round Delphi panel*. • TSC-associated epilepsy is also an orphan disease, so there are similar issues related to a lack of published evidence on resource use. The SLR conducted by the company did not identify any relevant studies to inform the economic model. • Therefore, as noted in the ACD: "Annual healthcare resource use based on seizure frequency for people with TSC-associated epilepsy was sourced from a two-round Delphi panel" (of 10 clinical experts).	Comment noted. Based on clinical expert advice at the second meeting, the committee agreed that healthcare resource use was likely overestimated in the company's modelling. It preferred the ERG's assumption reducing hospital admissions by 50% which better aligned with those in the technology appraisals for Lennox Gastaut and Dravet Syndromes. See FAD section 3.12.

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The Delphi method is well suited for this as it is a widely used and accepted method (e.g. it is recommended by NICE in PMG20) for achieving convergence of opinions concerning real-world knowledge solicited from experts.
In the absence of published data in this orphan disease, the output of the two-round Delphi panel is the best evidence available to inform the model, and is a recognised standard in NICE's hierarchy of evidence.
In line with more standard practice on deterministic sensitivity analysis (DSA), where the lower and upper values for each parameter included in the DSA are either obtained from the literature, based on clinical opinion or varied across a specified range to test uncertainty in the absence of a benchmark or analogue, the company has conducted a sensitivity analysis on the hospitalisation rates elicited from the Delphi panel. Table 1 below shows the ICERs around the company's base case when the hospitalisation rates from the Delphi panel are varied up to the ERG's arbitrary -50%. The same sensitivity analyses are also provided when a severity modifier is included (see Table 2 below and Comment 2 above).

Table 1: Cannabidiol hospitalisation rate sensitivity analysis (around base case)*
<table>
<tr><th colspan="2">Average dose</th><th>12 mg/kg/day</th></tr>
<tr><td rowspan="6">Hospitalisation rate</td><td>Base case#</td><td>£11,833</td></tr>
<tr><td>-10%</td><td>[redacted]</td></tr>
<tr><td>-20%</td><td>[redacted]</td></tr>
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Table 2: Cannabidiol hospitalisation rate sensitivity analysis (with severity modifier)*
<table>
<tr><th colspan="2">Average dose</th><th>12 mg/kg/day</th></tr>
<tr><td>Hospitalisation</td><td>Base case#</td><td>£9,861</td></tr>
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</table>
* Note: the ICERs are based on the company's revised base case incorporating the NICE Committee's preferred assumptions as outlined in Comment 4 above
# Hospitalisation rates as elicited from the 2-round Delphi panel

This sensitivity analysis shows that, across a range of hospitalisation rates, the ICERs are within the Committee's stated acceptable range.
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<tr><td>8</td><td>Company</td><td>GW Research Ltd / Jazz Pharmaceuticals</td><td>
<u>Updated NHS Reference Costs</u>
• In line with section 5.5.1 of NICE's Process and Methods Guide 2013 (PMG9), the company has updated the cost utility model with the most recent NHS Reference Costs (2020/21).
o Source: https://www.england.nhs.uk/wp-content/uploads/2022/07/2_National_schedule_of_NHS_costs_FY20-21.xlsx).
• The unit costs that have been updated in the model (tab "Resource Use Costs") were provided to the NICE Technical team via e-mail on 22nd November 2022, so that the ERG could conduct an independent validation.
• For reference only, if the now out-of-date 2019/20 NHS reference costs are applied in the updated model (incorporating all the changes outlined in Comment 4 above) then the company's base case ICER would be [redacted].

The application of a disease severity QALY modifier would reduce this ICER to [redacted] per QALY.
</td><td>Comment noted. The committee considered analyses including the updated NHS reference costs in the second committee meeting. See FAD section 3.12.</td></tr>
<tr><td>9</td><td>Company</td><td>GW Research Ltd / Jazz Pharmaceuticals</td><td>
<u>Institutionalisation calculation by the ERG</u>
As communicated to the NICE Technical Team (by e-mail on 22/11 2022) and accepted by the ERG (in the e-mail from the NICE Technical Team on 24/11/2022), there was a calculation error in the ERG's model (model labelled "ERG base case_ID1416_CBD in TSC_CE model AICCIC_PMB8Sep22 committees preferred assumptions") regarding institutionalisation, as follows:
</td><td>Comment noted. The committee considered analyses including the updated modelling of institutionalisation in the second committee meeting. See FAD section 3.16.</td></tr>
</table>

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
			One of the preferred assumptions of the Committee was that the caregivers of adult patients with TSC who are institutionalised have a 50% decrease in their disutility, associated with no longer having to care full time for their dependent. This is currently implemented in the model in cell K12 of tab "*Utilities*" (cell name "*UT_averageNcarer_ERG6*"). The coding for this cell is as follows: =(1-0.31)*UT_averageNcarer+0.31*(IF(ERG!F9=1,0.5,IF(ERG!F26=2,0.5*UT_averageNcarer,UT_averageNcarer))) However, the ERG has reduced the disutility of caregivers not by decreasing the disutility calculation itself, but by reducing the average number of caregivers per patient by 50% for the proportion of caregivers whose dependents are institutionalised (31%, as predicted by the Delphi panel). This coding does not do this, as the term "**UT_averageNcarer*" is missing from the calculation. The correct coding is shown below: =(1-0.31)*UT_averageNcarer+0.31*(IF(ERG!F9=1,0.5*UT_averageNcarer,UT_averageNcarer)) The company's updated model with our new base case has this correction implemented.	
10	Company	GW Research Ltd / Jazz Pharmaceuticals	**<u>Long term efficacy</u>** • The company notes the Committee's conclusion that "Cannabidiol reduces seizure frequency and increases the number of seizure-free days compared with usual care alone, but long-term efficacy is uncertain". • We reiterate that there is now a significant body of evidence (across three indications, TSC-associated epilepsy, LGS and DS) that demonstrates the long-term durability of efficacy outcomes with cannabidiol. • As noted in the ACD, our submission provided interim data from the GWPCARE6 OLE (Open Label Extension) study in TSC-associated epilepsy up to 72 weeks. • 3-year (156-week) efficacy data from the GWPCARE6 OLE will be presented by Thiele, E et al. at the American Epilepsy Society (AES) congress in December 2022. The results demonstrate that add-on cannabidiol treatment was well-tolerated and produced sustained reductions in TSC-associated seizures for up to 156 weeks in patients who continued on treatment:	Comment noted. The committee considered the 3-year data from the open lab extension study in the second committee meeting. See FAD section 3.5.

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			o Median reduction from baseline in TSC-associated seizures ranged from [redacted] across 12-week windows through 156 weeks o Reductions in TSC-associated seizures ≥50%, ≥75%, and 100% were maintained up to 156 weeks, ranging from [redacted], [redacted], and [redacted], respectively.	
1	Stakeholder	Tuberous Sclerosis Association	We believe that NICE Appraisal Committee has overlooked the following key areas that are extremely important to people living with Tuberous Sclerosis Complex (TSC) and their family and carers: • **The massive positive impact on quality of life that seizure reduction can have on people living with TSC.** Even if someone is not seizure free having fewer and more predictable seizures can really make a big difference • **The role of seizure reduction in care responsibilities and challenges**. Care for people with TSC (which is often at least two-to-one) can lead to secondary challenges in employment, financial security, social interactions and the wider family unit (such as the impact on siblings). Seizure reduction can play a major part in making these challenges easier In addition, we feel the need to highlight the unacceptable inequality in access to TSC-related epilepsy medicines in the UK. Decision-makers in Wales and Scotland have already made correct choices to fund Epidyolex®. TSC-related epilepsy treatment is available to some people but not others depending on where they live in the UK, which the TSA completely disagrees with. The committee has reviewed evidence relating to the **reduction in frequency of refractory epilepsy with a significant focus on the 5% who were seizure free**, and not those who had a reduced seizure frequency. For people with TSC and for those caring for them, even a modest seizure reduction can change their lives. Even if someone is not seizure free, having fewer, predictable seizures can really make a big difference to their overall wellbeing. The TSA interviewed seven families living with TSC who have had the opportunity to try Epidyolex®. We carried out a half-hour telephone interview with each family using a standard set of questions about TSC, epilepsy and Epidyolex®. The information from these interviews was collated and used to inform the TSA's submission to NICE at an earlier stage of the process.	Comment noted. The benefits of an increased number of seizure free days were considered by committee. See FAD section 3.1 and 3.5.

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			During these interviews, we asked people living with TSC and their families and carers to share the aspects of living with TSC that are not met by currently available treatments. All of these families said that their child's seizures, epilepsy and behaviour problems are the areas that need addressing most urgently. These areas impact the most on their day-to-day lives and they would welcome help and support in addressing these unmet needs. One mother who cares for an adult daughter who lives with TSC (aged 37 years old) told us that TSC-related seizures "*affects everything; we take her out to a meal, and she can have a seizure whilst waiting for food and then she doesn't want to eat. Usually, mum goes to the restaurant first, whilst dad waits in the car with daughter and they only go in when the food is on the table. Or if she has a seizure during the meal then you are rushing to get out to leave and don't bother eating. Everything you do, you have to think about how it's going to affect her. It's pointless going out as more often than not, she's had a seizure.* *Seizures can go on all day or some days there are only a few. She has some type of seizure every day and she has different ones. She has broken every bone in her left foot through drop seizures, it's so swollen that it's difficult to get shoes. She has been in and out of hospital. She's knocked two teeth out right up into her gum through her cheek – had to be stitched up.* *She has to have two people with her 24 hours a day because of seizures and behaviour. She has no idea of danger so she could just walk into the road and be hit by a car and she wouldn't know what to do. You have to keep everything out of her way as she will drink whatever is in the cupboard, she would pick up and eat whatever is lying around so she has to be monitored. She has had problems with breathing as she doesn't chew properly so it becomes a choking hazard. She has to be fed to make sure she has swallowed properly otherwise she'll continue eating even whilst choking. You cannot leave her with food, she would choke, she would die. Food has to be cut up or mashed*." Another mum, who is the main carer to her 19-year old daughter, was forced to give up work to care for her daughter full-time. She organises all hospital appointments for her daughter which she describes as "lots of them". The mum said this takes a toll on the family and has a huge impact on her young son. Four out of seven families who were interviewed to inform TSA's initial response to NICE described the improvements to their loved one's epilepsy as 'life-changing' following treatment with Epidyolex®. One family with a young child (aged 7) said:	

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			"*Epidyolex® was life changing in terms of sleep. My husband and I were able to have an entire night's sleep. His behaviour was much better at school. Epidyolex® massively reduced seizures in combination with Clobazam. He was having nine seizures a day before starting the medicine, but within five months of taking it, he was having a total of seven seizures in a month. His seizures reduced in severity, he would only experience chin twitches. He was calm and happy, and slept much better. He said Epidyolex® tastes nice – like strawberry. Epidyolex® was a godsend.*" Of the three patients still taking the drug at the time of interview, they told us: "*Epidyolex® has been life changing for our son (aged 16). It has unlocked a part of him that the family had lost. He now has an opinion, he is not as vulnerable, he asks for the toilet. He is more rounded. He is more alert. He says no to things he doesn't like or doesn't want to do. He has had no drop seizures and the Epidyolex® has reduced the frequency of other seizures, although he still has some seizures during the night."* The family went on to say with joy that "*Epidyolex® has given him the energy to live in society and has unlocked the monkey in him.*" Another family told us of the massive benefits they have experienced and witnessed as a result of Epidyolex®: "*Our son (aged 12) was seizure free for nine months at first, and he now has around 4-5 seizures a day. He has more emotions since taking Epidyolex®. If seizure frequency increases, then I take him to the GP as this usually means that he has some sort of infection. He is more awake, he sleeps less, and he is happier going to school.*" In forming this response document to NICE, the TSA has carried out an additional survey of the TSC community to understand what having fewer seizures would mean for them or the person that they care for, and how would a reduction in seizures improve their quality of life. Responses to our survey (both carers and people living with TSC) include the following: "*A life without seizure control is a terrible situation.*" "*Epilepsy impacts on my confidence, levels of fatigue and concentration as well as my ability to travel further afield. I currently feel uncomfortable forming personal relationships and my seizures were a big factor in the break-up of my marriage.* *I'm a dad who also cares for my son who has TSC and seizure disorder. If he had the confidence and reassurance of being seizure free, he would be able to more things*	

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			independently. He would be less anxious (he is being treated for ADHD and anxiety associated with TSC) and wants to be able to learn to drive - something I am not able to do myself, but I cannot promise to him that he will be able to do either, due to his seizures." "*Fewer seizures would massively improve our lives, my child would have more chance to learn a chance for days out a chance to make friends go to nursery all the things every other child can do and takes for granted we cannot because seizures ruin lives! I would have a happier child, more sleep, better chance to make memories and do nice things, more time to spend with her sister would massively improve every area of all our lives.*" "*This horrendous uncontrolled condition (TSC) has robbed her of her independence, stolen her of her previous cognitive ability and given us a life we never imagined. I have given up work to care for her full time. She had a full year out of college and this year she went into regression (caused by multiple uncontrollable seizure activity). She has commenced only on a 3 day vocational course. I cannot believe that professionals can judge medication only on controlling seizures - even a reduction of seizure activity gives a better quality of life to both the person living with epilepsy and the family. If all meds were judged on full control, there would be no anti-epilepsy drugs passed!!!*" "*For my daughter, the frequency with which she has seizures (on a daily basis) makes it incredibly hard for her to learn and retain skills. It has a massive impact on her quality of life and her development. Of all the symptoms that arise from tuberous sclerosis, it is seizures that impacts her most negatively. Having some kind of seizure control (even if it isn't complete seizure freedom) would enable her to have such a better quality of life, reduce anxiety, increase her capacity for learning, give her better mental as well as physical help. In short, it would be invaluable."* *"We have been following families in a similar situation who have access to cannabidiol and the results seem staggering. Any reduction at all in our son's seizures would improve his quality of life. Instead of 30 to 40 daily if he had say 10 it would make a massive difference to him and to us."* *"Less chance of a severe status seizure that could end life, ability to allow someone else to watch my child so I can have time with partner, less medication, better ability to learn and retain information and become the person she's capable to be."*	

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			"*Reduced seizures would change his life. When he has less seizures he thinks more clearly, he speaks better and concentrates of life more. He becomes engaged in activities and is less tired and nervous.*" "*He would be able to develop, maybe talk and say mum. He wouldn't be exhausted all the time and would stop deteriorating. I may get a few more years with him. I am able to leave the room. I would be able to have me time. I would be able to go to work and be able to go to uni to become a paramedic.*" "*It would mean she could go and have play dates and sleepovers at her friends' houses, it would mean she could sleep on her own instead of mum in bed with her.*" "*For my son, as for many TSC suffers, the chance of living life with less seizures is actually a chance to live the life they deserve. More independence, more clarity in their concentration - more life!*" *"My son has suffered from seizures every day since being an infant as a symptom of TSC. He has been taken to hospital countless times over the years via ambulance due to this. As a small child he was in non-convulsive status for a period of time until a medication was found to get him out of that. He couldn't stand for more than a few seconds, could not eat properly without biting his tongue which was awful to watch and care for, and for him I can't imagine what it must have been like."*	
2	Stakeholder	Tuberous Sclerosis Association	We also wish to draw your attention to an additional piece of evidence which supports the draft proposal to fund Epidyolex® for TSC-related epilepsy in England. Research published by Public Health England (PHE) in 2018 has found that the number of annual deaths of epilepsy patients has increased by 70 per cent between 2001 to 2014. Deaths occur on average eight years earlier than those for the rest of the population. With the right treatment, over 60% of people with epilepsy could stop having seizures altogether. Of all the neurological conditions studied by PHE only epilepsy was found to have a significant relationship with deprivation, with 13 deaths per 100,000 population in the most deprived areas compared to five deaths per 100,000 in the least deprived. (Summary from HSJ article on 19 March 2018). Access to Epidyolex® would have the potential to further reduce the number of annual deaths related to epilepsy in England.	Comment noted. The committee acknowledged that tuberous sclerosis complex is a severe and multisystemic disease that significantly affects the quality of life of patients, carers and families. It agreed that the severity of disease should be considered in the decision making. See FAD section 3.19.
3	Stakeholder	Tuberous Sclerosis Association	Another critical area that the committee has not fully considered is the **significant burden and impact of care needs on families and carers of people with TSC, regardless of the number of carers involved**. The carers of those living with TSC also	Comment noted. The committee noted the significant burden of care required by people with tuberous

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			experience a significant impact on their physical and mental health as a result of caring for someone with the condition. TSC is a systemic disease with multiple physical and psychological problems that has a profound impact on both the patient and their family and carers. Care for people with TSC that is two-to-one does not therefore demonstrate a reduced burden on the two carers compared to if it was a single carer. In a family unit, two-to-one care often leads to massive secondary care challenges in employment, financial security, social interactions and the wider family unit such as the impact on siblings as the focus of both parents becomes wholly on the person with TSC. Seizure reduction can play a major part in making these challenges easier for all carers. If seizures can be reduced in frequency and severity, carers of those with TSC can begin to rebuild their own lives and thereby improve the lives of entire family units. Those responding to the TSA reported improvements to the physical and mental health of family members - both parents and siblings - as well as patients themselves - as a result of treatment with Epidyolex®: A mother of a 12 year-old who has been taking Epidyolex® told us: "*My daughter's grandad used to baby sit during the 9-month seizure free period, so that my partner and I could go out for food. We usually take it in turns to go out and look after her. As she now has less seizures, this means we can go out for food together and socially it has made a huge difference for my family.* *It has been a huge weight off her siblings' shoulders. It's upsetting for them to watch their sister go through a seizure which usually lasts for 40-50 seconds, but it feels like two hours. Everyone's mood has lifted, and her siblings are not so worried all the time. Mental health wise, a huge cloud has lifted. The teachers in school were happy for her too*." Family with a young child (aged 7) said: "*Epidyolex® was life changing in terms of sleep. My husband and I were able to have an entire night's sleep. His behaviour was much better at school. Epidyolex® massively reduced seizures in combination with Clobazam. He was having nine seizures a day before starting the medicine, but within five months of taking it, he was having a total of seven seizures in a month. His seizures reduced in severity, he would only experience chin twitches. He was calm and happy, and slept much better. He said Epidyolex® tastes nice – like strawberry. Epidyolex® was a godsend."* One mum who is the sole carer of her 16-year-old son with TSC shared with us:"*As a*	sclerosis complex. See section 3.14.

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			single parent of a child with TSC, the seizures are very difficult to control. I have always been aware the 'best we can get them' is the reality, anything more than that would be more like a miracle and we've had our fair share of those! It is always a very stressful and anxious time starting any new medication, but you can't give up. The combination of Clobozam and Cannabidiol has been phenomenal for us, but if we hadn't been given the opportunity to try it, I dread to think where we would be now. *I have been doing this for 16 years so I'm sure you can appreciate after that amount of time, trying all kinds of different medications and having my son being the best he has ever been is just amazing and I thank my lucky stars every day. I fully support that Cannabidiol should be made available to patients. It could be the 'miracle' they have waited so very long for and it could completely change their lives for the better. It's not a cure, but it's improved our lives dramatically. Why should others be denied the chance to at least be given the opportunity to try it when it could massively improve their life too.*" Respondents to our further survey developed for this response shared with us how reduced seizures would impact their lives as carers: "*It would quite simply improve my mental and physical well-being. Seizure control (or a lack of it) is a constant worry and something we as parents carry with us always. As our daughter can have seizures at any time of day and has them on a daily basis, it is something that is always on the back of our mind, as well as that of her younger sister who is only 7 and has been able to identify them since a young age*." "*If our son was having less seizures then I might be able to get better sleep at night and my husband and I could also have a better quality of life. I sleep with a baby monitor on my bedside table and are up at least 2 or 3 times a night with him fitting - he is 18 but I am 58. If he had less seizures in the day, he wouldn't sleep as much so he would sleep better at night.*" "*For me personally it would mean I could take him out on my own without feeling too afraid he was going to have a seizure out. He is a big lad now and I'm 65 so keeping him safe is difficult, less seizures means less difficulties for me (and injuries). We could take holidays abroad without the worry*." "*I wouldn't be living life on the edge all the time waiting for phone calls from my daughter to say pick up the kids from school, come get the kids as J is having a tonic clonic. I wouldn't have to worry constantly that my granddaughter is missing out on so much*	

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			because of seizures." "*A reduction of seizures and or loss of seizures would mean less juggling of care within the family and greater freedom. Peace of mind.*" "*As a parent and carer, a reduction in seizures is everything. To watch my son have seizures every day is not only heart-breaking, it's tiring. It's as if normal family life goes on hold for periods of time when seizures decide to increase, change pattern or appearance.* *Sleeping with an eye open is difficult and obviously puts a stain on most things that I can think of.*" "*I live in constant fear of my son having a seizure which requires hospitalisation, and also of SUDEP. Improved seizure control would he alleviate the risks. I currently work, but if his epilepsy doesn't improve, I may have to stop working. I receive ad hoc support from NHS to deal with the mental toll his epilepsy has on me - anti anxiety medication, counselling etc. It adversely affects the whole family.*" "*I could work, sleep at night, not have to tap into expensive social care respite services, have less ineffective epilepsy medications, less NHS appointment and basically save the government money.*" "*I have watched uncontrolled epilepsy rob my child of the life she was leading. To see improvements would bring a joy to my heart and decrease the pain and stress we live with everyday watching our daughter and the regression that is occurring due to this horrendous condition. Achieving decreased seizures would improve her cognitive ability -fewer seizures, less recovery time, less sleeping. Increase confidence. Ability to interact more with peers. Improve ability to follow academic studies-the list is endless.*" "*Wouldn't be as anxious and on edge watching him waiting for another one to happen.*" "*A weight off our minds. Relief for a brighter future. Normality*"	
4	Stakeholder	Tuberous Sclerosis Association	The Tuberous Sclerosis Association is supportive of the proposal that Epidyolex® should be funded for people with TSC-related epilepsy. The addition of Epidyolex® therapy for refractory epilepsy will have a vast positive impact on equality and health inequality in this patient group. It is clear that refractory epilepsy is a major cause of the severe intellectual impairment which is common in TSC.	Comment noted. Cannabidiol is recommended for routine use for treating people with seizures caused by tuberous sclerosis complex in the NHS. See FAD section 3.22.

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			This in turn results in psychological problems such as autistic spectrum disorder, severe anxiety and depression, impulsiveness and self-harm. The experience amongst families and the evidence from natural history studies show that the better controlled epilepsy is, and the younger the age at which this occurs, the better the outcome for intellectual development, with amelioration of the above-mentioned problems. In general, this patient group has previously had poor access to care because of the variety and severity of their problems. The availability of effective treatments like Epidyolex® 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). Epilepsy is the most common neurological feature of TSC, affecting approximately 84 per cent of people living with the condition. More than 50 per cent of people with TSC who have epilepsy will not respond to standard anti-epilepsy medicines and may need an alternative form of treatment. These individuals will have a better quality of life if Epidyolex® can provide better seizure control. **Seven out of seven families answered yes to our question: *If Epidyloex® were available, would (patient) prefer to try this treatment first, before trying other treatments?*** One mum said: "*We would have tried this first – even if it doesn't work it's well worth giving it a go*." Another family said "*Yes as Epidyloex® has non-toxic side effects."* Third family told us: "*We have been asking for CBD for years but it was never licenced.*" Fourth family also agreed that it is worth a try: "*None of the other treatments have worked fully. Epidyolex® was no worse than anything else. It is worth a try – it could work well for others.*" One parent that was surveyed told us "*Our daughter has tried countless anti-epileptics drugs and having access to cannabidiol would be of great benefit as I understand it uses a different pathway within the body and therefore offers an alternative potential remedy to address seizures. It also seems those of us who happen to live in England are not being treated equally given that cannabidiol is approved in Scotland and Wales and therefore accessible by those affected by TSC in those areas*."	
1	Stakeholder	Young Epilepsy	Young Epilepsy urges NICE to recommend cannabidiol for seizures caused by tuberous sclerosis complex (TSC). Research shows that cannabidiol plus usual care can reduce seizure frequency and increase the number of seizure-free days. Seizure frequency can	Comment noted. Cannabidiol is recommended for routine use for treating people with seizures caused

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			have a significant impact on quality of life for people living with epilepsy, as well as their family. A recommendation for cannabidiol to be used for seizures associated with TSC would ensure that more people living with the condition can have access to a range of treatment options. If treatment is found to be ineffective for an individual, it can be discontinued. We are concerned that the draft decision not to recommend cannabidiol will create inequalities in treatment access for people with TSC across the UK. Authorities in Wales and Scotland have already approved the treatment for people with TSC	by tuberous sclerosis complex in the NHS. See FAD section 3.22.

Document processed	Organisation name – Stakeholder or respondent	Disclosure on tobacco funding / links	Number of comments extracted	Comments

NICE National Institute for Health and Care Excellence

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

Consultation on the appraisal consultation document – deadline for comments 5pm on 29 November 2022. Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**GW Research Ltd / Jazz Pharmaceuticals**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Comment	Comments

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number	
1 Summary – company's updated base case	• Based on the feedback from the NICE Committee in the ACD, the company has made changes to its base case. • As outlined in more detail in Comment 4 below, we have updated our base case to incorporate many of the Committee's preferred assumptions (as stated in the e-mail from the NICE TA team dated 03/11/2022) as follows: o Using a 6.61 day cut-off for the proportion of people who are seizure-free over 7 days o Using the health state utilities from the company's vignette o Assuming a cumulative 1.8 carers o Adjusting for institutionalisation using the ERG's approach* o Including cost and benefits for TAND aspects for people aged 2 to 6 years, using the utility benefit from the company's base case. * Note that this includes an updated calculation for institutionalisation as communicated to the NICE Technical Team on 22/11/2022 (see Comment 9 below for more detail) • The company maintains that the average dose of cannabidiol (12 mg/kg/day – as accepted by NICE for the DS and LGS appraisals) used in our cost-effectiveness analysis is reasonable and justified, based on robust evidence, feedback from clinical experts and as observed in real-world prescribing data from 118 patients in Germany since 2019 (please see Comment 6 below for more detail). • As per section 5.5.1 of NICE's PMG9, the company has updated healthcare resource use costs in the economic model to include the latest NHS reference costs (from the National Schedule of NHS Costs - Year 2020-21) • The company's updated base case ICER incorporating all the above changes is **£11,833** per QALY. • The application of a disease severity QALY modifier (to appropriately reflect the severity of TSC-associated epilepsy – see Comment 2 below) would reduce the company's revised base case ICER to **£9,861** per QALY.
2 Severity of the disease	• The NICE Committee has recognised the severity of TSC-associated epilepsy and that it "severely affects the quality of life of patients, carers and their families". • TSC-associated epilepsy is a rare (orphan), devastating and life-threatening form of epilepsy that presents early in childhood and is associated with refractory seizures and poor outcomes. In addition to the high seizure burden, the associated cognitive and behavioural difficulties known as TSC-associated neuropsychiatric disorders (TAND) prevent children from achieving independence in adult life. Mortality rates for people with TSC are higher than in the general population, with uncontrolled epilepsy among the most common causes of death in TSC as a result of status epilepticus or Sudden Unexpected Death in Epilepsy (SUDEP). • The Committee's recognition of the severity of the disease also reflects the brave and comprehensive testimony of the parent/patient expert at the Committee meeting on 15th September 2022. The patient expert outlined the stark reality of living day to day with a child with TSC-associated epilepsy and the profound impact on the quality of life of both the patient and the family as a result of the seizures and TAND.

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Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

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	• The company further notes from the ACD that "half of people with tuberous sclerosis complex have associated learning difficulties, which is a protected characteristic under the Equality Act 2010". • We note that the NICE methods guidance was updated in February 2022 in order to support patients with severe diseases. This updated 2022 guidance introduced new criteria to reflect, in exceptional circumstances, the severity of disease within decision making. The company is aware that this submission is being assessed under the old methods guidance (the invitation to participate was sent to us on 18th January 2022, just two weeks before the new guidance was introduced on 1st February 2022). However, given the subsequent long delays in the appraisal process, we consider it appropriate to include the severity of TSC-associated epilepsy and the impact of this on the economic analysis. As detailed in our submission, cannabidiol in a patient population with TSC-associated seizures satisfies the criteria laid out by NICE under the new methods for a severity of disease modifier. Given the severe impact of TSC-associated epilepsy, a QALY weight of 1.2 (applicable for the absolute loss of between 12 to 18 QALYs) should be applied in the context of decision making. • The application of a disease severity QALY modifier (to appropriately reflect the severity of TSC-associated epilepsy) reduces the company's revised base case ICER (of £11,833) to £9,861 per QALY. • Of note, using *all* the NICE Committee's preferred assumptions (as stated in the e-mail from the NICE TA team dated 03/11/2022, that is: using a 6.61 day cut-off for the proportion of people who are seizure-free over 7 days; using an average dose of 15 mg/kg/day; using the health state utilities from the company's vignette; assuming a cumulative 1.8 carers; adjusting for institutionalisation using the ERG's approach (with an updated calculation as outlined in Comment 9 below); including cost and benefits for TAND aspects for people aged 2 to 6 years using the utility benefit from the company's base case), the ICER is £22,401 per QALY (and with the severity modifier applied, it is £18,668 per QALY), which is well within the Committee's stated 'acceptable ICER' range.
3 Additional benefits of cannabidiol not captured in the current model / economic analysis	There are additional benefits of cannabidiol that are not captured in the current model/economic analysis. For example, the cost-effectiveness estimates do not include the value of: • A beneficial impact on the mortality related to Sudden Unexpected Death in Epilepsy (SUDEP) that is associated with effective seizure control • The broader impact on TAND (not captured in the very conservative assumptions used in the current model) • Improving the quality of life of the wider family, including siblings and other family members • Increasing caregiver productivity and the associated societal benefits of the parent(s)/primary caregiver(s) not needing to give up work to care for a patient with TSC-associated epilepsy • Reducing the duration/severity of seizures (the model only captures seizure frequency) • The long-term impact of improved seizure control on comorbidities and injuries
4 NICE's preferred assumptions	The company noted the preferred assumptions from the NICE Committee. In order to avoid any further delays in patients with TSC-associated epilepsy and their families having access to a much-needed treatment for this severe condition, we have adopted the majority of these assumptions in our revised company base case. However, we reiterate below why we consider that they are extremely conservative and/or may lead to the ICER being over-estimated: • **Impact of cannabidiol on TAND aspects**

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	The Committee has recognised *some* of the potential impact of cannabidiol on TAND, since aspects of TAND can have a huge impact on the lives of patients with TSC-associated epilepsy and their caregivers. As noted in the ACD: "patient experts highlighted the significant quality-of-life impact from TAND for patients and families. Severe learning difficulties occur in around 30% of people and may impede speech. Impaired movement may also limit all aspects of daily living. Poor behaviour including anger, mood swings, aggression and a lack of perception of risk often makes daily activities impossible and people may need round the clock care. People with the condition also have disrupted sleep, which can impact on the mental health of the entire family". Even though the Committee's preferred base case only includes a very conservative assumption on TAND, we consider that it is important to include it in the analysis and that there is potential *additional benefit* from the impact of cannabidiol on TAND that it is not possible to capture in the economic model. • **6.61 versus 6.5 cut-off for people seizure-free over 7 days** We note that the NICE Committee considered that "the proportion of people who are seizure-free over 7 days in the model is uncertain but a 6.61 day cut-off is most appropriate for decision making". Although we accept that NICE's preference was to use the ERG's very conservative approach, we maintain that there were robust methodological reasons for choosing the 6.5 cut-off and that this better reflected the trial outcomes in the model. • **1.8 carers** We note that the Committee considered that "The effect on carers' quality of life should be modelled and the ERG's assumption using 1.8 carers is most appropriate". Whilst the significant impact of TSC-associated epilepsy on caregiver quality of life has been recognised by NICE, in our submission and in our responses to the ERG report, the company included utilities for *two* caregivers. This reflects the impact of TSC-associated epilepsy on the quality of life of the wider family. We acknowledge that not every patient will have two primary caregivers (although many will need more than two). However, the company is aware that there are often many other people contributing to the care of the patient (for example, siblings, grandparents, aunts, uncles, family friends). Each family carer has the burden, worry and psychological distress of caring for a patient at risk of injury and even death from their seizures. Thus, it would be expected that incorporating the full and cumulative effect of TSC-associated epilepsy on the lives of *all* family members would result in a further reduction of the ICER. • **Institutionalisation*** We note that the NICE Committee concluded that it is appropriate to include a reduction in carer disutility associated with institutionalisation of a patient. However, we also note that the Committee considered that "the increase in carer quality of life in the company and ERG's analyses were not supported by data and other scenarios would be equally plausible...Given the lack of evidence to support the size of this reduction, it considered the ERG's approach preferable". Based on this, although we accept that NICE's preference was to use the ERG's very conservative approach, the company's approach is equally valid. We also refer back to the patient expert's comments: "the patient expert agreed that although carers had more free time if a person with TSC was institutionalised, concerns and guilt would remain, especially about exposure to abuse".

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	* Note that the company's base case includes an updated calculation for institutionalisation (see Comment 9 below for more detail) • **Different values of the seizure-free health states for carers** The ERG adjusted the caregiver utility for the seizure-free health state to that of an average adult aged 45. The company accepted this adjustment from the ERG at the Technical Engagement stage of the appraisal process and it is reflected in the company's revised base case. With regard to the scenarios using different values, we note from the ACD that the NICE Committee concluded that "Scenarios varying the seizure-free utility value for carers had minimal impact on the ICER".
5 NICE process for handling uncertainty	The company noted that the NICE Committee has changed the standard threshold for the ICER: *"…the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)"* We would like to make the following observations on this: • TSC-associated epilepsy is a severe and orphan disease • As presented in the Committee meeting on 15th September 2022, both the previous company base case (before the updates outlined in Comment 4 above) and the ERG base case ICERs were substantially under £20,000 per QALY gained compared with usual-care (ERG base case ICER was £16,928; previous Company base case ICER was £14,594) • The ACD document makes reference on numerous occasions to the ERG's 'conservative' assumptions being the Committee's preferred option. In this context, it is difficult to understand why, when all these 'conservative' assumptions have been used in the Committee's preferred base case, the acceptable ICER threshold is then set much lower than for other rare (orphan) and severe diseases • The threshold is also not in line with previous appraisals of cannabidiol in severe epilepsies – in TA614 (Dravet syndrome) and TA615 (Lennox-Gastaut syndrome), the accepted ICERs were £32,471 and £33,721, respectively. This was because the Committee recognised the additional benefits of cannabidiol that could not be captured in the economic model. Based on the above, the Committee's 'acceptable ICER' threshold appears unreasonable considering that many elements of the Committee's preferred base case remove uncertainty or are noted in the ACD as being 'conservative'.
6 Dose of cannabidiol in clinical practice	The company maintains that the average dose of cannabidiol (12 mg/kg/day – as accepted by NICE for the DS and LGS appraisals) used in our cost-effectiveness analysis for cannabidiol in TSC-associated epilepsy is reasonable and justified, based on robust evidence, feedback from clinical experts and as observed in real-world data from 118 patients with TSC. *Evidence base* In the company's submission, and in our responses to the ERG report and technical engagement, the *average* dose of cannabidiol used in the cost-effectiveness analysis base case is 12 mg/kg/day reflecting that, *across a cohort* of UK patients with TSC-associated epilepsy in clinical practice, there

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	will be a spectrum of doses ranging from ≤ 10 mg/kg/day to the maximum of 25 mg/kg/day. We have provided a large body of evidence in support of this (please refer to the ID1416 Committee Papers for more detailed information, which is not reproduced here). In particular, we have provided recent and robust real-world data from a large cohort in Germany that demonstrates that lower doses of cannabidiol are used in clinical practice. As noted in the ACD, data from 118 patients in Germany indicate that the median cannabidiol dose in the real world was 12.2 mg/kg/day in children and 7.8 mg/kg/day in adults. *NICE Committee's view on cannabidiol dose (from the ACD)* The company noted that the NICE Committee: • "Agreed that the dose of cannabidiol that would be used in clinical practice is unknown, but an average dose of 15 mg/kg/day should be used for decision making". • "Decided that the ERG's scenario using an *average* dose of 15 mg/kg/day for cannabidiol is appropriate" This was even though the clinical expert at the Committee meeting contradicted the ERG's scenario, stating: 15 mg/kg/day is likely to be the *maximum* dose of cannabidiol used in clinical practice as a trade-off between efficacy and side effects. However, many people would have a dose closer to the company's modelled estimate of 12 mg/kg/day. *Fenfluramine appraisal (Dravet syndrome)* In the ACD, it is stated that the Committee noted that a 15 mg/kg/day average dose for cannabidiol was 'accepted' in NICE's technology appraisal guidance on fenfluramine for treating seizures associated with Dravet syndrome. We would like to draw attention to some key aspects of the fenfluramine appraisal that are of relevance (information taken from NICE TA808, where appropriate): • In the pre-consultation version of the fenfluramine model, the fenfluramine manufacturer used a dosage of *12 mg/kg/day* for cannabidiol, which was in line with the dosage accepted in NICE's technology appraisal guidance on cannabidiol in DS/LGS. However, the fenfluramine manufacturer then changed its mind, arguing that the typical maintenance dosage of cannabidiol used in the UK was likely to be higher, and increased this to a dosage of 15 mg/kg/day in its updated model (note: this change was not requested by either the ERG or the NICE technical team). This large increase in the average dose of cannabidiol used in the fenfluramine model is perhaps not unexpected, given that demonstrating the possible cost-effectiveness of fenfluramine relied on a comparison with the cost of cannabidiol. Of note, the 'typical' dose of fenfluramine was not increased similarly in the updated model. • The fenfluramine manufacturer aimed to justify the large increase in the average dose of cannabidiol with information including the following: o Evidence from a study on slow titration of cannabidiol add-on in drug-resistant epilepsies (D'Onofrio *et al*., 2020), which was conducted in France. This looked at slow titrations to improve safety without affecting the efficacy of cannabidiol. For all indications (not just DS), the study showed that dosages increased from 10 mg/kg/day to 15.5 mg/kg/day from month 1 to month 6. The study included only 5 patients with TSC.

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	o Evidence from a study of 6 people with Dravet syndrome in 1 centre in the UK, which reported an average cannabidiol dose of 13.3 mg/kg/day (Desai *et al*., 2021). Of note, the same study reported an average cannabidiol dose of 9.3 mg/kg/day for 9 patients with LGS. No patients with TSC were included. o Testimony from the fenfluramine manufacturer's clinical experts (who remain anonymous) that the average dose of cannabidiol in the UK could be 15 mg/kg/day or higher. • The following are quoted directly from TA808: o "The clinical experts said that there was no reason to expect that patients in the UK would be treated differently to patients in Europe". o "The committee noted that, while it would prefer not to disconnect the effects from the drug from the amount of drug given, it considered this to be an exceptional situation. It noted that treatments to reduce seizures are not used in the same way as other treatments that aim to reach the maximum tolerable dose. And it heard from clinical experts that the dose used would be a balance between seizure reductions and adverse effects of treatment". o "In this case, the committee concluded that it was reasonable to *use the real-world evidence presented by the company* to determine the dosages of both treatments in the model". <u>*Dosing evidence for cannabidiol in the current appraisal compared with the fenfluramine appraisal*</u> In the current appraisal of cannabidiol in TSC-associated epilepsy, the clinical expert present at the NICE Committee meeting on 15th September 2022 (Dr Sam Amin, who is highly experienced in managing patients with TSC-associated epilepsy) stated that "many people would have a dose closer to the company's modelled estimate of 12 mg/kg/day". In addition, the company has provided robust real-world cannabidiol dosing evidence from Germany, indicating that the observed median dose in clinical practice in 118 patients with TSC was 12.21 mg/kg/day in children and 7.77 mg/kg/day in adults. This testimony and evidence is stronger and more appropriate than the sources cited by the manufacturer in the fenfluramine DS submission for the following reasons: • The D'Onofrio study included only 5 patients specifically with TSC-associated epilepsy. • The Desai study included no patients with TSC at all, and was largely anecdotal. • Regarding the testimony about cannabidiol dosing from clinical experts provided by the manufacturer at the fenfluramine appraisal, the ERG noted that the company chose not to share any details about who these "highly-respected UK experts" were. Thus, it remains unclear if these anonymous experts had any experience of using cannabidiol in clinical practice and thus whether they were qualified to comment on its dosing. • The real-world German data provided for the current appraisal: o Are based on a significantly larger dataset – a cohort of 118 patients with TSC-associated epilepsy (identified within a national dataset covering approximately 64 million patients) o Are more recent, allowing time for clinical experts to become familiar with the usage/dosage of cannabidiol in TSC-associated epilepsy.

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	Conclusions Overall, it is reasonable to expect that the NICE Committee would not base its decision regarding the appropriate cannabidiol dose for the economic analysis in this current appraisal solely on relatively weak sources of evidence/anonymous clinician testimony from a prior appraisal for a competitor product in a different indication. It is also reasonable to expect that the NICE Committee would apply the same general principles it adopted in the fenfluramine appraisal (as outlined above) to the current appraisal, specifically: • Accepting clinical expert testimony. • Acknowledging that patients in the UK would not be treated differently to patients in Europe. • Recognising that treatments to reduce seizures are not used in the same way as other treatments that aim to reach the maximum tolerable dose: the dose used would be a balance between seizure reductions and adverse effects of treatment. • Using the real-world evidence presented by the company to determine the dosage in the model. Based on the above: • The real-world evidence from Germany represents the best available evidence on which to determine the dose of cannabidiol in TSC-associated epilepsy • A clinical expert highly experienced in managing patients with TSC-associated epilepsy confirmed at the Committee meeting on 15th September 2022 that 15 mg/kg/day is likely to be the *maximum* dose of cannabidiol used in clinical practice and that many people would have a dose closer to 12 mg/kg/day. • The company retains 12 mg/kg/day as the average dose in its base case.
7 HCRU estimates	The company noted from the ACD that the NICE Committee considered that “healthcare resource use is likely overestimated in the company’s model”. The ERG provided a scenario that reduced the hospitalisation rates used in the model by an arbitrary 50%. The Committee noted that “the hospitalisation rates used in the ERG’s scenario *were not underpinned by evidence*, so the true resource use for people with tuberous sclerosis complex was unknown”. However, despite this cited lack of evidence, the Committee concluded that healthcare resource use is likely overestimated in the company’s model and considered the ERG’s scenario (with a 50% reduction in admissions) in its decision making. We note from the e-mail from the NICE TA team (dated 03/11/2022) that the ERG’s scenario of reducing hospitalisation rates by 50% “informed the Committee’s decision-making process” but was not a “strictly preferred assumption”. Even though this was not one of the Committee’s preferred assumptions, the company would like to make the following points:

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- For the TA614 and TA615 appraisals of cannabidiol in DS and LGS, in the absence of published evidence on resource use (both DS and LGS are orphan diseases, so this is not unexpected), some of the HCRU estimates were informed by *interviews with clinicians*. For the current appraisal, we took on board NICE's feedback from TA614 and TA615 – i.e. to use a more robust method for estimating HCRU – and have used a *two-round Delphi panel*.
- TSC-associated epilepsy is also an orphan disease, so there are similar issues related to a lack of published evidence on resource use. The SLR conducted by the company did not identify any relevant studies to inform the economic model.
- Therefore, as noted in the ACD: "Annual healthcare resource use based on seizure frequency for people with TSC-associated epilepsy was sourced from a two-round Delphi panel" (of 10 clinical experts).
- The Delphi method is well suited for this as it is a widely used and accepted method (e.g. it is recommended by NICE in PMG20) for achieving convergence of opinions concerning real-world knowledge solicited from experts.
  In the absence of published data in this orphan disease, the output of the two-round Delphi panel is the *best evidence available* to inform the model, and is a recognised standard in NICE's hierarchy of evidence.

In line with more standard practice on deterministic sensitivity analysis (DSA), where the lower and upper values for each parameter included in the DSA are either obtained from the literature, based on clinical opinion or *varied across a specified range* to test uncertainty in the absence of a benchmark or analogue, the company has conducted a sensitivity analysis on the hospitalisation rates elicited from the Delphi panel. Table 1 below shows the ICERs around the company's base case when the hospitalisation rates from the Delphi panel are varied up to the ERG's arbitrary -50%. The same sensitivity analyses are also provided when a severity modifier is included (see Table 2 below and Comment 2 above).

Table 1: Cannabidiol hospitalisation rate sensitivity analysis (around base case)*

Average dose		**12 mg/kg/day**
Hospitalisation rate	Base case#	**£11,833**
	-10%	[redacted]
	-20%	[redacted]
	-30%	[redacted]
	-40%	[redacted]
	-50%	[redacted]

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<table>
<tr><td></td><td>
Table 2: Cannabidiol hospitalisation rate sensitivity analysis (with severity modifier)*
<table>
<tr><th colspan="2">Average dose</th><th>12 mg/kg/day</th></tr>
<tr><td rowspan="6">Hospitalisation rate</td><td>Base case#</td><td>£9,861</td></tr>
<tr><td>-10%</td><td>[redacted]</td></tr>
<tr><td>-20%</td><td>[redacted]</td></tr>
<tr><td>-30%</td><td>[redacted]</td></tr>
<tr><td>-40%</td><td>[redacted]</td></tr>
<tr><td>-50%</td><td>[redacted]</td></tr>
</table>
* Note: the ICERs are based on the company's revised base case incorporating the NICE Committee's preferred assumptions as outlined in Comment 4 above
# Hospitalisation rates as elicited from the 2-round Delphi panel

This sensitivity analysis shows that, across a range of hospitalisation rates, the ICERs are within the Committee's stated acceptable range.
</td></tr>
<tr><td>8 Updated NHS Reference Costs</td><td>
• In line with section 5.5.1 of NICE's Process and Methods Guide 2013 (PMG9), the company has updated the cost utility model with the most recent NHS Reference Costs (2020/21).
o Source: https://www.england.nhs.uk/wp-content/uploads/2022/07/2_National_schedule_of_NHS_costs_FY20-21.xlsx).
• The unit costs that have been updated in the model (tab "Resource Use Costs") were provided to the NICE Technical team via e-mail on 22nd November 2022, so that the ERG could conduct an independent validation.
• For reference only, if the now out-of-date 2019/20 NHS reference costs are applied in the updated model (incorporating all the changes outlined in Comment 4 above) then the company's base case ICER would be [redacted].
• The application of a disease severity QALY modifier would reduce this ICER to [redacted] per QALY.
</td></tr>
<tr><td>9 Institutionalisation calculation by the</td><td>As communicated to the NICE Technical Team (by e-mail on 22/11 2022) and accepted by the ERG (in the e-mail from the NICE Technical Team on 24/11/2022), there was a calculation error in the ERG's model (model labelled "ERG base case_ID1416_CBD in TSC_CE model AICCIC_PMB8Sep22 committees preferred assumptions") regarding institutionalisation, as follows:</td></tr>
</table>

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ERG	One of the preferred assumptions of the Committee was that the caregivers of adult patients with TSC who are institutionalised have a 50% decrease in their disutility, associated with no longer having to care full time for their dependent. This is currently implemented in the model in cell K12 of tab "*Utilities*" (cell name "*UT_averageNcarer_ERG6*"). The coding for this cell is as follows: =(1-0.31)*UT_averageNcarer+0.31*(IF(ERG!F9=1,0.5,IF(ERG!F26=2,0.5*UT_averageNcarer,UT_averageNcarer))) However, the ERG has reduced the disutility of caregivers not by decreasing the disutility calculation itself, but by reducing the average number of caregivers per patient by 50% for the proportion of caregivers whose dependents are institutionalised (31%, as predicted by the Delphi panel). This coding does not do this, as the term "**UT_averageNcarer*" is missing from the calculation. The correct coding is shown below: =(1-0.31)*UT_averageNcarer+0.31*(IF(ERG!F9=1,0.5*UT_averageNcarer,UT_averageNcarer)) The company's updated model with our new base case has this correction implemented.
10 Long term efficacy	• The company notes the Committee's conclusion that "Cannabidiol reduces seizure frequency and increases the number of seizure-free days compared with usual care alone, but long-term efficacy is uncertain". • We reiterate that there is now a significant body of evidence (across three indications, TSC-associated epilepsy, LGS and DS) that demonstrates the long-term durability of efficacy outcomes with cannabidiol. • As noted in the ACD, our submission provided interim data from the GWPCARE6 OLE (Open Label Extension) study in TSC-associated epilepsy up to 72 weeks. • 3-year (156-week) efficacy data from the GWPCARE6 OLE will be presented by Thiele, E et al. at the American Epilepsy Society (AES) congress in December 2022. The results demonstrate that add-on cannabidiol treatment was well-tolerated and produced sustained reductions in TSC-associated seizures for up to 156 weeks in patients who continued on treatment: o Median reduction from baseline in TSC-associated seizures ranged from [redacted] across 12-week windows through 156 weeks o Reductions in TSC-associated seizures ≥50%, ≥75%, and 100% were maintained up to 156 weeks, ranging from [redacted], [redacted], and [redacted], respectively.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

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- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**Tuberous Sclerosis Association**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row.

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	Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We believe that NICE Appraisal Committee has overlooked the following key areas that are extremely important to people living with Tuberous Sclerosis Complex (TSC) and their family and carers: • **The massive positive impact on quality of life that seizure reduction can have on people living with TSC.** Even if someone is not seizure free having fewer and more predictable seizures can really make a big difference • **The role of seizure reduction in care responsibilities and challenges**. Care for people with TSC (which is often at least two-to-one) can lead to secondary challenges in employment, financial security, social interactions and the wider family unit (such as the impact on siblings). Seizure reduction can play a major part in making these challenges easier In addition, we feel the need to highlight the unacceptable inequality in access to TSC-related epilepsy medicines in the UK. Decision-makers in Wales and Scotland have already made correct choices to fund Epidyolex®. TSC-related epilepsy treatment is available to some people but not others depending on where they live in the UK, which the TSA completely disagrees with. The committee has reviewed evidence relating to the **reduction in frequency of refractory epilepsy with a significant focus on the 5% who were seizure free**, and not those who had a reduced seizure frequency. For people with TSC and for those caring for them, even a modest seizure reduction can change their lives. Even if someone is not seizure free, having fewer, predictable seizures can really make a big difference to their overall wellbeing. The TSA interviewed seven families living with TSC who have had the opportunity to try Epidyolex®. We carried out a half-hour telephone interview with each family using a standard set of questions about TSC, epilepsy and Epidyolex®. The information from these interviews was collated and used to inform the TSA's submission to NICE at an earlier stage of the process. During these interviews, we asked people living with TSC and their families and carers to share the aspects of living with TSC that are not met by currently available treatments. All of these families said that their child's seizures, epilepsy and behaviour problems are the areas that need addressing most urgently. These areas impact the most on their day-to-day lives and they would welcome help and support in addressing these unmet needs. One mother who cares for an adult daughter who lives with TSC (aged 37 years old) told us that TSC-related seizures "*affects everything; we take her out to a meal, and she can have a seizure whilst waiting for food and then she doesn't want to eat. Usually, mum goes to the restaurant first, whilst dad waits in the car with daughter and they only go in when the food is on the table. Or if she has a seizure during the meal then you are rushing to get out to leave and don't bother eating. Everything you do, you have to think about how it's going to affect her. It's pointless going out as more often than not, she's had a seizure.* *Seizures can go on all day or some days there are only a few. She has some type of*

seizure every day and she has different ones. She has broken every bone in her left foot through drop seizures, it's so swollen that it's difficult to get shoes. She has been in and out of hospital. She's knocked two teeth out right up into her gum through her cheek – had to be stitched up.

She has to have two people with her 24 hours a day because of seizures and behaviour. She has no idea of danger so she could just walk into the road and be hit by a car and she wouldn't know what to do. You have to keep everything out of her way as she will drink whatever is in the cupboard, she would pick up and eat whatever is lying around so she has to be monitored. She has had problems with breathing as she doesn't chew properly so it becomes a choking hazard. She has to be fed to make sure she has swallowed properly otherwise she'll continue eating even whilst choking. You cannot leave her with food, she would choke, she would die. Food has to be cut up or mashed."

Another mum, who is the main carer to her 19-year old daughter, was forced to give up work to care for her daughter full-time. She organises all hospital appointments for her daughter which she describes as "lots of them". The mum said this takes a toll on the family and has a huge impact on her young son.

Four out of seven families who were interviewed to inform TSA's initial response to NICE described the improvements to their loved one's epilepsy as 'life-changing' following treatment with Epidyolex®. One family with a young child (aged 7) said: "*Epidyolex® was life changing in terms of sleep. My husband and I were able to have an entire night's sleep. His behaviour was much better at school. Epidyolex® massively reduced seizures in combination with Clobazam. He was having nine seizures a day before starting the medicine, but within five months of taking it, he was having a total of seven seizures in a month. His seizures reduced in severity, he would only experience chin twitches. He was calm and happy, and slept much better. He said Epidyolex® tastes nice – like strawberry. Epidyolex® was a godsend.*"

Of the three patients still taking the drug at the time of interview, they told us: "*Epidyolex® has been life changing for our son (aged 16). It has unlocked a part of him that the family had lost. He now has an opinion, he is not as vulnerable, he asks for the toilet. He is more rounded. He is more alert. He says no to things he doesn't like or doesn't want to do. He has had no drop seizures and the Epidyolex® has reduced the frequency of other seizures, although he still has some seizures during the night."* The family went on to say with joy that "*Epidyolex® has given him the energy to live in society and has unlocked the monkey in him.*"

Another family told us of the massive benefits they have experienced and witnessed as a result of Epidyolex®: "*Our son (aged 12) was seizure free for nine months at first, and he now has around 4-5 seizures a day. He has more emotions since taking Epidyolex®. If seizure frequency increases, then I take him to the GP as this usually means that he has some sort of infection. He is more awake, he sleeps less, and he is happier going to school.*"

In forming this response document to NICE, the TSA has carried out an additional survey of the TSC community to understand what having fewer seizures would mean for them or the person that they care for, and how would a reduction in seizures improve their quality of life. Responses to our survey (both carers and people living with TSC) include the following:

Cannabidiol for treating seizures caused by tuberous sclerosis complex [ID1416]

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	"*A life without seizure control is a terrible situation.*" "*Epilepsy impacts on my confidence, levels of fatigue and concentration as well as my ability to travel further afield. I currently feel uncomfortable forming personal relationships and my seizures were a big factor in the break-up of my marriage.* *I'm a dad who also cares for my son who has TSC and seizure disorder. If he had the confidence and reassurance of being seizure free, he would be able to more things independently. He would be less anxious (he is being treated for ADHD and anxiety associated with TSC) and wants to be able to learn to drive - something I am not able to do myself, but I cannot promise to him that he will be able to do either, due to his seizures."* "*Fewer seizures would massively improve our lives, my child would have more chance to learn a chance for days out a chance to make friends go to nursery all the things every other child can do and takes for granted we cannot because seizures ruin lives! I would have a happier child, more sleep, better chance to make memories and do nice things, more time to spend with her sister would massively improve every area of all our lives.*" "*This horrendous uncontrolled condition (TSC) has robbed her of her independence, stolen her of her previous cognitive ability and given us a life we never imagined. I have given up work to care for her full time. She had a full year out of college and this year she went into regression (caused by multiple uncontrollable seizure activity). She has commenced only on a 3 day vocational course. I cannot believe that professionals can judge medication only on controlling seizures - even a reduction of seizure activity gives a better quality of life to both the person living with epilepsy and the family. If all meds were judged on full control, there would be no anti-epilepsy drugs passed!!!*" "*For my daughter, the frequency with which she has seizures (on a daily basis) makes it incredibly hard for her to learn and retain skills. It has a massive impact on her quality of life and her development. Of all the symptoms that arise from tuberous sclerosis, it is seizures that impacts her most negatively. Having some kind of seizure control (even if it isn't complete seizure freedom) would enable her to have such a better quality of life, reduce anxiety, increase her capacity for learning, give her better mental as well as physical help. In short, it would be invaluable."* *"We have been following families in a similar situation who have access to cannabidiol and the results seem staggering. Any reduction at all in our son's seizures would improve his quality of life. Instead of 30 to 40 daily if he had say 10 it would make a massive difference to him and to us."* *"Less chance of a severe status seizure that could end life, ability to allow someone else to watch my child so I can have time with partner, less medication, better ability to learn and retain information and become the person she's capable to be."* "*Reduced seizures would change his life. When he has less seizures he thinks more clearly, he speaks better and concentrates of life more. He becomes engaged in activities and is less tired and nervous.*" "*He would be able to develop, maybe talk and say mum. He wouldn't be exhausted all the time and would stop deteriorating. I may get a few more years with him. I am able to leave the room. I would be able to have me time. I would be able to go to work and be able to go*

	to uni to become a paramedic." "*It would mean she could go and have play dates and sleepovers at her friends' houses, it would mean she could sleep on her own instead of mum in bed with her.*" "*For my son, as for many TSC suffers, the chance of living life with less seizures is actually a chance to live the life they deserve. More independence, more clarity in their concentration - more life!*" *"My son has suffered from seizures every day since being an infant as a symptom of TSC. He has been taken to hospital countless times over the years via ambulance due to this. As a small child he was in non-convulsive status for a period of time until a medication was found to get him out of that. He couldn't stand for more than a few seconds, could not eat properly without biting his tongue which was awful to watch and care for, and for him I can't imagine what it must have been like."*
2	We also wish to draw your attention to an additional piece of evidence which supports the draft proposal to fund Epidyolex® for TSC-related epilepsy in England. Research published by Public Health England (PHE) in 2018 has found that the number of annual deaths of epilepsy patients has increased by 70 per cent between 2001 to 2014. Deaths occur on average eight years earlier than those for the rest of the population. With the right treatment, over 60% of people with epilepsy could stop having seizures altogether. Of all the neurological conditions studied by PHE only epilepsy was found to have a significant relationship with deprivation, with 13 deaths per 100,000 population in the most deprived areas compared to five deaths per 100,000 in the least deprived. (Summary from HSJ article on 19 March 2018). Access to Epidyolex® would have the potential to further reduce the number of annual deaths related to epilepsy in England.
3	Another critical area that the committee has not fully considered is the **significant burden and impact of care needs on families and carers of people with TSC, regardless of the number of carers involved**. The carers of those living with TSC also experience a significant impact on their physical and mental health as a result of caring for someone with the condition. TSC is a systemic disease with multiple physical and psychological problems that has a profound impact on both the patient and their family and carers. Care for people with TSC that is two-to-one does not therefore demonstrate a reduced burden on the two carers compared to if it was a single carer. In a family unit, two-to-one care often leads to massive secondary care challenges in employment, financial security, social interactions and the wider family unit such as the impact on siblings as the focus of both parents becomes wholly on the person with TSC. Seizure reduction can play a major part in making these challenges easier for all carers. If seizures can be reduced in frequency and severity, carers of those with TSC can begin to rebuild their own lives and thereby improve the lives of entire family units. Those responding to the TSA reported improvements to the physical and mental health of family members - both parents and siblings - as well as patients themselves - as a result of treatment with Epidyolex®: A mother of a 12 year-old who has been taking Epidyolex® told us: "*My daughter's grandad used to baby sit during the 9-month seizure free period, so that my partner and I could go out for food. We usually take it in turns to go out and look after her. As she now has less seizures, this means we can go out for food together and socially it has made a huge*

	difference for my family. *It has been a huge weight off her siblings' shoulders. It's upsetting for them to watch their sister go through a seizure which usually lasts for 40-50 seconds, but it feels like two hours. Everyone's mood has lifted, and her siblings are not so worried all the time. Mental health wise, a huge cloud has lifted. The teachers in school were happy for her too*." Family with a young child (aged 7) said: "*Epidyolex® was life changing in terms of sleep. My husband and I were able to have an entire night's sleep. His behaviour was much better at school. Epidyolex® massively reduced seizures in combination with Clobazam. He was having nine seizures a day before starting the medicine, but within five months of taking it, he was having a total of seven seizures in a month. His seizures reduced in severity, he would only experience chin twitches. He was calm and happy, and slept much better. He said Epidyolex® tastes nice – like strawberry. Epidyolex® was a godsend."* One mum who is the sole carer of her 16-year-old son with TSC shared with us:"*As a single parent of a child with TSC, the seizures are very difficult to control. I have always been aware the 'best we can get them' is the reality, anything more than that would be more like a miracle and we've had our fair share of those! It is always a very stressful and anxious time starting any new medication, but you can't give up. The combination of Clobozam and Cannabidiol has been phenomenal for us, but if we hadn't been given the opportunity to try it, I dread to think where we would be now.* *I have been doing this for 16 years so I'm sure you can appreciate after that amount of time, trying all kinds of different medications and having my son being the best he has ever been is just amazing and I thank my lucky stars every day. I fully support that Cannabidiol should be made available to patients. It could be the 'miracle' they have waited so very long for and it could completely change their lives for the better. It's not a cure, but it's improved our lives dramatically. Why should others be denied the chance to at least be given the opportunity to try it when it could massively improve their life too.*" Respondents to our further survey developed for this response shared with us how reduced seizures would impact their lives as carers: "*It would quite simply improve my mental and physical well-being. Seizure control (or a lack of it) is a constant worry and something we as parents carry with us always. As our daughter can have seizures at any time of day and has them on a daily basis, it is something that is always on the back of our mind, as well as that of her younger sister who is only 7 and has been able to identify them since a young age*." "*If our son was having less seizures then I might be able to get better sleep at night and my husband and I could also have a better quality of life. I sleep with a baby monitor on my bedside table and are up at least 2 or 3 times a night with him fitting - he is 18 but I am 58. If he had less seizures in the day, he wouldn't sleep as much so he would sleep better at night.*" "*For me personally it would mean I could take him out on my own without feeling too afraid he was going to have a seizure out. He is a big lad now and I'm 65 so keeping him safe is difficult, less seizures means less difficulties for me (and injuries). We could take holidays abroad without the worry*."

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	"*I wouldn't be living life on the edge all the time waiting for phone calls from my daughter to say pick up the kids from school, come get the kids as J is having a tonic clonic. I wouldn't have to worry constantly that my granddaughter is missing out on so much because of seizures*." "*A reduction of seizures and or loss of seizures would mean less juggling of care within the family and greater freedom. Peace of mind.*" "*As a parent and carer, a reduction in seizures is everything. To watch my son have seizures every day is not only heart-breaking, it's tiring. It's as if normal family life goes on hold for periods of time when seizures decide to increase, change pattern or appearance. Sleeping with an eye open is difficult and obviously puts a stain on most things that I can think of.*" "*I live in constant fear of my son having a seizure which requires hospitalisation, and also of SUDEP. Improved seizure control would he alleviate the risks. I currently work, but if his epilepsy doesn't improve, I may have to stop working. I receive ad hoc support from NHS to deal with the mental toll his epilepsy has on me - anti anxiety medication, counselling etc. It adversely affects the whole family.*" "*I could work, sleep at night, not have to tap into expensive social care respite services, have less ineffective epilepsy medications, less NHS appointment and basically save the government money.*" "*I have watched uncontrolled epilepsy rob my child of the life she was leading. To see improvements would bring a joy to my heart and decrease the pain and stress we live with everyday watching our daughter and the regression that is occurring due to this horrendous condition. Achieving decreased seizures would improve her cognitive ability -fewer seizures, less recovery time, less sleeping. Increase confidence. Ability to interact more with peers. Improve ability to follow academic studies-the list is endless.*" "*Wouldn't be as anxious and on edge watching him waiting for another one to happen.*" "*A weight off our minds. Relief for a brighter future. Normality*"
4	The Tuberous Sclerosis Association is supportive of the proposal that Epidyolex® should be funded for people with TSC-related epilepsy. The addition of Epidyolex® therapy for refractory epilepsy will have a vast positive impact on equality and health inequality in this patient group. It is clear that refractory epilepsy is a major cause of the severe intellectual impairment which is common in TSC. This in turn results in psychological problems such as autistic spectrum disorder, severe anxiety and depression, impulsiveness and self-harm. The experience amongst families and the evidence from natural history studies show that the better controlled epilepsy is, and the younger the age at which this occurs, the better the outcome for intellectual development, with amelioration of the above-mentioned problems. In general, this patient group has previously had poor access to care because of the variety and severity of their problems. The availability of effective treatments like Epidyolex® 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).

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	Epilepsy is the most common neurological feature of TSC, affecting approximately 84 per cent of people living with the condition. More than 50 per cent of people with TSC who have epilepsy will not respond to standard anti-epilepsy medicines and may need an alternative form of treatment. These individuals will have a better quality of life if Epidyolex® can provide better seizure control. **Seven out of seven families answered yes to our question: *If Epidyloex® were available, would (patient) prefer to try this treatment first, before trying other treatments?*** One mum said: "*We would have tried this first – even if it doesn't work it's well worth giving it a go*." Another family said "*Yes as Epidyloex® has non-toxic side effects."* Third family told us: "*We have been asking for CBD for years but it was never licenced.*" Fourth family also agreed that it is worth a try: "*None of the other treatments have worked fully. Epidyolex® was no worse than anything else. It is worth a try – it could work well for others.*" One parent that was surveyed told us "*Our daughter has tried countless anti-epileptics drugs and having access to cannabidiol would be of great benefit as I understand it uses a different pathway within the body and therefore offers an alternative potential remedy to address seizures. It also seems those of us who happen to live in England are not being treated equally given that cannabidiol is approved in Scotland and Wales and therefore accessible by those affected by TSC in those areas*."
5	
6	

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Young Epilepsy
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]

Comment number	Comments Insert each comment in a new row.

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Example 1	We are concerned that this recommendation may imply that ……..
1	Young Epilepsy urges NICE to recommend cannabidiol for seizures caused by tuberous sclerosis complex (TSC). Research shows that cannabidiol plus usual care can reduce seizure frequency and increase the number of seizure-free days. Seizure frequency can have a significant impact on quality of life for people living with epilepsy, as well as their family. A recommendation for cannabidiol to be used for seizures associated with TSC would ensure that more people living with the condition can have access to a range of treatment options. If treatment is found to be ineffective for an individual, it can be discontinued. We are concerned that the draft decision not to recommend cannabidiol will create inequalities in treatment access for people with TSC across the UK. Authorities in Wales and Scotland have already approved the treatment for people with TSC.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	**GW Research Ltd / Jazz Pharmaceuticals**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**
Name of commentator person completing form:	[redacted]

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Comment number	Comments	EAG response
1 Summary – company's updated base case	• Based on the feedback from the NICE Committee in the ACD, the company has made changes to its base case. • As outlined in more detail in Comment 4 below, we have updated our base case to incorporate many of the Committee's preferred assumptions (as stated in the e-mail from the NICE TA team dated 03/11/2022) as follows: o Using a 6.61 day cut-off for the proportion of people who are seizure-free over 7 days o Using the health state utilities from the company's vignette o Assuming a cumulative 1.8 carers o Adjusting for institutionalisation using the ERG's approach* o Including cost and benefits for TAND aspects for people aged 2 to 6 years, using the utility benefit from the company's base case. * Note that this includes an updated calculation for institutionalisation as communicated to the NICE Technical Team on 22/11/2022 (see Comment 9 below for more detail) • The company maintains that the average dose of cannabidiol (12 mg/kg/day – as accepted by NICE for the DS and LGS appraisals) used in our cost-effectiveness analysis is reasonable and justified, based on robust evidence, feedback from clinical experts and as observed in real-world prescribing data from 118 patients in Germany since 2019 (please see Comment 6 below for more detail). • As per section 5.5.1 of NICE's PMG9, the company has updated healthcare resource use costs in the economic model to include the latest NHS reference costs (from the National Schedule of NHS Costs - Year 2020-21) • The company's updated base case ICER incorporating all the above changes is **£11,833** per QALY. • The application of a disease severity QALY modifier (to appropriately reflect the severity of TSC-associated epilepsy – see Comment 2 below) would reduce the company's revised base case ICER to **£9,861** per QALY.	See below for EAG response to each element separately.
2 Severity of the disease	• The NICE Committee has recognised the severity of TSC-associated epilepsy and that it "severely affects the quality of life of patients, carers and their families".	The EAG fully acknowledges the severity of TSC-associated epilepsy, and supports inclusion of

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	• TSC-associated epilepsy is a rare (orphan), devastating and life-threatening form of epilepsy that presents early in childhood and is associated with refractory seizures and poor outcomes. In addition to the high seizure burden, the associated cognitive and behavioural difficulties known as TSC-associated neuropsychiatric disorders (TAND) prevent children from achieving independence in adult life. Mortality rates for people with TSC are higher than in the general population, with uncontrolled epilepsy among the most common causes of death in TSC as a result of status epilepticus or Sudden Unexpected Death in Epilepsy (SUDEP). • The Committee's recognition of the severity of the disease also reflects the brave and comprehensive testimony of the parent/patient expert at the Committee meeting on 15th September 2022. The patient expert outlined the stark reality of living day to day with a child with TSC-associated epilepsy and the profound impact on the quality of life of both the patient and the family as a result of the seizures and TAND. • The company further notes from the ACD that "half of people with tuberous sclerosis complex have associated learning difficulties, which is a protected characteristic under the Equality Act 2010". • We note that the NICE methods guidance was updated in February 2022 in order to support patients with severe diseases. This updated 2022 guidance introduced new criteria to reflect, in exceptional circumstances, the severity of disease within decision making. The company is aware that this submission is being assessed under the old methods guidance (the invitation to participate was sent to us on 18th January 2022, just two weeks before the new guidance was introduced on 1st February 2022). However, given the subsequent long delays in the appraisal process, we consider it appropriate to include the severity of TSC-associated epilepsy and the impact of this on the economic analysis. As detailed in our submission, cannabidiol in a patient population with TSC-associated seizures satisfies the criteria laid out by NICE under the new methods for a severity of disease modifier. Given the severe impact of TSC-associated epilepsy, a QALY weight of 1.2 (applicable for the absolute loss of between 12 to 18 QALYs) should be applied in the context of decision making. • The application of a disease severity QALY modifier (to appropriately reflect the severity of TSC-associated epilepsy) reduces the company's revised base case ICER (of £11,833) to £9,861 per QALY. • Of note, using *all* the NICE Committee's preferred assumptions (as stated in the e-mail from the NICE TA team dated 03/11/2022, that is: using a 6.61 day cut-off for the proportion of people who are seizure-free over 7 days; using an average dose of 15 mg/kg/day; using the health state utilities from the company's vignette; assuming a cumulative 1.8 carers; adjusting for institutionalisation using the ERG's approach (with an updated calculation as outlined in Comment 9 below); including cost and benefits for TAND	relevant elements of disease severity into the decision making as long as this is possible and consistent with other TAs. Technically, the methods guide of before February 1st 2022 should still apply, and so the EAG is of the opinion that application of the disease severity modifier is not relevant for this TA. Also, the EAG would like to reiterate, as already explained in their response to Technical Engagement, that applying the disease severity modifier to all QALYs (patient and caregiver) gained is not correct in the view of the EAG. As stated in the TE response 'the EAG holds the opinion that when the QALY weight is based on patient QALYs, it is also only the patient QALYs that should be weighted'. The QALY weight of 1.2 was derived correctly by the company by looking at the QALY loss of TSC-related epilepsy of the patients only (not including the caregiver QALYs here). But then applying this modifier of 1.2 to all QALYs (including those of the caregivers) is not the correct procedure. The severity modifier should only be used to weight those QALYs that

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	aspects for people aged 2 to 6 years using the utility benefit from the company's base case), the ICER is £22,401 per QALY (and with the severity modifier applied, it is £18,668 per QALY), which is well within the Committee's stated 'acceptable ICER' range.	are actually relevant for the modifier, so patient QALYs only. For the company base-case, this means that, according to the EAG, the correct ICER after applying the disease severity modifier would be £10,786 per QALY (instead of £9,861 as per the company's calculations).
3 Additional benefits of cannabidiol not captured in the current model / economic analysis	There are additional benefits of cannabidiol that are not captured in the current model/economic analysis. For example, the cost-effectiveness estimates do not include the value of: • A beneficial impact on the mortality related to Sudden Unexpected Death in Epilepsy (SUDEP) that is associated with effective seizure control • The broader impact on TAND (not captured in the very conservative assumptions used in the current model) • Improving the quality of life of the wider family, including siblings and other family members • Increasing caregiver productivity and the associated societal benefits of the parent(s)/primary caregiver(s) not needing to give up work to care for a patient with TSC-associated epilepsy • Reducing the duration/severity of seizures (the model only captures seizure frequency) • The long-term impact of improved seizure control on comorbidities and injuries	Most of the additional benefits mentioned here would also apply to TA614 and TA615 and in fact to many other appraisals. The EAG considers the additional benefits to be real and potentially important but as they cannot be quantified within the terms of the NICE methods guide there is no basis for weighting or comparing these benefits between appraisals.
4 NICE's preferred assumptions	The company noted the preferred assumptions from the NICE Committee. In order to avoid any further delays in patients with TSC-associated epilepsy and their families having access to a much-needed treatment for this severe condition, we have adopted the majority of these assumptions in our revised company base case. However, we reiterate below why we consider that they are extremely conservative and/or may lead to the ICER being over-estimated: • **Impact of cannabidiol on TAND aspects** The Committee has recognised *some* of the potential impact of cannabidiol on TAND, since aspects of TAND can have a huge impact on the lives of patients with TSC-associated epilepsy and their caregivers. As noted in the ACD: "patient experts highlighted the significant quality-of-life impact from TAND for patients and families. Severe learning difficulties occur in around 30% of people and may impede speech. Impaired movement may also limit all aspects of daily living. Poor behaviour including anger, mood swings, aggression and a lack of perception of risk often makes daily activities impossible and people may need	With respect to the committee's preferred assumptions the EAG wants to mainly state that these are not necessarily extremely conservative in many aspects, specifically: • **Impact of cannabidiol on TAND aspects** As emphasized in the EAG report, the EAG acknowledges the fact that TSC-related epilepsy can have an impact on TAND but the

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	round the clock care. People with the condition also have disrupted sleep, which can impact on the mental health of the entire family". Even though the Committee's preferred base case only includes a very conservative assumption on TAND, we consider that it is important to include it in the analysis and that there is potential *additional benefit* from the impact of cannabidiol on TAND that it is not possible to capture in the economic model. • **6.61 versus 6.5 cut-off for people seizure-free over 7 days** We note that the NICE Committee considered that "the proportion of people who are seizure-free over 7 days in the model is uncertain but a 6.61 day cut-off is most appropriate for decision making". Although we accept that NICE's preference was to use the ERG's very conservative approach, we maintain that there were robust methodological reasons for choosing the 6.5 cut-off and that this better reflected the trial outcomes in the model. • **1.8 carers** We note that the Committee considered that "The effect on carers' quality of life should be modelled and the ERG's assumption using 1.8 carers is most appropriate". Whilst the significant impact of TSC-associated epilepsy on caregiver quality of life has been recognised by NICE, in our submission and in our responses to the ERG report, the company included utilities for *two* caregivers. This reflects the impact of TSC-associated epilepsy on the quality of life of the wider family. We acknowledge that not every patient will have two primary caregivers (although many will need more than two). However, the company is aware that there are often many other people contributing to the care of the patient (for example, siblings, grandparents, aunts, uncles, family friends). Each family carer has the burden, worry and psychological distress of caring for a patient at risk of injury and even death from their seizures. Thus, it would be expected that incorporating the full and cumulative effect of TSC-associated epilepsy on the lives of *all* family members would result in a further reduction of the ICER. • **Institutionalisation*** We note that the NICE Committee concluded that it is appropriate to include a reduction in carer disutility associated with institutionalisation of a patient. However, we also note that the Committee considered that "the increase in carer quality of life in the company and ERG's analyses were not supported by data and other scenarios would be equally plausible...Given the lack of evidence to support the size of this reduction, it considered the ERG's approach preferable". Based on this, although we accept that NICE's preference was to use the ERG's very conservative approach, the company's approach is equally valid. We also refer back to the patient expert's comments:	uncertainty around the multiple assumptions used in the calculation is substantial. • **6.61 versus 6.5 cut-off for people seizure-free over 7 days** To the EAG it is not clear on why the 6.61 would be considered as conservative, as in general 7 days would be understood as 7 days. Also, because 'seizure free over 7 days' was not an outcome in the trial it is not possible to align this cut-off value to outcomes as observed in the trial. • **1.8 carers** the EAG wants to re-iterate that the number of 1.8 carers is in line with previous TAs of cannabidiol and does not actually mean that less than 2 carers are involved, the 1.8 is about the impact on carer QoL. • **Institutionalisation** the EAG heard the patient expert's explanation at the committee meeting and agrees that worries and guilt will remain once a patient is institutionalized. However,

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	"the patient expert agreed that although carers had more free time if a person with TSC was institutionalised, concerns and guilt would remain, especially about exposure to abuse". * Note that the company's base case includes an updated calculation for institutionalisation (see Comment 9 below for more detail) • **Different values of the seizure-free health states for carers** The ERG adjusted the caregiver utility for the seizure-free health state to that of an average adult aged 45. The company accepted this adjustment from the ERG at the Technical Engagement stage of the appraisal process and it is reflected in the company's revised base case. With regard to the scenarios using different values, we note from the ACD that the NICE Committee concluded that "Scenarios varying the seizure-free utility value for carers had minimal impact on the ICER".	quality of life does not only consist of these elements. Notably, the 5 dimensions of the EuroQoL-5D (NICE's preferred instrument to measure QoL) are: mobility, self-care, daily activities, pain/discomfort, and anxiety/depression. The EAG considers that daily activities will be affected positively when a patient is institutionalised, and anxiety and depression may or may not be affected. Therefore, even though it is uncertain to what extent the disutility would change, some improvement may be expected. • **Different values of the seizure-free health states for carers** the EAG wants to point out that having caregiver utility set equal to a utility of an adult in the general population is far from a conservative assumption. As stated in the EAG report, the seizures are not the only aspect of the disease, and the fact that a patient is seizure-free does not make him or her healthy. Nor is it likely that as soon as a patient is seizure free for 7

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		days, caregiver utility will immediately adjust, because worry and uncertainty remain (as argued above for the matter of institutionalisation). Also, the EAG would not classify the impact that the value of the seizure-free carer utility has on the ICER as minimal.
5 NICE process for handling uncertainty	The company noted that the NICE Committee has changed the standard threshold for the ICER: *"…the committee agreed that an acceptable ICER would be towards the middle of the range normally considered a cost-effective use of NHS resources (£20,000 to £30,000 per QALY gained)"* We would like to make the following observations on this: • TSC-associated epilepsy is a severe and orphan disease • As presented in the Committee meeting on 15th September 2022, both the previous company base case (before the updates outlined in Comment 4 above) and the ERG base case ICERs were substantially under £20,000 per QALY gained compared with usual-care (ERG base case ICER was £16,928; previous Company base case ICER was £14,594) • The ACD document makes reference on numerous occasions to the ERG's 'conservative' assumptions being the Committee's preferred option. In this context, it is difficult to understand why, when all these 'conservative' assumptions have been used in the Committee's preferred base case, the acceptable ICER threshold is then set much lower than for other rare (orphan) and severe diseases • The threshold is also not in line with previous appraisals of cannabidiol in severe epilepsies – in TA614 (Dravet syndrome) and TA615 (Lennox-Gastaut syndrome), the accepted ICERs were £32,471 and £33,721, respectively. This was because the Committee recognised the additional benefits of cannabidiol that could not be captured in the economic model. Based on the above, the Committee's 'acceptable ICER' threshold appears unreasonable considering that many elements of the Committee's preferred base case remove uncertainty or are noted in the ACD as being 'conservative'.	This is a matter of judgement for the committee and not for the EAG to respond to. Nevertheless, the EAG wants to point out that given confidential discounts for comparators and subsequent treatments, the actual ICERs that decisions in the past were based on are usually not disclosed in the committee papers.

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6 Dose of cannabidiol in clinical practice	The company maintains that the average dose of cannabidiol (12 mg/kg/day – as accepted by NICE for the DS and LGS appraisals) used in our cost-effectiveness analysis for cannabidiol in TSC-associated epilepsy is reasonable and justified, based on robust evidence, feedback from clinical experts and as observed in real-world data from 118 patients with TSC. *Evidence base* In the company's submission, and in our responses to the ERG report and technical engagement, the *average* dose of cannabidiol used in the cost-effectiveness analysis base case is 12 mg/kg/day reflecting that, *across a cohort* of UK patients with TSC-associated epilepsy in clinical practice, there will be a spectrum of doses ranging from ≤ 10 mg/kg/day to the maximum of 25 mg/kg/day. We have provided a large body of evidence in support of this (please refer to the ID1416 Committee Papers for more detailed information, which is not reproduced here). In particular, we have provided recent and robust real-world data from a large cohort in Germany that demonstrates that lower doses of cannabidiol are used in clinical practice. As noted in the ACD, data from 118 patients in Germany indicate that the median cannabidiol dose in the real world was 12.2 mg/kg/day in children and 7.8 mg/kg/day in adults. *NICE Committee's view on cannabidiol dose (from the ACD)* The company noted that the NICE Committee: • "Agreed that the dose of cannabidiol that would be used in clinical practice is unknown, but an average dose of 15 mg/kg/day should be used for decision making". • "Decided that the ERG's scenario using an *average* dose of 15 mg/kg/day for cannabidiol is appropriate" This was even though the clinical expert at the Committee meeting contradicted the ERG's scenario, stating: 15 mg/kg/day is likely to be the *maximum* dose of cannabidiol used in clinical practice as a trade-off between efficacy and side effects. However, many people would have a dose closer to the company's modelled estimate of 12 mg/kg/day. *Fenfluramine appraisal (Dravet syndrome)* In the ACD, it is stated that the Committee noted that a 15 mg/kg/day average dose for cannabidiol was 'accepted' in NICE's technology appraisal guidance on fenfluramine for treating seizures associated with	The EAG maintains their previous argumentation (see EAG report) with respect to dosage. Of note, the company states that recent and robust real-world data from a large cohort in Germany were provided – the EAG were not actually provided with these data though, but were only presented (in the clarification phase) with the results in terms of average dosage as also stated here.

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	Dravet syndrome. We would like to draw attention to some key aspects of the fenfluramine appraisal that are of relevance (information taken from NICE TA808, where appropriate): • In the pre-consultation version of the fenfluramine model, the fenfluramine manufacturer used a dosage of *12 mg/kg/day* for cannabidiol, which was in line with the dosage accepted in NICE's technology appraisal guidance on cannabidiol in DS/LGS. However, the fenfluramine manufacturer then changed its mind, arguing that the typical maintenance dosage of cannabidiol used in the UK was likely to be higher, and increased this to a dosage of 15 mg/kg/day in its updated model (note: this change was not requested by either the ERG or the NICE technical team). This large increase in the average dose of cannabidiol used in the fenfluramine model is perhaps not unexpected, given that demonstrating the possible cost-effectiveness of fenfluramine relied on a comparison with the cost of cannabidiol. Of note, the 'typical' dose of fenfluramine was not increased similarly in the updated model. • The fenfluramine manufacturer aimed to justify the large increase in the average dose of cannabidiol with information including the following: o Evidence from a study on slow titration of cannabidiol add-on in drug-resistant epilepsies (D'Onofrio *et al*., 2020), which was conducted in France. This looked at slow titrations to improve safety without affecting the efficacy of cannabidiol. For all indications (not just DS), the study showed that dosages increased from 10 mg/kg/day to 15.5 mg/kg/day from month 1 to month 6. The study included only 5 patients with TSC. o Evidence from a study of 6 people with Dravet syndrome in 1 centre in the UK, which reported an average cannabidiol dose of 13.3 mg/kg/day (Desai *et al*., 2021). Of note, the same study reported an average cannabidiol dose of 9.3 mg/kg/day for 9 patients with LGS. No patients with TSC were included. o Testimony from the fenfluramine manufacturer's clinical experts (who remain anonymous) that the average dose of cannabidiol in the UK could be 15 mg/kg/day or higher. • The following are quoted directly from TA808: o "The clinical experts said that there was no reason to expect that patients in the UK would be treated differently to patients in Europe". o "The committee noted that, while it would prefer not to disconnect the effects from the drug from the amount of drug given, it considered this to be an exceptional situation. It noted that treatments to reduce seizures are not used in the same way as other treatments that aim to reach the maximum tolerable dose. And it heard from clinical experts that the dose used would be a balance between seizure reductions and adverse effects of treatment".	

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	o "In this case, the committee concluded that it was reasonable to *use the real-world evidence presented by the company* to determine the dosages of both treatments in the model". *Dosing evidence for cannabidiol in the current appraisal compared with the fenfluramine appraisal* In the current appraisal of cannabidiol in TSC-associated epilepsy, the clinical expert present at the NICE Committee meeting on 15th September 2022 (Dr Sam Amin, who is highly experienced in managing patients with TSC-associated epilepsy) stated that "many people would have a dose closer to the company's modelled estimate of 12 mg/kg/day". In addition, the company has provided robust real-world cannabidiol dosing evidence from Germany, indicating that the observed median dose in clinical practice in 118 patients with TSC was 12.21 mg/kg/day in children and 7.77 mg/kg/day in adults. This testimony and evidence is stronger and more appropriate than the sources cited by the manufacturer in the fenfluramine DS submission for the following reasons: • The D'Onofrio study included only 5 patients specifically with TSC-associated epilepsy. • The Desai study included no patients with TSC at all, and was largely anecdotal. • Regarding the testimony about cannabidiol dosing from clinical experts provided by the manufacturer at the fenfluramine appraisal, the ERG noted that the company chose not to share any details about who these "highly-respected UK experts" were. Thus, it remains unclear if these anonymous experts had any experience of using cannabidiol in clinical practice and thus whether they were qualified to comment on its dosing. • The real-world German data provided for the current appraisal: o Are based on a significantly larger dataset – a cohort of 118 patients with TSC-associated epilepsy (identified within a national dataset covering approximately 64 million patients) o Are more recent, allowing time for clinical experts to become familiar with the usage/dosage of cannabidiol in TSC-associated epilepsy. *Conclusions* Overall, it is reasonable to expect that the NICE Committee would not base its decision regarding the appropriate cannabidiol dose for the economic analysis in this current appraisal solely on relatively weak sources of evidence/anonymous clinician testimony from a prior appraisal for a competitor product in a different indication.	

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	It is also reasonable to expect that the NICE Committee would apply the same general principles it adopted in the fenfluramine appraisal (as outlined above) to the current appraisal, specifically: • Accepting clinical expert testimony. • Acknowledging that patients in the UK would not be treated differently to patients in Europe. • Recognising that treatments to reduce seizures are not used in the same way as other treatments that aim to reach the maximum tolerable dose: the dose used would be a balance between seizure reductions and adverse effects of treatment. • Using the real-world evidence presented by the company to determine the dosage in the model. Based on the above: • The real-world evidence from Germany represents the best available evidence on which to determine the dose of cannabidiol in TSC-associated epilepsy • A clinical expert highly experienced in managing patients with TSC-associated epilepsy confirmed at the Committee meeting on 15th September 2022 that 15 mg/kg/day is likely to be the *maximum* dose of cannabidiol used in clinical practice and that many people would have a dose closer to 12 mg/kg/day. • The company retains 12 mg/kg/day as the average dose in its base case.	
7 HCRU estimates	The company noted from the ACD that the NICE Committee considered that "healthcare resource use is likely overestimated in the company's model". The ERG provided a scenario that reduced the hospitalisation rates used in the model by an arbitrary 50%. The Committee noted that "the hospitalisation rates used in the ERG's scenario *were not underpinned by evidence*, so the true resource use for people with tuberous sclerosis complex was unknown". However, despite this cited lack of evidence, the Committee concluded that healthcare resource use is likely overestimated in the company's model and considered the ERG's scenario (with a 50% reduction in admissions) in its decision making. We note from the e-mail from the NICE TA team (dated 03/11/2022) that the ERG's scenario of reducing hospitalisation rates by 50% "informed the Committee's decision-making process" but was not a "strictly	The ACD information shared with the EAG did not contain a further specification on how strict the preference of the committee was with regard to the 50% reduction in hospitalization. So the EAG maintained the 50% reduction in their updated base-case. An additional scenario was run where the reduction in hospitalization was set to 25% to explore the impact of uncertainty around this assumption.

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preferred assumption". Even though this was not one of the Committee's preferred assumptions, the company would like to make the following points:

- For the TA614 and TA615 appraisals of cannabidiol in DS and LGS, in the absence of published evidence on resource use (both DS and LGS are orphan diseases, so this is not unexpected), some of the HCRU estimates were informed by *interviews with clinicians*. For the current appraisal, we took on board NICE's feedback from TA614 and TA615 – i.e. to use a more robust method for estimating HCRU – and have used a *two-round Delphi panel*.
- TSC-associated epilepsy is also an orphan disease, so there are similar issues related to a lack of published evidence on resource use. The SLR conducted by the company did not identify any relevant studies to inform the economic model.
- Therefore, as noted in the ACD: "Annual healthcare resource use based on seizure frequency for people with TSC-associated epilepsy was sourced from a two-round Delphi panel" (of 10 clinical experts).
- The Delphi method is well suited for this as it is a widely used and accepted method (e.g. it is recommended by NICE in PMG20) for achieving convergence of opinions concerning real-world knowledge solicited from experts.
  In the absence of published data in this orphan disease, the output of the two-round Delphi panel is the *best evidence available* to inform the model, and is a recognised standard in NICE's hierarchy of evidence.

In line with more standard practice on deterministic sensitivity analysis (DSA), where the lower and upper values for each parameter included in the DSA are either obtained from the literature, based on clinical opinion or *varied across a specified range* to test uncertainty in the absence of a benchmark or analogue, the company has conducted a sensitivity analysis on the hospitalisation rates elicited from the Delphi panel. Table 1 below shows the ICERs around the company's base case when the hospitalisation rates from the Delphi panel are varied up to the ERG's arbitrary -50%. The same sensitivity analyses are also provided when a severity modifier is included (see Table 2 below and Comment 2 above).

Table 1: Cannabidiol hospitalisation rate sensitivity analysis (around base case)*

Average dose		**12 mg/kg/day**
	Base case#	**£11,833**

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	<table><tr><td rowspan="5">Hospitalisation rate</td><td>-10%</td><td>[redacted]</td></tr><tr><td>-20%</td><td>[redacted]</td></tr><tr><td>-30%</td><td>[redacted]</td></tr><tr><td>-40%</td><td>[redacted]</td></tr><tr><td>-50%</td><td>[redacted]</td></tr></table> **Table 2: Cannabidiol hospitalisation rate sensitivity analysis (with severity modifier)*** <table><tr><td colspan="2">Average dose</td><td>12 mg/kg/day</td></tr><tr><td rowspan="6">Hospitalisation rate</td><td>Base case#</td><td>£9,861</td></tr><tr><td>-10%</td><td>[redacted]</td></tr><tr><td>-20%</td><td>[redacted]</td></tr><tr><td>-30%</td><td>[redacted]</td></tr><tr><td>-40%</td><td>[redacted]</td></tr><tr><td>-50%</td><td>[redacted]</td></tr></table> * Note: the ICERs are based on the company's revised base case incorporating the NICE Committee's preferred assumptions as outlined in Comment 4 above # Hospitalisation rates as elicited from the 2-round Delphi panel This sensitivity analysis shows that, across a range of hospitalisation rates, the ICERs are within the Committee's stated acceptable range.	
8 Updated NHS Reference Costs	• In line with section 5.5.1 of NICE's Process and Methods Guide 2013 (PMG9), the company has updated the cost utility model with the *most recent* NHS Reference Costs (2020/21).	Costs for in particular the pediatric hospital admission have risen dramatically between the 19/20 and 20/21 NHS reference costs. The

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	o Source: https://www.england.nhs.uk/wp-content/uploads/2022/07/2_National_schedule_of_NHS_costs_FY20-21.xlsx). • The unit costs that have been updated in the model (tab "Resource Use Costs") were provided to the NICE Technical team via e-mail on 22nd November 2022, so that the ERG could conduct an independent validation. • For reference only, if the now out-of-date 2019/20 NHS reference costs are applied in the updated model (incorporating all the changes outlined in Comment 4 above) then the company's base case ICER would be [redacted]. • The application of a disease severity QALY modifier would reduce this ICER to [redacted] per QALY.	EAG cannot judge whether this is indeed because of an increase in costs, or that methodology of assessing these costs within the NHS was slightly changed between years. In line with the company's analyses, the EAG use the 20/21 cost level in their base-case analysis but ran a scenario with the 'old' 19/20 cost level. The EAG also re-ran their scenario with TA614 and TA615 resource use estimates.
9 Institutionalisation calculation by the ERG	As communicated to the NICE Technical Team (by e-mail on 22/11 2022) and accepted by the ERG (in the e-mail from the NICE Technical Team on 24/11/2022), there was a calculation error in the ERG's model (model labelled "ERG base case_ID1416_CBD in TSC_CE model AICCIC_PMB8Sep22 committees preferred assumptions") regarding institutionalisation, as follows: One of the preferred assumptions of the Committee was that the caregivers of adult patients with TSC who are institutionalised have a 50% decrease in their disutility, associated with no longer having to care full time for their dependent. This is currently implemented in the model in cell K12 of tab "*Utilities*" (cell name "*UT_averageNcarer_ERG6*"). The coding for this cell is as follows: =(1-0.31)*UT_averageNcarer+0.31*(IF(ERG!F9=1,0.5,IF(ERG!F26=2,0.5*UT_averageNcarer,UT_averageNcarer))) However, the ERG has reduced the disutility of caregivers not by decreasing the disutility calculation itself, but by reducing the average number of caregivers per patient by 50% for the proportion of caregivers whose dependents are institutionalised (31%, as predicted by the Delphi panel). This coding does not do this, as the term "**UT_averageNcarer*" is missing from the calculation. The correct coding is shown below: =(1-0.31)*UT_averageNcarer+0.31*(IF(ERG!F9=1,0.5*UT_averageNcarer,UT_averageNcarer)) The company's updated model with our new base case has this correction implemented.	As communicated earlier by email to the NICE Technical Team, the EAG is agreed with this adjustment.

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10 Long term efficacy	• The company notes the Committee's conclusion that "Cannabidiol reduces seizure frequency and increases the number of seizure-free days compared with usual care alone, but long-term efficacy is uncertain". • We reiterate that there is now a significant body of evidence (across three indications, TSC-associated epilepsy, LGS and DS) that demonstrates the long-term durability of efficacy outcomes with cannabidiol. • As noted in the ACD, our submission provided interim data from the GWPCARE6 OLE (Open Label Extension) study in TSC-associated epilepsy up to 72 weeks. • 3-year (156-week) efficacy data from the GWPCARE6 OLE will be presented by Thiele, E et al. at the American Epilepsy Society (AES) congress in December 2022. The results demonstrate that add-on cannabidiol treatment was well-tolerated and produced sustained reductions in TSC-associated seizures for up to 156 weeks in patients who continued on treatment: o Median reduction from baseline in TSC-associated seizures ranged from [redacted] across 12-week windows through 156 weeks o Reductions in TSC-associated seizures ≥50%, ≥75%, and 100% were maintained up to 156 weeks, ranging from [redacted], respectively.	The longer-term data from GPWCARE6 OLE was from a single arm, without a comparator. Therefore, any interpretations from such data will need to be tentative. Hence, they are described as 'uncertain'.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

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