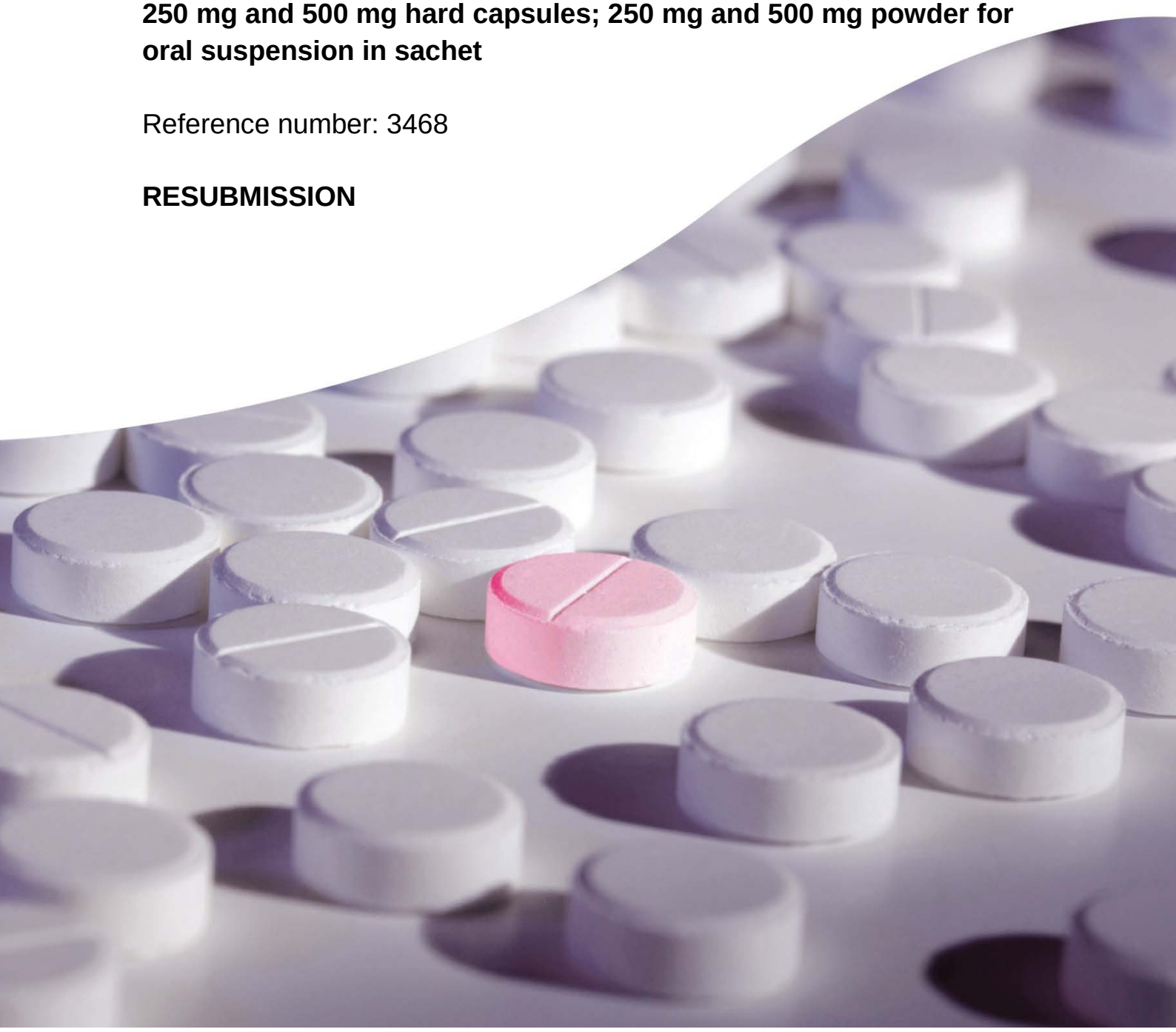
AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

AWMSG SECRETARIAT ASSESSMENT REPORT

Stiripentol (Diacomit®)
250 mg and 500 mg hard capsules; 250 mg and 500 mg powder for oral suspension in sachet

Reference number: 3468

RESUBMISSION



PAMS
Patient Access to Medicines Service
Mynediad Claf at Wasanaeth Meddyginiaethau

This report has been prepared by the All Wales Therapeutics & Toxicology Centre (AWTTC).

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AWMSG Secretariat Assessment Report
Stiripentol (Diacomit®) 250 mg and 500 mg hard capsules; 250 mg and 500 mg powder for oral suspension in sachet

This assessment report is based on evidence submitted by Biocodex[1].

1.0 PRODUCT DETAILS

Licensed indication under consideration	Stiripentol (Diacomit®) is indicated for use in conjunction with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI; Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate[2].
Dosing	Dose is calculated on a mg/kg body weight basis, and the daily dose may be given in 2 or 3 divided doses. Starting adjunctive therapy with stiripentol should be gradual using upwards dose escalation to reach the recommended dose of 50 mg/kg per day, given in conjunction with clobazam and valproate. Refer to the Summary of Product Characteristics for further information about dosing[2].
Marketing authorisation date	4 January 2007[2]
UK launch date	18 February 2008[1]

2.0 DECISION CONTEXT

2.1 Background

Dravet syndrome, also called severe myoclonic epilepsy of infancy, is a severe and difficult-to-treat form of childhood epilepsy that usually starts during the first year of life[3,4]. Initial presentation is with generalised tonic-clonic or one-sided seizures, often prolonged, which are usually associated with fever[3,4]. Seizures then increase in frequency and begin to occur without fever[3]. Later a range of other seizure types appear, most commonly myoclonic seizures (single jerks), and focal or atypical absence seizures[3,4]. The child's development during the first year of life is usually normal, but from the second year onwards their development slows down or regresses, sometimes severely[3]. They often have problems with mobility, particularly ataxia[3]. Features of autism and attention deficit hyperactivity disorder are common[3]. Children with Dravet syndrome have a higher risk of sudden unexplained death than children with other types of epilepsy[3]; death from status epilepticus, injury or drowning is also a significant risk[4]. Dravet syndrome is a rare disease: in Europe, its estimated prevalence is 1 in 25,000[5].

Treatment for Dravet syndrome focuses on controlling or minimising seizures using anti-epileptic medicines[3]. The National Institute for Health and Care Excellence (NICE) guideline for managing epilepsies recommends sodium valproate or topiramate as first-line therapy for Dravet syndrome; if these are not effective or not tolerated then adjunctive treatment with clobazam or stiripentol is recommended[6]. Other organisations, however, recommend the combined use of stiripentol with both clobazam and sodium valproate[7,8].

Stiripentol (Diacomit®) is an alpha-ethylene alcohol that has activity in the central nervous system[9]. The mechanism of its anticonvulsant action is not known, but it is thought to affect gamma-aminobutyric acid uptake and to potentiate the effects of other anti-epileptic medicines[9]. Stiripentol is licensed in combination with clobazam and valproate to treat Dravet syndrome in patients whose seizures are not adequately controlled with clobazam and valproate[2]. The conditional marketing authorisation granted in 2007 by the European Medicines Agency was changed to a full marketing authorisation in 2014[10]. Stiripentol is the only medicine specifically licensed for treating Dravet syndrome in the UK.

The All Wales Medicines Strategy Group (AWMSG) has previously appraised stiripentol (Diacomit®) and did not recommend its use to treat severe myoclonic epilepsy in infancy (Dravet syndrome), stating that the economic evidence submitted was not sufficient to assess the cost-effectiveness[11]. A resubmission has been made which includes additional clinical data and a revised economic evaluation[1].

2.2 Comparators

The comparators included in the company's submission are:

- clobazam plus valproate[1].

2.3 Guidance and related advice

- North American Consensus Panel (2017) Optimizing the diagnosis and management of Dravet syndrome[8]
- International League Against Epilepsy guideline (2015) Recommendations for the management of infantile seizures[7]
- NICE guideline CG137 (2012) Epilepsies: diagnosis and management (last updated in 2016)[6]

3.0 SUMMARY OF EVIDENCE ON CLINICAL EFFECTIVENESS

The company's submission includes data from two randomised double-blind phase III studies of the efficacy of stiripentol as add-on therapy to clobazam and valproate in 66 patients with Dravet syndrome; both studies are discussed further below[1]. The company also highlights new evidence from an open-label study conducted in 30 patients with Dravet syndrome in Japan which provides longer term efficacy data; and a post-marketing study (DIAVEY) of stiripentol treatment in 152 patients with Dravet syndrome which provides additional safety data; both studies are summarised below[1]. The submission also includes other supportive studies, including a retrospective chart review and studies using doses of stiripentol other than the licensed dose; these are not discussed further.

3.1 STICLO-France and STICLO-Italy phase III studies

These multicentre studies were of identical design. Both enrolled patients aged 3–18 years (mean age 9 years) with Dravet syndrome who were experiencing at least four clonic or tonic-clonic generalised seizures per month; 42 patients in France and 24 in Italy[9,12,13]. Before entering the study, patients had to be receiving valproate (≤ 30 mg/kg/day) and clobazam (maximum 20 mg/day). All patients received valproate (≤ 30 mg/kg/day) and clobazam (0.5 mg/kg/day) during a four-week baseline period. After this, they were randomised to receive additional treatment with stiripentol at a dose of 50 mg/kg/day (given as capsules in two or three divided doses) or placebo for an eight-week double-blind comparison period[12]. During the study, doses of valproate could be decreased by 10 mg/kg daily in case of loss of appetite, and doses of clobazam could be reduced by 25% in cases of drowsiness or hyperexcitability[12].

The primary outcome was the number of responders in each group, defined as patients who had at least a 50% reduction in the number of clonic or tonic-clonic seizures during the second month of the comparison period compared with baseline[12]. Patients

presenting with status epilepticus during the double-blind period were regarded as non-responders. Secondary endpoints included: the percentage change from baseline in seizure frequency, variation in number of seizures compared with baseline, and study withdrawals[12]. In the STICLO-France study one patient could not be assessed and in the STICLO-Italy study one patient withdrew before starting treatment. The primary endpoint was met: adjunctive stiripentol treatment statistically significantly reduced the number of clonic or tonic-clonic generalised seizures by at least 50% after two months of treatment. The secondary endpoints were generally supportive of the primary endpoint. The results are presented in Table 1. The STICLO-France study was stopped early, with no further recruitment, because of the significant differences observed between treatments[9].

Table 1. Results from STICLO-France and STICLO-Italy studies of stiripentol as an adjunct to clobazam and valproate treatment [12,14,15]

STICLO-France	**Stiripentol (n = 21)**	**Placebo (n = 20)**	**p-value**
Primary endpoint: patients with > 50% reduction in seizures during treatment (2nd month)			
Number of responders (%)	15 (71.4%)	1 (5%)	p < 0.00002
95% Confidence interval (%)	52.1 to 90.7	0.0 to 14.6	
Secondary endpoints:			
Mean percentage change from baseline in tonic-clonic seizure frequency:			
Month 1	-83.2%	+11.3%	p < 0.001
Month 2	-68.6%	+7.4%	p < 0.002
Number of seizure-free patients at the end of month 2	9 (45%)	0	p < 0.01
Number of patients who withdrew from treatment	1 (5%)	4 (20%)	p = 0.184
STICLO-Italy	**Stiripentol (n = 12)**	**Placebo (n = 11)**	**p-value**
Primary endpoint: patients with > 50% reduction in seizures during treatment (2nd month)			
Number of responders (%)	8 (66.7%)	1 (9.1%)	p = 0.009
95% Confidence interval (%)	34.9 to 90.2	0.0 to 41.3	
Secondary endpoints:			
Mean percentage change from baseline in tonic-clonic seizure frequency:			
Month 1	-89.5%	+5.5%	p < 0.05
Month 2*	-74.3%	-12.7%	NS
Number of seizure-free patients at the end of month 2*	3 (27%)	0	p = 0.05
Number of patients who withdrew from treatment	1 (9%)	2 (18%)	N/R
* For month 2, 11 patients were evaluable in the stiripentol group and 9 patients in the placebo group N/R: not reported; NS not significant			

3.2 STP-1: an open-label, long-term study

The efficacy and safety of stiripentol administration over 12 weeks and 52 weeks were evaluated in Japanese patients with Dravet syndrome whose seizures were not adequately controlled with clobazam and valproate treatment (with or without bromide)[16]. In the four-week baseline period, patients continued to receive their stable doses of clobazam (up to 0.5 mg/kg/day) and valproate (up to 30 mg/kg/day). Of the 27 patients who entered the baseline period, 24 (aged 1–24 years) started stiripentol treatment, beginning with a dose of 20 mg/kg/day (maximum 1,000 mg/day) which was increased by 10 mg/kg/day (maximum 500 mg/day) each week up to a dose of 50 mg/kg/day (maximum 2,500 mg/day). Stiripentol was then continued at a dose of 50 mg/kg/day for 12 weeks (fixed-dose period)[16]. During the dose-adjustment and fixed-dose periods, dose reductions were allowed for valproate (by 30%) and clobazam (by 25%) if patients experienced an adverse event related to either treatment[16]. No dose adjustments were allowed for bromide[16]. After the 12-week fixed-dose period patients continued stiripentol for another 40 weeks during which time the dose could be

modified according to response[17]. In exceptional cases, patients were allowed to continue using bromide that had been started before enrolment[17]. The median stiripentol dose at the end of the study was 48.7 mg/kg/day (range 29.9 to 65.3 mg/kg/day)[17].

The primary efficacy endpoint was responder rate, defined as the proportion of patients with a ≥ 50% reduction in clonic or tonic-clonic seizures over the last four weeks of fixed-dose treatment and long-term treatment compared with the baseline period[16]. All 24 patients completed the 12-week fixed dose period and of the 21 patients who then entered the long-term treatment period, 19 completed the study. After 12 weeks of treatment, 16 patients were responders, giving a responder rate of 66.7% (95% confidence interval [CI]: 44.7 to 84.4). Four patients became free from clonic or tonic-clonic seizures[16]. After the long-term treatment period (52 weeks) the responder rate was 54% (95% CI: 34.2–74.1[18]); two patients were free of clonic or tonic-clonic seizures throughout the period of treatment with stiripentol[17].

3.3 Safety

Safety data come from the two STICLO studies and pooled data from six other studies, including STP-1, DIAVEY and four other studies of various treatment durations (one ranging 3-5 years). These give a total of 438 patients with Dravet syndrome who were treated with stiripentol[1]. In the six pooled studies approximately 55% of patients received doses of stiripentol either below 40 mg/kg/day or above 60 mg/kg/day.

Most of the adverse events reported in the STICLO studies were neurological (mainly sleepiness/drowsiness) or gastrointestinal in origin (mainly loss of appetite and weight loss), and occurred more frequently in the stiripentol group compared with the placebo group: 90% and 75% of stiripentol-treated patients in the STICLO-France and STICLO-Italy studies respectively, reported at least one neurological adverse event, compared with 25% and 27% in the placebo groups. At least one gastrointestinal event was reported in 67% and 58% of stiripentol-treated patients in the STICLO-France and STICLO-Italy studies respectively, compared with 35% and 9% of placebo-treated patients[9]. Similarly, somnolence, loss of appetite and ataxia were the most frequently reported drug-related adverse events in STP-1[17]. Withdrawal due to adverse events in stiripentol-treated patients was low (< 5%) across all studies[1]. In the STICLO studies, no serious adverse events were judged to be related to stiripentol[1]. In the other studies, including STP-1, the most common serious adverse events associated with stiripentol were decreased appetite (7 patients), pyrexia (7), somnolence (5) and infections (16); relationship to stiripentol treatment does not appear to have been assessed. There were no deaths in any study that were judged to be related to stiripentol treatment[1].

In the pooled STICLO studies elevated transaminases were observed more frequently in stiripentol-treated patients than in placebo-treated patients (48.5% versus 22.6%), though the difference was not statistically significant and most cases were mild; increased transaminases were also mostly mild in the other studies[1]. Elevated liver enzymes (gamma-glutamyltransferase) were also reported frequently in STP-1[1]. Mild or moderate neutropenia was reported in 21.1% of patients treated with stiripentol compared with 9.7% of placebo-treated patients in the pooled STICLO studies, though again the difference was not statistically significant[1]. Neutropenia, mostly mild, was also observed in the other pooled studies (17 mild, 2 moderate). Across all clinical studies, 29 patients treated with stiripentol developed thrombocytopenia and in most cases this was mild to moderate[1]. The Summary of Product Characteristics reflects these findings and recommends six-monthly blood count and liver function checks[2].

The Committee for Medicinal Products for Human Use has suggested that many of the observed adverse events may be related to the increased serum concentrations of concomitant medicines, because their plasma levels are increased by stiripentol's action on the cytochrome P450 enzyme system[1,9].

A post-marketing study (DIAVEY), conducted in the EU during 2007–2012, analysed data from 152 patients with Dravet syndrome treated with stiripentol[19]. All enrolled patients were followed-up for a minimum of one year and for at least one year after stopping stiripentol treatment. In this study, 89 patients (58.6%) had at least one adverse drug reaction (ADR), 21 (13.8%) had at least one serious ADR[19] and 19 patients (12.5%) reported at least one ADR that lead to them stopping stiripentol treatment[19]. Most of the serious ADRs were related to nervous system disorders and were mainly 'status epilepticus', convulsions and decreased appetite[19]. The survey did not show that stiripentol had a negative impact on growth in height or weight, or on the mental development or behaviour of patients. However, due to the frequency of gastrointestinal adverse effects with stiripentol (and valproate), the Summary of Product Characteristics recommends monitoring the growth rate of children treated with this combination[2]. Overall, no ADRs were identified that raised major safety concerns[19].

3.4 AWTTC critique

- Dravet syndrome is a rare and difficult-to-treat disease that begins early in childhood. Stiripentol, used in combination with valproate and clobazam[2], is the only medicine specifically licensed for treating patients with Dravet syndrome in the UK. Clinical expert opinion sought by AWTTC confirms that adjunctive stiripentol is currently widely used within NHS Wales.
- The key evidence for clinical effectiveness is taken from two small randomised controlled studies comparing stiripentol plus clobazam plus valproate with placebo plus clobazam plus valproate. Results showed that adjunctive stiripentol was significantly better than placebo in reducing seizure frequency by 50% or more[12,13]. The anticonvulsant activity of stiripentol may in part result from its inhibition of the enzymes that metabolise concomitant anti-epileptic medicines[9].
- The STICLO studies provide efficacy data for only two months of treatment with stiripentol[12,13]. Data from the open-label STP-1 study support longer-term efficacy (up to one year)[16]. Data for stiripentol treatment for longer than one year are available and are limited to prospective open-label studies, post-marketing studies designed to collect information on adverse effects, and retrospective studies.
- The comparator used in the submission is valproate in combination with clobazam. This dual therapy regimen is included in the NICE epilepsies guideline and clinical experts have confirmed that this is used in NHS Wales. Clinical experts have indicated that other dual and triple therapy regimens may also be used, in particular regimens including the unlicensed use of levetiracetam and topiramate. The company states that indirect treatment comparisons with unlicensed medicines are not possible due to a lack of suitable data.
- The age of patients in the STICLO studies was 3–18 years. The stiripentol licence and company submission do not limit its use to this age group, though the Summary of Product Characteristics does acknowledge the lack of data in patients aged under 3 years and in adults, and cautions use in these groups accordingly.
- The key studies only assessed reductions in tonic-clonic or clonic generalised seizures[12,13,16,17]. Children with Dravet syndrome also have other types of seizures.
- It is not known whether stiripentol reduces cognitive and psychomotor retardation in children with Dravet syndrome[16].
- Robust long-term safety data are lacking but, to date, no major safety concerns have been identified with the use of stiripentol in patients with Dravet syndrome. In the STICLO and STP-1 studies adverse events were common and were managed by dose adjustments. The Summary of Product Characteristics recommends using dose escalation to reach the recommended dose when

starting adjunctive treatment with stiripentol and monitoring plasma levels of concomitant anti-epileptic medicines[2].

- The capsule and sachet formulations are not bioequivalent. This is reflected in the Summary of Product Characteristics; switching between formulations is recommended to be done under clinical supervision[2].

4.0 SUMMARY OF THE EVIDENCE ON COST-EFFECTIVENESS

4.1 Cost-effectiveness evidence

4.1.1 Context

The company's submission includes a cost-utility analysis comparing stiripentol given with valproate and clobazam versus valproate and clobazam alone for treating patients in Wales with Dravet syndrome whose seizures are not adequately controlled with valproate and clobazam.

The company uses a Markov modelling approach to assess the cost-effectiveness of stiripentol given with valproate and clobazam for treating Dravet syndrome. The company states that the model was based on a Canadian model for stiripentol[20] and a model from the NICE guideline on epilepsies[6].

Dual therapy with valproate and clobazam is the only comparator included in the model and the company states that this is required treatment for this indication in Wales. The economic evaluation does not consider comparisons with other antiepileptic medicines.

The cost-utility analysis uses a Markov model to estimate the expected costs and quality-adjusted life year (QALY) gains over a 15-year time horizon in a cohort of patients (baseline age 3 years) first treated with valproate and clobazam, whose seizures are not adequately controlled. The model uses cycles of three months and simulates disease progression in people with Dravet syndrome through several health states defined by reductions in seizure frequency (refractory generalized tonic-clonic seizures), treatment management and death.

Five health states are included in the model: (i) seizure-free; (ii) not seizure-free; (iii) not adequately controlled; (iv) maintenance therapy; and (v) death. Patients start adjunctive therapy with stiripentol and move to one of the three seizure-related health states after the first cycle. Thereafter, patients who are seizure-free can either remain seizure-free or transition to the not-seizure-free state while patients who are not-seizure-free can either stay not-seizure-free or move to the not-adequately-controlled state. In each cycle, a proportion of patients transition from the seizure-free and not-seizure-free health states to the maintenance therapy state. Patients automatically transition from the not-adequately-controlled state to the maintenance therapy state after one cycle. Patients can die at any time within the model. Costs and benefits are discounted at 3.5%.

The transition probabilities used in the model were derived from the two STICLO studies (STICLO-France and STICLO-Italy) and the DIAVEY long-term study: the two STICLO studies for the first three-month cycle and the DIAVEY study thereafter. Mortality rates vary by health state, with higher mortality rates for patients in the not-seizure-free, not-adequately-controlled and maintenance therapy health states than for patients in the seizure-free health state.

The costs included in the model are the costs of drug therapy, monitoring, changing therapy, status epilepticus and managing adverse events. The associated resource utilisation was obtained from the STICLO studies, the Canadian stiripentol model[20], the NICE model[6] and expert opinion. Unit costs were obtained from published sources.

Utility values were taken from the Canadian stiripentol model[20]. These values were derived from a study eliciting utilities by time-trade off interviews for Lennox-Gastaut syndrome among the UK general public[21]. The company states that Lennox-Gastaut syndrome is a form of epilepsy more comparable with Dravet syndrome than general infantile epilepsy. Utility decrements are applied for adverse events.

Scenario analyses focus on the impact of: (i) the model assumption about waning of effect and discontinuation; (ii) reducing the number of inpatient visits in the not-adequately-controlled health state; (iii) using utility values from an observational study comparing the health status benefits associated with the start of adjunctive therapy with a range of anti-epileptic medicines[22]; and (iv) using utility values from an individual sampling model for evaluating anti-epileptic medicines used to treat focal epilepsies in children[23]. In addition, extensive deterministic sensitivity analyses and probabilistic sensitivity analyses were undertaken to assess parameter uncertainty.

4.1.2 Results

Results of the base case analysis for the cost-utility analysis are presented in Table 2. The results show total treatment costs of £233,558 for adjunctive stiripentol compared with £231,067 for valproate and clobazam. Total QALYs gained are 5.670 for adjunctive stiripentol compared with 5.444 for valproate and clobazam. This resulted in an incremental cost per QALY gained of £11,009 for adjunctive stiripentol compared with valproate and clobazam alone.

Table 2. Company-reported results of the base case analysis (cost-utility analysis[1]

Results per patient	Adjunctive STP	VPA + CLB	Incremental
Cost outcomes:			
Drug costs	£37,882	£24,558	£13,323
Management costs	£188,508	£199,221	-£10,713
Ongoing therapy costs	£858	£959	-£101
Status epilepticus costs	£5,999	£6,206	-£207
Adverse event costs	£311	£122	£188
Total	**£233,558**	**£231,067**	**£2,491**
Efficacy outcomes:			
QALYs	**5.670**	**5.444**	**0.226**
Life years	10.137	10.102	0.035
Cost-effectiveness outcomes:			
Cost per QALY gained	**£11,009**		

CLB: clobazam; QALY: quality-adjusted life year; STP: stiripentol; VPA: valproate

The company conducted scenario analyses to test key areas of uncertainty in the model. The results of the scenario analyses are summarised in Table 3. In Scenario 1, after the first cycle (3 months) patients stay in the same health state (seizure-free, not-seizure-free, not-adequately-controlled) except to transition to the death state. Patients cannot discontinue and transition to maintenance therapy as per the base case.

In Scenario 2, inpatient visits in the not-adequately-controlled health state are reduced (from six to three per year). Scenario 3 uses utility values from an observational study comparing the health status benefits associated with the start of adjunctive therapy with a range of anti-epileptic medicines[22]. The utility estimates for all health states are

systematically higher than the respective values in the base case analysis. Scenario 4 uses utility values from an individual sampling model to evaluate anti-epileptic medicines used to treat children with focal epilepsies[23]. For the four scenario analyses conducted, adjunctive stiripentol is either dominant or cost-effective, within the £30,000 cost per QALY gained threshold, compared with valproate and clobazam.

Table 3. Company-reported results of the scenario analyses

Scenarios	ICER (adjunctive STP versus VPA + CLB)	Plausibility
Base case analysis	£11,009	-
Scenario 1 Alternative assumption on waning of effect and discontinuation	STP dominant	This is a plausible scenario as the base case makes an assumption which may vary in practice.
Scenario 2 Alternative assumption on inpatient stay in not-adequately-controlled health state	£9,529	This is a plausible scenario as inpatient stay in the not-adequately-controlled state is based on assumption and may vary between patients.
Scenario 3 Alternative source of utilities from observational study	£25,173	This is a plausible scenario as the utility values were not estimated directly and may vary from those used in the base case.
Scenario 4 Alternative source of utilities from individual sampling model	£24,918	This is a plausible scenario as the utility values were not estimated directly and may vary from those used in the base case.
CLB: clobazam; ICER: incremental cost-effectiveness ratio; STP: stiripentol; VPA: valproate		

On request, the company provided results for additional scenario analyses on the time horizon and proportion of patients receiving treatment after 18 years. The results of these are summarised in Table 4. In the first set of additional scenario analyses, the company varied the time horizon from 20 years to 45 years. The treatment duration (in both arms) was maintained throughout the whole time horizon according to the transition probabilities and discontinuation rate applied in the base case analysis.

In the second set of additional scenario analyses, a proportion of patients remain on treatment at 18 years. The company reported results for 10%, 20% and 30% of patients remaining on treatment at 18 years. In these scenario analyses, the time horizon was extended to 40 years in order to capture all costs and benefits associated with treatment. The treatment duration (in both arms) was maintained throughout the whole 40 year time horizon.

For the additional scenario analyses conducted, increasing the time horizon up to 45 years has minimal impact on the results. However, including a proportion of patients who continue treatment at 18 years (≥ 10%) and increasing the time horizon to 40 years adjunctive stiripentol is not cost-effective, within the £30,000 cost per QALY gained threshold, compared with valproate and clobazam.

Table 4. Company-reported results of the additional scenario analyses requested

Scenarios	ICER (adjunctive STP versus VPA + CLB)	Plausibility
Base case analysis	£11,009	-
Scenario Time horizon increased to 20 years	£11,883	This is a plausible scenario given the age of patients included in the economic model.
Scenario Time horizon increased to 45 years	£13,156	This is a plausible scenario given the age of patients included in the economic model.
Scenario 10% of patients remain on treatment at 18 years and 40 year time horizon	£36,555	This is a plausible scenario because the SPC does not exclude treatment in patients over 18 years. Clinical expert opinion sought by AWTTC also suggests that many patients would continue treatment beyond 18 years.
Scenario 30% of patients remain on treatment at 18 years and 40 year time horizon	£60,565	This is a plausible scenario because the SPC does not exclude treatment in patients over 18 years. Clinical expert opinion sought by AWTTC also suggests that many patients would continue treatment beyond 18 years.
AWTTC: All Wales Therapeutics & Toxicology Centre; CLB: clobazam; ICER: incremental cost-effectiveness ratio; SPC: Summary of Product Characteristics; STP: stiripentol; VPA: valproate		

The results of the deterministic sensitivity analysis show that the incremental cost-effectiveness ratio (ICER) is most sensitive to the starting age of patients, probability of experiencing a status epilepticus inpatient stay, monitoring costs of maintenance therapy for inpatient care, costs of maintenance therapy for both strategies, and monitoring costs for not-seizure-free patients. Adjunctive stiripentol dominates valproate and clobazam with the lower values for probability of experiencing a status epilepticus inpatient stay (adjunctive stiripentol arm), monitoring cost for not-seizure-free patients and the cost of maintenance therapy (adjunctive stiripentol arm). Similarly, adjunctive stiripentol dominates valproate and clobazam with the higher values for probability of experiencing a status epilepticus inpatient stay (valproate and clobazam arm), monitoring costs of maintenance therapy for inpatient care and the cost of maintenance therapy (valproate and clobazam arm). ICERs in all one-way sensitivity analyses ranged from adjunctive stiripentol being dominant to £66,690 per QALY gained. The probabilistic sensitivity analysis estimates the probability that adjunctive stiripentol is cost-effective against valproate and clobazam alone for the different values of the willingness-to-pay per QALY (cost-effectiveness thresholds). At a cost-effectiveness threshold of £20,000 per QALY gained, the probability of adjunctive stiripentol being cost-effective against valproate and clobazam is 53.7%. When considering the higher threshold of £30,000 per QALY gained, this probability is 57.5%.

4.1.3 AWTTC critique

The company's model used to calculate cost-effectiveness is well structured and well defined.

Limitations of the economic evidence include:

- The only comparator included in the model is dual therapy with valproate and clobazam, based on expert opinion from one clinician in Wales. The economic evaluation does not consider comparisons with other antiepileptic medicines which may be used in NHS Wales for the treatment of Dravet syndrome, in particular unlicensed use of topiramate and levetiracetam. The company state that the data

available for these treatments are weak and would therefore not enable a robust comparison.

- The company uses a time horizon of 15 years for the base case analysis, which is based on treatment for patients aged 3–18 years. However, the stiripentol Summary of Product Characteristics does not exclude treatment in children under 3 years. Similarly, the Summary of Product Characteristics does not exclude continuing treatment in patients over 18 years. Instead, it states that treatment should be continued for as long as efficacy is observed. Clinical expert opinion sought by AWTTC suggests that many patients would continue treatment with stiripentol beyond 18 years of age. The additional scenario analyses requested show that including a proportion of patients who continue treatment at 18 years (≥ 10%), and increasing the time horizon to 40 years, increases the cost per QALY gained to over £30,000.
- The transition probabilities for the first three-month cycle were derived from the STICLO studies. Pooled response rates at the end of the two-month studies were used in the model at the end of the first cycle, i.e. three months. However, there is no confirmation that the difference between the two treatment arms would be maintained for an additional month.
- The transition probabilities after three months were derived from a post-hoc analysis of the DIAVEY study, a post marketing study whose objective was to collect adverse drug reactions and safety information for patients newly prescribed stiripentol for Dravet syndrome. The study only provided transition probabilities for the adjunctive stiripentol arm, which were then assumed to be the same for the valproate and clobazam arm. There are no comparative data beyond the two-month data from the STICLO studies and the company did not justify the assumption used.
- Patients in the DIAVEY study were treated for one to five years. Although the transition probabilities derived from it were from the full five-year period, they were applied over the full 15-year time horizon of the model without any assessment of whether this assumption would be expected in clinical practice. A full summary of the results from the DIAVEY study, including the post-hoc analyses, is not included in the company's submission.
- The dose of stiripentol is based on a mean patient age of 9 years, as per the STICLO studies. This may not reflect the expected mean age of patients treated with adjunctive stiripentol in Wales.
- Other resource utilisation was estimated based on the two epilepsy models[6,20], assumption and expert opinion. The model developed for the NICE guideline on epilepsies was for treating children with focal epilepsy not Dravet syndrome, though the resource utilisation was validated by clinical experts, one of whom was based in NHS Wales.

4.2 Review of published evidence on cost-effectiveness

Standard literature searches conducted by AWTTC identified one relevant economic evaluation. This was an evaluation of the cost-effectiveness of adjunctive stiripentol (in conjunction with valproate and clobazam) compared with valproate and clobazam for the treatment of Dravet syndrome in Canada[20]. This was a Markov model with four health states: seizure-free, not-seizure-free, not-adequately-controlled and death. The analysis included a five-year time horizon with cycles of one-year duration and was conducted from the perspective of both the Canadian Ministry of Health and society. Adjunctive stiripentol was shown to be cost-effective, compared with valproate and clobazam, from both a Canadian Ministry of Health and societal perspective[20].

5.0 SUMMARY OF EVIDENCE ON BUDGET IMPACT

5.1 Budget impact evidence

5.1.1 Context and methods

The company presented a budget impact assessment for the use of adjunctive stiripentol in Wales. The company estimates that there are 23 patients with Dravet syndrome in Wales, based on 566,472 individuals aged 3 to 18 in Wales as per the 2011 Census[24], and a prevalence of Dravet syndrome of 0.40 per 10,000 from the European Medicines Agency[5]. They estimate one newly diagnosed patient per year, based on an incidence of 0.24 per 10,000[25] and 33,361 live births in Wales in 2015[26]. Hence, the company estimates the number of patients eligible for treatment to rise from 23 to 27 in the first five years after the introduction of stiripentol.

The company assumes that all patients with Dravet syndrome in Wales are currently treated and that 30% of them are refractory to conventional dual therapy, making them eligible for stiripentol[27]. Thus, the number of patients eligible for treatment with stiripentol is seven in Year 1, increasing to eight in Year 5. The company bases its estimate of budget impact on the assumption that stiripentol will acquire an increasing proportion of the market share starting at 60% in Year 1 and increasing to 100% in Year 5. Therefore, the number of patients who receive adjunctive stiripentol increases from four in Year 1 to eight in Year 5.

The company has based its budget impact analyses on the same assumptions used in the cost-utility analysis, i.e. the cost estimate was calculated as the cost of the first year of stiripentol use from the economic model, including discontinuation and mortality, for a patient starting stiripentol at age 9 years.

5.1.2 Results

The company estimates the costs associated with introducing adjunctive stiripentol for treating Dravet syndrome in patients whose seizures are not adequately controlled with valproate and clobazam in Wales. The net medicine acquisition cost increases from £32,344 in Year 1 to £64,689 in Year 5. This is due to the uptake of stiripentol increasing over time. As the net supportive medicine cost was £0 each year, the overall net financial cost is the same as the net medicine acquisition cost.

The estimated number of patients and the associated costs as described by the company in its budget impact analysis are summarised in Table 5.

Table 5. Company-reported net costs associated with the use of adjunctive stiripentol for treating Dravet syndrome in patients in Wales whose seizures are not adequately controlled with valproate and clobazam[1]

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients (indication covered in this submission)	7	7	7	8	8
Uptake of stiripentol (%)	60%	70%	80%	90%	100%
Patients treated with stiripentol	4	5	6	7	8
Net medicine acquisition cost	£32,344	£40,431	£48,517	£56,603	£64,689
Net supportive medicines cost	£0	£0	£0	£0	£0
Overall net financial cost	**£32,344**	**£40,431**	**£48,517**	**£56,603**	**£64,689**

The company conducted scenario analyses to assess the impact of varying input parameters on the overall budget impact. It estimates best and worst case scenarios. For the best case scenario, the cost estimate was calculated as the cost of yearly stiripentol use from the economic model, including discontinuation and mortality, for a patient starting stiripentol treatment at 3 years old and being treated for five years. For the worst case, the cost estimate was based on the unit cost of stiripentol for a patient starting stiripentol at 9 years old. In addition, the worst case scenario assumes 100% compliance and 100% market share for stiripentol each year for the five years. The results of the scenario analyses are shown in Table 6.

Table 6. Company-reported results of the scenario analyses of net budget impact

	Overall net financial cost				
	Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**
Base case	**£32,344**	**£40,431**	**£48,517**	**£56,603**	**£64,689**
Best case	£19,460	£27,962	£37,809	£49,172	£62,533
Worst case	£68,058	£68,058	£68,058	£77,780	£77,780

On request, the company conducted sensitivity analysis for the acquisition price of stiripentol. Increasing the stiripentol acquisition price by 20% increased overall net financial cost to £38,813 in Year 1 and £77,627 in Year 5. Similarly, decreasing the stiripentol acquisition price by 20% decreased overall net financial cost to £25,876 in Year 1 and £51,751 in Year 5.

5.1.3 AWTTC critique

The cost estimates used in the budget impact are derived from the company's cost-utility analysis, therefore the limitations and uncertainties associated with the cost-utility analysis also apply to the budget impact analysis.

- Because of the lack of epidemiological data for Dravet syndrome in Wales, estimating the number of patients is based on assumptions and data drawn from published studies. Consequently, there is uncertainty about the number of patients eligible for treatment with stiripentol in Wales. However, one of the scenario analyses was for a higher number of patients treated with adjunctive stiripentol.
- The company limits the analysis to patients aged 3–18 years whereas treatment can start earlier and may continue beyond 18 years.
- Stiripentol dose is calculated using the mean age of patients in the STICLO studies, which was 9 years. This may not reflect the expected mean age of patients treated with adjunctive stiripentol in Wales.

5.2 Comparative unit costs

Table 7 shows example comparative acquisition costs of stiripentol and other anti-epileptic medicines, based on current British National Formulary and Monthly Index of Medical Specialities list prices.

Table 7. Examples of costs per patient of medicines used for treating Dravet syndrome

Regimens	Maximum daily dose	Cost per patient per 30 days
Stiripentol (Diacomit®) 500 mg capsules	50 mg/kg/day	£739.50
Stiripentol (Diacomit®) 500 mg powder	50 mg/kg/day	£739.50
Clobazam (non-proprietary [includes Frisium®]) 10 mg tablets	1 mg/kg/day	£8.97
Clobazam (Perizam®) 2 mg/ml oral suspension	1 mg/kg/day	£285.00
Sodium valproate (Epilim®) 200 mg/5 ml liquid	30 mg/kg/day	£17.50
Topiramate (Topamax®) 200 mg tablets	400 mg daily	£110.23
Topiramate (Topamax®) 50 mg sprinkle capsules	400 mg daily	£145.80
Levetiracetam (Keppra®) 100 mg/ml oral solution	60 mg/kg/day	£9.59
Notes: (i) costs based on British National Formulary, August 2017[28] and Monthly Index of Medical Specialities, August 2017[29]; (ii) costs of administration and monitoring are not included; (iii) this table does not imply therapeutic equivalence of drugs at the stated doses; (iv) costs are based on the cost per patient per 30 days for a 30 kg patient receiving the maximum daily dose.		

6.0 ADDITIONAL INFORMATION

6.1 Prescribing and supply
AWTTC is of the opinion that, if recommended, stiripentol (Diacomit®) for the indication under consideration may be appropriate for use within NHS Wales prescribed under specialist recommendation.

6.2 Ongoing studies
The company submission states that there are no ongoing studies from which additional evidence is likely to be available within the next 6–12 months.

6.3 AWMSG review
This assessment report will be considered for review three years from the date of the Final Appraisal Recommendation.

6.4 Evidence search
Date of evidence search: 23 June 2017
Date range of evidence search: No date limits were applied to database searches.

6.5 Consideration of AWMSG policy relating to orphan and ultra-orphan medicines and medicines developed specifically for rare diseases
The applicant company suggests that stiripentol (Diacomit®), for the indication under consideration, meets the criteria to be considered under the AWMSG orphan, ultra-orphan and medicines developed specifically for rare diseases policy. In this policy AWMSG defines an ultra-orphan medicine as a medicine that has been granted

European Medicines Agency (EMA) designated orphan status and is used to treat conditions affecting not more than 1 in 50,000 in the UK (or 60 patients in Wales)[30]. The definition applies to the full population of the licensed indication[30].

Stiripentol (Diacomit®) no longer has EMA designated orphan status[31]. However, AWMSG will apply the same process and principles of consideration to a medicine developed specifically to treat an equivalent size population, irrespective of whether it is designated by the EMA as an orphan medicine. The prevalence of Dravet syndrome is 0.4 per 10,000[5]; this equates to 23 patients aged 3–18 years in Wales. Stiripentol is only licensed for the adjunctive treatment of refractory generalised tonic-clonic seizures in patients with Dravet syndrome whose seizures are not adequately controlled with valproate and clobazam. The company estimates that 30% of Dravet syndrome patients are refractory to conventional dual therapy[27], making them eligible for adjunctive treatment with stiripentol. This results in seven patients being eligible for adjunctive treatment with stiripentol in Wales. Based on feedback from clinical experts in Wales, it is possible that the percentage of patients eligible to receive adjunctive stiripentol could be higher than 30%. However, even if all patients aged 3-18 years with Dravet syndrome in Wales were refractory to dual therapy the number of patients eligible for adjunctive stiripentol would be less than 60.

AWTTC considers stiripentol eligible to be considered as a medicine developed specifically to treat rare diseases. Should NMG and AWMSG consider that the orphan and ultra-orphan medicines and medicines for rare diseases policy applies to stiripentol, the criteria for assessing clinical effectiveness and cost-effectiveness will be the same as those applied for other medicines, whilst recognising that the evidence base may be weaker. NMG and AWMSG will consider evidence on the factors in Table 8 to inform their decisions.

Table 8. Orphan and ultra-orphan medicines and medicines specifically developed for rare diseases, considerations for NMG/AWMSG

NMG/AWMSG considerations	AWTTC comments
The degree of severity of the disease as presently managed, in terms of quality of life and survival	Dravet syndrome is characterised by high epilepsy-related premature mortality and a marked young age at death. The company estimates that premature mortality can affect up to 21% of Dravet syndrome patients. The causes of death in infants and children with Dravet syndrome include sudden death, seizures, status epilepticus, accidents and drowning[32,33]. Dravet syndrome is a devastating disease for patients and their families. Patients with Dravet syndrome generally experience significant limitations in daily activities and reduced quality of life, requiring significant care. This can have a major impact on family life with one parent often not working in order to be able to support the child.
Whether the medicine addresses an unmet need (e.g. no other licensed medicines)	Stiripentol is the only medicine licensed specifically for treating Dravet syndrome in the UK. It is used as adjunctive treatment after failure of conventional therapy (valproate and clobazam). The company states that it is the only treatment that has demonstrated efficacy in this specific population of patients.
Whether the medicine can reverse, rather than stabilise the condition	Stiripentol stabilises the condition by reducing the frequency of seizures, with some patients becoming seizure-free. It does not reverse or cure the condition.
Whether the medicine may bridge a gap to a “definitive” therapy (e.g. gene therapy), and that this “definitive” therapy is currently in development	There is no evidence that stiripentol bridges the gap to curative therapy.

NMG/AWMSG considerations	AWTTC comments
The innovative nature of the medicine	No specific evidence of innovation has been presented. Instead, the company claims that stiripentol is the only product demonstrating effectiveness and tolerance in Dravet syndrome and thus provides an option when other treatments have reached their limits in effectiveness and tolerance. Stiripentol was made available before marketing authorisation in Europe through compassionate use.
Added value to the patient which may not be adequately captured in the QALY (e.g. impact on quality of life such as ability to work or continue in education/function, symptoms such as fatigue, pain, psychological distress, convenience of treatment, ability to maintain independence and dignity).	Patients develop Dravet syndrome during the first year of life. The children have normal development before their first seizure. They then experience a dramatic loss of their intellectual and physical capabilities which results in an increase in their medico-social support needs. Dravet syndrome slows down motor, cognitive and language development. The company states that the use of adjunctive stiripentol should result in less deceleration in psychomotor and cognitive development, fewer behavioural problems, better interpersonal relationships, fewer obstacles with daily living, less placement in specialised nursing homes and easier co-ordination between carers and other medical and social factors, though no data to support this are presented.
Added value to the patient's family (e.g. impact on a carer or family life).	The company suggests that the use of adjunctive stiripentol may prevent or at least limit psychomotor retardation in children with Dravet syndrome and therefore help them to become more independent. This would have a positive impact on family life, reducing the need for external help and associated costs. No data to support this are presented.
AWMSG: All Wales Medicines Strategy Group; AWTTC: All Wales Therapeutics & Toxicology Centre; NMG: New Medicines Group; QALY: quality-adjusted life-year	

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