Cost-effectiveness of stiripentol (Diacomit®), prescribed in combination with valproate and clobazam, for adjunctive treatment of refractory, generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI; Dravet's syndrome) whose seizures are not adequately controlled with valproate and clobazam.

The NCPE has issued a recommendation regarding the cost-effectiveness of stiripentol (Diacomit®). Following assessment of the applicant's submission, the NCPE recommends that stiripentol (Diacomit®), prescribed in combination with clobazam and valproate, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.

The HSE asked the National Centre for Pharmacoeconomics (NCPE) to carry out an assessment of the applicant's (Biocodex) economic dossier on the cost effectiveness of stiripentol (Diacomit®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified. Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

National Centre for Pharmacoeconomics **May 2019**

Summary

In July 2018, Biocodex submitted an economic dossier examining the cost-effectiveness of stiripentol (Diacomit®), prescribed in combination with valproate and clobazam, for adjunctive treatment of refractory, generalised tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (SMEI; Dravet's syndrome) whose seizures are not adequately controlled with valproate and clobazam.

Dravet syndrome, formerly known as severe myoclonic epilepsy of infancy (SMEI), is a rare and catastrophic form of intractable epilepsy. It is a rare, genetic condition caused by mutations in the sodium voltage-gated channel α-sub-unit 1 (SCN1A) gene. Clinical features of Dravet Syndrome develop over time. The initial presentation in a young child is quite characteristic. In older, previously undiagnosed children and adults, in whom the early childhood history is not available, the diagnosis can be more challenging.

Stiripentol is structurally unrelated to any other anticonvulsant compound. It appears to have two types of mechanism involved in its anticonvulsant effect in Dravet syndrome. Firstly, stiripentol enhances transmission of gamma-aminobutyric acid (GABA). Secondly, an established pharmacokinetic interaction exists between stiripentol and clobazam, whereby stiripentol increases plasma levels of clobazam and its active metabolite, norclobazam.

1. Comparative effectiveness of stiripentol

The clinical evidence supporting the efficacy of stiripentol is predominantly derived from the pivotal STICLO trials (STICLO-France (n=42) and STICLO-Italy (n=23)). Both studies were randomised controlled, multi-centre, double-blind, placebo-controlled trials, of approximately 3 months duration. Following a one-month baseline period, patients were randomly allocated stiripentol or placebo as add-on therapy to their conventional treatment with clobazam and valproate. Response to stiripentol treatment was defined as achieving ≥50% reduction in seizure frequency during month two of the double-blind treatment period. In both STICLO trials, compared to placebo, stiripentol demonstrated a statistically significant increase in the number of 'responders'. In STICLO-France, the percentage of patients achieving ≥50% reduction in seizure frequency was 71.4% in the stiripentol-treated group (95% CI 52.1% - 90.7%; $p<0.0001$) and 5% in the placebo-treated group (95% CI 0% - 14.6%; $p<0.0001$). In STICLO-Italy, the percentage of patients achieving ≥50% reduction in seizure frequency was 66.7% in the

stiripentol-treated group (95% CI 34.9% - 90.2%; p=0.009) and 9.1% in the placebo-treated group (95% CI 0% - 41.3%; p=0.009).

The NCPE Review Group identified several limitations to the clinical trial evidence. The STICLO trials were of short duration, approximately 2 months of comparative evidence, and therefore do not provide evidence on the long-term efficacy and safety of stiripentol. Although statistically significant results were reported for the primary outcome, patient numbers were considered to be small (n=66). There have subsequently been several post-marketing trials, including the DIAVEY study, which investigated the longer term efficacy and safety of stiripentol. Once again the number of patients with Dravet syndrome, included in this study, is considered to be small (n=152).

Patients enrolled in the STICLO studies were aged between 3 and 18 years of age. The efficacy and safety of stiripentol in patients outside of this age range is, therefore, uncertain.
The number of patients who discontinued prematurely from the trials is greater in the placebo group compared to the stiripentol group. It is unclear as to how missing data were handled and to what extent this affects study results. For the purposes of the cost-effectiveness model, patients with missing data were assumed to be non-responders to treatment.
The NCPE Review Group also noted that the dose of clobazam prescribed in the STICLO studies was at the middle to lower range of that which may be prescribed in clinical practice. When stiripentol is added to existing clobazam treatment, it increases plasma concentrations of clobazam and its active metabolite. This is an established pharmacokinetic interaction. In the STICLO studies, patients in the placebo group were receiving a dose lower than that normally used in practice. This may have resulted in this patient group experiencing a suboptimal response to treatment, thereby overestimating clinical effectiveness of stiripentol in the treatment group.

Although both STICLO studies indicated that the intention to treat (ITT) populations were used for analysis of efficacy outcomes, only per protocol (PP) populations were analysed for some. One example is the variance in seizure frequency during treatment period compared to baseline. The results for this outcome were measured based on 36 patients in STICLO-France and 20 patients in STICLO-Italy – the per protocol populations. In STICLO-France, although the study indicated that ITT analyses were performed

on available data only. Therefore, data analyses were not performed in true ITT populations in both studies.

2. Safety of stiripentol

In the pivotal STICLO trials, adverse events were higher in the stiripentol-treated patient groups compared to placebo (100% vs 45% and 83% vs 27% for STICLO-France and STICLO-Italy, respectively). The most common adverse events associated with stiripentol are anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia and dystonia. Pharmacokinetic interactions between stiripentol and other associated medicines have been identified. It is acknowledged that many of the adverse effects observed with stiripentol are potentially related to elevation in serum concentrations of associated drugs. It is, therefore, important that prescribing physicians be cognisant of the effects resulting from such interactions.

3. Cost effectiveness of stiripentol

Methods

A Markov model was used to assess the cost-effectiveness of stiripentol (in combination with clobazam and valproate) versus clobazam with valproate. The model simulated the disease progression of Dravet syndrome patients through several health states defined by levels of reduction in seizure frequency, treatment management, and death. These health states were:

- Seizure Free (SF): having no seizure at all after treatment.
- Not Seizure Free (NSF): having between ≥50% to <100% reduction in seizure frequency.
- Not Adequately Controlled (NAC): having less than a 50% reduction in seizure frequency.
- Maintenance: discontinue due to adverse events or other reasons and switch to a maintenance therapy.
- Death: increased mortality was considered for patients in NSF, NAC and maintenance therapy health states compared to patients in SF.

Efficacy data from the STICLO RCTs and the single-armed DIAVEY study was used to inform the treatment effect. The RG believe that while these are the most appropriate sources available, an RCT of greater duration would have been preferable. The NCPE also note that both of these studies involve children only. According to expert clinical opinion, there may be a sizeable

proportion of adult patients with Dravet syndrome. Furthermore, the dose of clobazam used in the STICLO trials is lower than that which would normally be used in clinical practice.

Each treatment arm (stiripentol (with clobazam and valproate) or placebo (with clobazam and valproate)) was modelled separately based on what was observed at the end of the 2 month comparative period of the STICLO trials. Long term transitions were based on the DIAVEY study. Due to the lack of long-term evidence on the evolution of patients without stiripentol, the applicant assumed the same transition probabilities (TPs) after cycle one for the stiripentol and the comparator (placebo) arm. The RG had a number of concerns about the transition probabilities (TPs):

1. The applicant assumed that patients could not improve from Not Seizure Free or Not Adequately Controlled health states after the first cycle, although these transitions had been observed in the DIAVEY study.
2. The applicant initially assumed that all uncontrolled patients (patients having less than 50% reduction in seizure frequency) on stiripentol will discontinue their current treatment therapy after one cycle and will then switch to maintenance therapy, without being assessed again. However, expert clinical opinion indicated that a decision on lack of response would not be made at this early stage and the patient is likely to be on treatment longer than this before this decision is made. In addition, based on expert opinion, if a patient experienced a reduction in seizure frequency of as little as >25% they are likely to be continued on stiripentol. The cost-effectiveness study by Elliot *et al*. (2018) also assumes that patients who are not adequately controlled would stay on stiripentol for multiple cycles.

Both costs and QALYs were discounted at a rate of 5% in line with national guidelines.

Results

The applicant conducted an incremental analysis of the cost and benefits of stiripentol versus no stiripentol. In the original applicant base case, accounting for discrepancies corrected by RG, the ICER was €12,089/QALY (Incremental Costs: €2,569, Incremental QALYs: 0.213).

Given the concerns identified during the model appraisal process, the review group made a number of adjustments to the economic model in order to form the NCPE preferred base case:

1. A starting age of 9 was assumed rather than 3.
2. Changes were made to the definition of the NSF state in the Markov model such that patients would remain on stiripentol if they had a 20% reduction in seizure frequency rather than 50% reduction.
3. Changes were made to the transition probabilities such that it was possible for a patient to improve from NAC, which is in line with the Canadian cost-effectiveness model by Elliott *et al*. and the transitions observed in the long-term follow-up DIAVEY study.
4. The RG accounted for wastage in the model, as a sachet had to be used immediately once opened.

Under the NCPE preferred base-case, the review group estimated the deterministic ICER of stiripentol versus no stiripentol as €63,915/QALY (Incremental Costs, €10,933; Incremental QALYS, 0.171).

Analysis of uncertainty

The RG performed a number of scenario analyses on the NCPE preferred base case, which included the following:

1. In the base case, costs and utilities had not been updated to reflect the extended NSF state, given the uncertainty involved in the model. A scenario analysis was performed to update costs and utilities in the extended NSF state. When these are updated the ICER is €101,657/QALY.
2. In addition the RG found that the ICER was particularly sensitive to the starting age of the patient. A patient starting at age 3 (youngest age for the licence) implied an ICER of €15,138/QALY, while a patient starting at age 15 implied an ICER of €130,289/QALY.

Using the NCPE preferred base case, at a willingness-to-pay threshold of €20,000/QALY, the probability of being cost-effective is 22.8%, while at a willingness-to-pay threshold of €45,000/QALY, the probability of being cost-effective is 38.0%.

4. Budget impact of stiripentol

Stiripentol (Diacomit®) is formulated as hard capsules and as sachets containing powder for oral suspension. Both formulations are available in two strengths: 250mg and 500mg. Both formulations are priced equivalently for the same strength. The total acquisition cost (price to wholesale plus mark-up and mandatory rebate), to the HSE, per pack (pack size=60

capsules/sachets) of stiripentol 250mg hard capsules or sachets is €184.50. For the 500mg hard capsules or sachets, the total acquisition cost (price to wholesale plus mark-up and mandatory rebate), to the HSE is €369.00 per pack (pack size = 60 capsules/sachets). As it is proposed that stiripentol will be reimbursed under the High Tech Drug Arrangements, dispensing of Diacomit® would be subject to an additional dispensing fee of €62.03 per patient per calendar month. As stiripentol is dosed according to patient weight, the monthly and annual cost would vary between patients. Cost of stiripentol, to the HSE per patient, could range from €246.53 to €1169.03 per month and from €3001.50 to €14,232.94 per annum.

For the purpose of the budget impact analysis, the annual acquisition cost of stiripentol per patient was derived from the cost-effectiveness model. Mortality and discontinuation rates were accounted for. The model assumed the patient weight of a 9-year old corresponding to the average age of patients included in the STICLO trials. Uptake was assumed to start at 60% in year 1, increasing by 10% every year for five years. Uptake would be 100% by year 5. It was also assumed that patients were 100% compliant. Based on these assumptions, it is estimated that the total cost to the HSE would be €184,884 in Year 1 increasing to €321,835 by Year 5. The cumulative 5-year gross budget impact is estimated to be €1,266,798. It is not anticipated that stiripentol will result in cost off-sets due to displacement of other medicines. The net budget impact is therefore considered to be the same as the gross budget impact.

5. State if any patient submissions were received, and name submitting organisations.

No patient organisation submissions were received during the course of this assessment.

6. Conclusion

Following assessment of the applicant's submission, the NCPE recommends that stiripentol (Diacomit®), prescribed in combination with clobazam and valproate, be considered for reimbursement if cost-effectiveness can be improved relative to existing treatments. This recommendation should be considered while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.