5.06 STIRIPENTOL, Capsule, 250 mg and 500 mg, and Powder for oral suspension, 250 mg and 500 mg, Diacomit®, Emerge Health Pty Ltd.

1 Purpose of submission

1.1 The submission requested the Authority Required (Streamlined) listing of stiripentol (STP) as adjuvant therapy for severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) with primary generalised clonic and tonic-clonic (GCTC) seizures in patients not adequately controlled by valproate (VAL) and a benzodiazepine (usually clobazam, CLB).

1.2 Listing was requested on the basis of cost-effectiveness of STP plus VAL/CLB compared to placebo plus VAL/CLB. The submission however nominated standard care as the main comparator, noting that SMEI may be treated with other anti-epileptic drugs (AEDs) following inadequate response to VAL and a benzodiazepine.

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) with primary generalised clonic and tonic-clonic seizures in patients not adequately controlled by valproate (VAL) and a benzodiazepine (usually clobazam).
Intervention	Stiripentol 50mg/kg/day as adjunctive treatment with other antiepileptic treatments. Patients in the clinical evidence received stiripentol as adjunctive treatment to sodium valproate 30mg/kg/day (or less) and clobazam 0.5mg/kg/day (max. 20mg/day).
Comparator	Standard care, including other treatments and anti-epileptic drugs as adjuvant therapy, which the submission assumed as placebo (plus valproate and clobazam) for the clinical and economic comparisons. Patients in the clinical evidence received placebo plus sodium valproate 30mg/kg/day (or less) and clobazam 0.5mg/kg/day (max. 20mg/day).
Outcomes	Proportion of "responder" patients identified as >50% reduction in frequency of generalised clonic or tonic-clonic seizures during month 2 of the comparison period.
Clinical claim	In patients with SMEI whose seizures are not adequately controlled by valproate and clobazam, stiripentol added as adjunctive treatment to valproate and clobazam is superior in terms of effectiveness at producing treatment response, and inferior in terms of safety compared with placebo (plus valproate and clobazam).

Source: Table 9, pp2-3 of the submission.

2 Background

Registration status

2.1 STP was approved by the TGA on 13 September 2019 for the following indication: "adjunctive treatment of generalized tonic-clonic and clonic seizures associated with severe myoclonic epilepsy in infancy (SMEI, also known as Dravet syndrome) in

patients whose seizures are not adequately controlled with a benzodiazepine (usually clobazam) and valproate". CLB is currently not listed on the PBS.

2.2 Prior to TGA approval, Australian patients had access to STP through the Special Access Scheme, and it was also commonly funded by public hospitals.

For more detail on PBAC's view, see section 7 PBAC outcome.

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty (packs)	Max. Qty (units)	№. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
STIRIPENTOL, capsule, 250mg, 60	2	120	5	$[redacted]	
STIRIPENTOL, capsule, 500mg, 60	4	240	5	$[redacted]^	
STIRIPENTOL, powder for oral suspension sachet, 250mg, 60	2	120	5	$[redacted]	Diacomit®, Emerge Health Australia Pty Ltd
STIRIPENTOL, powder for oral suspension sachet, 500mg, 60	4	240	5	$[redacted]^	

Category/Program:	GENERAL – General Schedule (Code GE)
PBS indication:	Severe myoclonic epilepsy in infancy (SMEI, Dravet syndrome)
Treatment phase:	Initial and continuing
Restriction:	☒Streamlined
Treatment criteria:	Must be treated by a neurologist OR Must be treated by a paediatrician or general practitioner
Clinical criteria:	Patient must have primary generalised tonic-clonic and clonic seizures AND Patient must have seizures that are not adequately controlled with benzodiazepine (usually clobazam) and valproate AND The treatment must be adjunctive treatment AND The treatment must be initiated by a neurologist
Population criteria:	Patient must be under the age of 18 when treatment is initiated

^ The Sponsor requested a DPMQ of $[redacted] for the 500mg formulations based on incorrect wholesale mark-up (7.52% rather than $69.94 fixed) for the relevant maximum quantity supplied (i.e. 4 packs, AEMP > $930.06 threshold). The DPMQ was revised during the evaluation based on the requested AEMP for the 500mg formulations ($[redacted] per 60 capsules or oral powder sachet) and the correct mark-up's; DPMQ for 240 capsules or sachets = $[redacted] (AEMP) + $69.94 (whole sale mark-up) + $74.79 (AHI mark-up) + $7.39 (preparation fee) = $[redacted].

Source: Table 15, pp21, 23-24 of the submission

3.1 The requested PBS restriction was generally consistent with the approved TGA indication; however, the following issues were identified:

- The criterion specifying that "The treatment must be adjunctive treatment" does not specify co-administered AEDs, and therefore may allow for use as adjunctive therapy to AEDs other than VAL and a benzodiazepine. Comments by the Advisory Committee on Medicines suggest that adjunctive treatment with VAL and a benzodiazepine was the intention of the TGA indication in line with the trial

evidence. However, a retrospective study of SMEI[1] in the US found 56/104 (53.8%) patients treated with STP were not taking concomitant VAL plus CLB. Common combinations included STP with topiramate (TOP), levetiracetam (LEV), VAL (but not with CLB), CLB (but not with VAL), or others.

- The criterion that "Patients must have seizures that are not adequately controlled with benzodiazepines (usually clobazam) and valproate" is consistent with the approved TGA indication, but not wholly consistent with current practice. Two of the four Australian neurologists surveyed for the submission recommended TOP in combination with STP as first- and second-line treatment when status epilepticus was present. Further, as clobazam is not PBS-listed, it would be inappropriate for the restriction for STP to reference this as a prior treatment.
- The criterion that "Patient must be under the age of 18 when treatment is initiated" was not justified by the submission and may be unnecessary given SMEI is diagnosed in childhood (usually the first year of life). The TGA indication does not include any age criterion but the Product Information (PI) cautions use in children under 3 years and in adults given lack of trial evidence. The criterion may also prevent re-initiation of treatment if a patient aged over 18 years discontinues treatment, which may not be clinically appropriate. The Pre-Sub-Committee Response (PSCR) noted that this restriction reflected the maximum age allowable for recruitment in the two pivotal trials, but acknowledged that it would leave some patients uncovered and that it would be ethical to extend the listing past 18 years of age.
- The requested restriction does not include a response criterion, which is consistent with TGA indication (as well as the treatment guidelines and PBS listings for other AEDs), but is inconsistent with an assumption in the modelled economic evaluation that patients with <50% reduction in seizures will cease treatment after two months. In contrast, the submission assumed there will be no discontinuation of STP irrespective of treatment response in the financial estimates given additional therapies are added onto existing treatments when efficacy of therapies wane.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

4.1 SMEI is a rare refractory form of epilepsy and one of the most severe types of genetic epilepsy. It is characterised by febrile or afebrile, prolonged GCTC seizures that usually commence within the first year of life. Frequent and refractory seizures can also have an adverse effect on cognitive development. Mental retardation and behavioural

[1] Wirrell EC, Laux L, Franz DN, Sullivan J, Saneto RP, Morse RP, Devinsky O, Chugani H, Hernandez A & Hamiwka L. Stiripentol in Dravet syndrome: results of a retrospective US study. 2013, Epilepsia, 54(9):1595-1604.

disorders usually present after the age of two, patients may also suffer from autism, communication impairment, cardiovascular abnormality, poor dental health, autonomic nervous system dysfunction, immune dysregulation and sleep disturbances. It is also associated with an increased risk of death due to status epilepticus and sudden unexpected death in epilepsy (SUDEP), although there is considerable variation in the risk of mortality reported in the literature (3.75% to 17.5% after 10 years).

4.2 Treatment of SMEI includes avoiding seizure triggers (i.e. fever), rescue medication (i.e. benzodiazepines) for acute seizure and ongoing seizure prophylaxis with various AEDs. Patients may become seizure free for a time before relapsing and requiring treatment adjustment including changes in dose or addition of other AEDs. A number of AEDs are contraindicated in SMEI due to worsening seizures, including carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine, and vigabatrin.

4.3 The proposed algorithm indicated STP would be added onto VAL/benzodiazepine (usually CLB) as third-line therapy, thus displacing to fourth-line other AEDs (currently third-line) in patients whose seizures are not adequately controlled by STP. The submission noted that aside from STP, none of the other commonly prescribed AEDs recommended in the guidelines are TGA indicated specifically for SMEI or supported by randomised control trials for SMEI. The ESC considered it is unclear how STP will be used in clinical practice, noting that the treatment of SMEI is highly individualised.

4.4 The majority of evidence to date for the use of AEDs in SMEI has been based on non-comparative studies. Randomised trials are currently ongoing for new therapies (including fenfluramine and cannabidiol) for use as adjuvant therapy in SMEI.

4.5 Treatment guidelines also indicated that choice of AEDs depends on the presentation of the disease, rather than any standard line of therapy. For example, STP was commonly recommended as second-line treatment after TOP, particularly if patients presented with status epilepticus. There was a general consensus among the Australian neurologists surveyed in the submission that STP is highly effective in controlling status epilepticus for patients with SMEI and should be considered early in the treatment regimen. Due to the clinical heterogeneity of SMEI, there is variation in the recommended AEDs after STP, but the most common were TOP, VAL or LEV depending on previous therapy.

4.6 The ESC noted that there is an unmet clinical need for additional treatment options (outside of Special Access and public hospitals) in a rare and refractory population of patients who have failed multiple AEDs and continue to experience seizures.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

5.1 The submission nominated standard care (consisting of other treatments including AEDs) as the main comparator, noting that identifying a single relevant comparator was not possible. According to treatment guidelines, patients who fail treatment with VAL plus CLB may receive a range of treatments including other AEDs (as adjuvant treatment to VAL and CLB), such as STP, TOP, LEV, medical cannabis, ethosuximide, ketogenic diet, vagus nerve stimulation, phenobarbital and zonisamide. Typically, as efficacy of therapies wane, additional treatments are added onto existing treatments.

5.2 The submission however, did not present any comparison between STP and standard care as adjuvant treatment for SMEI. Instead, the submission presented a clinical comparison and economic model of STP versus placebo as adjuvant therapy to VAL and CLB, and estimated the financial impact of the proposed listing assuming no change to other AEDs. The ESC considered that given the variable and individualised nature of standard care in SMEI and that the place of STP in practice was likely to vary for individual patients, the evidence presented compared to placebo may still be informative in demonstrating the incremental benefit of STP against a standardised trial comparator (placebo).

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

6.1 There was no hearing for this item.

Consumer comments

6.2 The PBAC noted that no consumer comments were received for this item.

Clinical trials

6.3 The submission was based on two direct randomised trials comparing STP as add-on to VAL plus CLB compared to placebo (VAL plus CLB alone) in patients with SMEI: STICLO-France (N=42), and STICLO-Italy (N=23). The placebo-controlled STICLO trials were conducted in the late 1990s, prior to marketing authorisation of other recommended AEDs including TOP and LEV.

6.4 Details of the trials presented in the submission are provided in Table 2 below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Direct randomised trials (stiripentol vs placebo)		
STICLO France	A comparative study on the efficacy of stiripentol as add-on therapy in severe myoclonic epilepsy in infancy (SMEI): A multicenter, double blind, placebo-controlled, phase III study Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group.	Biocodex clinical study report 25 January 2000 Lancet. 2000 Nov 11;356(9242):1638-42
STICLO Italy	Comparative study of the efficacy of stiripentol used in combination in severe myoclonic epilepsy in infancy (SMEI). A double-blind, multicenter, placebo-controlled phase III study. Guerrini R, Tonnelier S, d'Athis P, Rey E, Vincent J, Pon G, Dalla Bemardina B, Ferrari AR, Veggiotti P, Veneselli E, Pascottol E, Vigevano F. Stiripentol in severe myoclonic epilepsy in infancy (SMEI): a placebo-controlled Italian trial.	Biocodex clinical study report September 2004 Epilepsia 2002; 43(8):155

Source: Table 20, pp33-35 of the submission

6.5 The key features of the direct randomised trials are summarised in Table 3 below. Both STICLO-France and STICLO-Italy were small, phase 3, double-blind, randomised, placebo-controlled superiority trials, of short duration (maximum follow-up of 2 months), which shared the same design. The ESC noted the age of the trials and other limitations around trial design and duration, which may limit the relevance of the results to current clinical practice.

Table 3: Key features of the included trials

Trial	N	Design / duration	Bias	Population	Outcomes
Stiripentol vs placebo					
STICLO-France	42	R, DB, PC / 2mths (+1mth BL)	Low	SMEI; age 3-18; ≥4 seizures/mth; AEDs: VAL+CLB	1°: number of responders^ 2°: change in seizure frequency#
STICLO-Italy	23				

Abbreviations: AED=anti-epileptic drug; BL=baseline phase; CLB=clobazam; DB=double blind; PC=placebo controlled; R=randomised; SMEI=severe myoclonic epilepsy in infancy; VAL=valproate; mth=month

^ success for a responder is defined as having experienced at least 50% reduction of clonic (or tonic-clonic) seizure frequency during the second month of the double-blind period compared to baseline.

(decrease in seizures: 100%, ≥50% to <100%, >0% to <50%; increase in seizures: >0% to <50%, ≥50%)

Source: compiled from STICLO-France and STICLO-Italy trial reports during the submission

6.6 Although most aspects of the trial design had a low risk of bias, the treatment effect estimated in the STICLO trials potentially favoured STP because the trial design limited daily doses of concomitant CLB below the currently recommended maximum dose but STP has a potentiating effect on plasma drug levels of CLB. As a result, some patients in the control arm may have received sub-therapeutic CLB whereas patients on STP were likely pushed into therapeutic levels.

6.7 Specifically, heavier patients in the trial may have been receiving sub-therapeutic CLB. That is, at the maximum capped dose of 20mg/day, patients weighing more than 40kg may have received less than 0.5mg/kg/day[2] of CLB. This is a potential issue given STP is known to increase the plasma levels of CLB (via inhibition of cytochrome P450

[2] Recommended dose is 0.3 to 1.0 mg/kg body weight daily.

enzymes) so patients receiving sub-therapeutic CLB in the STP arm may have been pushed into therapeutic levels, favouring the STP arm. The steady-state plasma levels of CLB and/or its active metabolite norCLB increased significantly from baseline in the STP arms in the trials, shown in Table 4, potentially overestimating the effect of STP.

Table 4: Median mg/L (range) steady-state plasma concentrations of VAL, CLB and norCLB at baseline and the comparison phase in STICLO-France and STICLO-Italy

		STICLO-France					STICLO-Italy				
		n	STP	n	Placebo	P^	n	STP	n	Placebo	P^
VAL	Baseline	21	66.7 (26.3-107)	18	66 (31-128)	NS	11	85.1 (41.4-128)	11	69.6 (58.7-98.4)	NS
	Month 2	20	66.5 (32.6-118)	17	58.7 (14-115)	NS	11	87.7 (57.1-149)	9	78.1 (48.4-116)	NS
CLB	Baseline	21	0.179 (0.13-0.29)	19	0.17 (0.081-0.326)	NS	11	0.177 (0.063-0.379)	11	0.189 (0.066-0.578)	NS
	Month 2	20	0.244 (0.106-0.606)	17	0.198 (0.105-0.318)	<0.01	11	0.225 (0.111-0.554)	9	0.201 (0.09-0.356)	NS
norCLB	Baseline	21	0.74 (0.33-6.72)	19	0.81 (0.24-3.1)	NS	11	0.625 (0.309-1.51)	11	0.45 (0.221-1.91)	NS
	Month 2	20	4.14 (2.68-7.06)	17	0.8 (0.224-3.42)	<0.001	11	4.01 (1.51-7.8)	9	0.49 (0.245-1.67)	<0.002

Abbreviations: NS=not significant; CLB=clobazam; norCLB=norclobazam; STP=stiripentol; VAL=valproate

^ p-value refers to the significance of the difference between groups in the median plasma concentrations of anti-epileptic drugs (magnitude of difference not presented in the trial reports).

Source: Compiled during the evaluation from Tables 10 and 16 of STICLO-France and Tables 7 and 12 of STICLO Italy trial reports.

Comparative effectiveness

6.8 Table 5 summarises the trial results and meta-analysis for the proportion of "responder" patients (the primary efficacy outcome) and the proportion of patients with ≥50% reduction in seizures from baseline during Month 2 of the comparison period in the STICLO trials. The key component of the composite "responder" outcome was the ≥50% reduction in GCTC seizures, which was also a separate secondary outcome. Only GCTC seizures were included for the efficacy outcomes in the STICLO trials despite several seizure types at baseline (e.g., myoclonic seizures, atypical absences, focal seizures). The ESC considered it would be reasonable to assume that these SMEI patients have many other seizure types (in addition to clonic or tonic-clonic) which would be relevant to clinical outcomes and quality of life, the results of which were not reported.

Table 5: Results of the percentage of "responders" (primary outcome) and the proportion of patients with a decrease in seizures by ≥50% from baseline during Month 2 in the STICLO trials

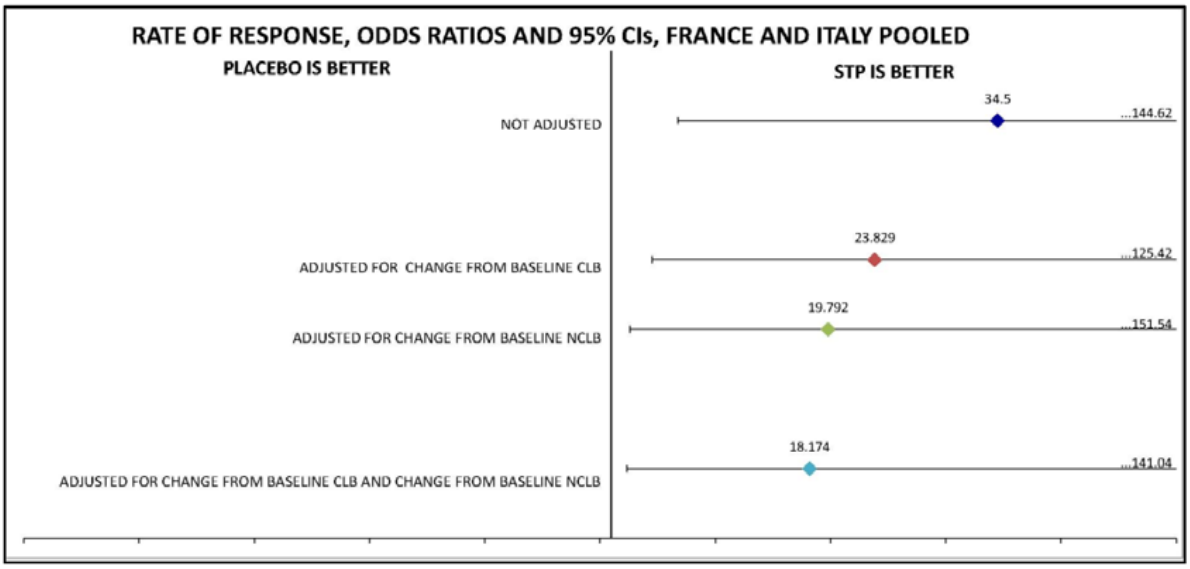
Trial ID	STP n/N (%)	Placebo n/N (%)	OR (95% CI)	RR (95% CI)	RD (95% CI)
Proportion of responders, ITT (primary outcome)					
STICLO-France	15/22 (68.2)	1/20 (5.0)	**40.71 (4.50-368.16)**	**13.64 (1.98-94.09)**	**0.63 (0.42-0.85)**
STICLO-Italy	8/12 (66.7)	1/11 (9.1)	**20.00 (1.85-216.18)**	**7.33 (1.08-49.58)**	**0.58 (0.26-0.89)**
Meta-analysis	23/34 (67.4)	2/31 (6.5)	**29.3 (5.83-147.70)**	**10.5 (2.7-40.8)**	**0.61 (0.43-0.79)**
Decrease seizures frequency ≥ 50%, ITT (secondary outcome)					
STICLO-France	15/22 (68.2)	1/20 (5.0)	**40.71 (4.50-368.16)**	**13.64 (1.98-94.09)**	**0.63 (0.42-0.85)**
STICLO-Italy	8/12 (66.7)	1/11 (9.1)	**20.00 (1.85-216.18)**	**7.33 (1.08-49.58)**	**0.58 (0.26-0.89)**
Meta-analysis	23/34 (67.4)	2/31 (6.5)	**29.3 (5.83-147.70)**	**10.5 (2.7-40.8)**	**0.61 (0.43-0.79)**

Abbreviations: CI=confidence interval; n=number of participants with event; N=total participants in group; OR=odds ratio; RR=relative risk; RD=risk difference; STP=stiripentol;
Bold text: statistical significance p<0.05
^ Percentage of "responder" defined as: ≥50% decrease in GCTC seizures (on a 30-day basis) at Month 2 vs baseline; Not dropped out due to status epilepticus; Seizures had not increased by ≥50% within 20 days compared to baseline and not having seizure increased by ≥50% at baseline compared to pre-inclusion and not returning to pre-inclusion level at month 1;
Source: Table 28, p51 and Table 32, p59 of the submission

6.9 The trial results demonstrated a significantly higher number of responders with STP compared with placebo as adjuvant treatment to VAL and CLB, with pooled response rates of 67.4% for STP and 6.5% for placebo. The proportion of patients who achieved ≥50% reduction in GCTC seizures during Month 2 of the comparison period compared with baseline (secondary outcome) was identical to the proportion who achieved response (primary outcome). As discussed above, the capped dose of CLB in the STICLO trials below the maximum recommended dose may have resulted in some patients receiving sub-therapeutic treatment in the control arm but not in the treatment arm.

6.10 Figure 1 summarises a post-hoc analysis of the primary outcome adjusted by the change in baseline plasma concentrations of CLB and norCLB across the arms. After the adjustment, the odds ratio (OR) decreased from 34.5 (p<0.01) to 18.2 (p<0.01). The analysis did not account for the changes in VAL levels, presumably because the change from baseline was less prominent. The small discrepancy between the unadjusted ORs presented in Table 5 and Figure 1 was likely due to slightly different populations (intention-to-treat vs per protocol) and the statistical method of analysis.

Figure 1: Comparison of "responders" in the STICLO trials (pooled), unadjusted and adjusted for CLB and/or norCLB plasma concentrations



Abbreviations: STP=stiripentol
Source: Figure 6, p62 of the submission and Figure 12, p78 of the DIACOMIT - TGA Clinical Evaluation Report Round 1

6.11 The submission argued that the post-hoc analysis demonstrated any potential bias associated with the dosing of CLB and norCLB in the STICLO trials was small. Whilst the adjusted analysis in Figure 1 would indicate that STP is still superior to placebo, the submission did not quantify the impact of this adjustment on the absolute treatment effect. A similar change in the OR occurs by assuming that an additional 1 to 2 patients in the placebo arm of the pooled results will also achieve response, corresponding to roughly 3 to 6 fewer patients achieving a response on STP for every 100 patients treated.

6.12 The unadjusted distribution of the reduction in GCTC seizures from the STICLO trials (100%, 50-99% and less than 50% reductions) was used in the modelled economic evaluation. Results were not reported for other relevant outcomes in SMEI, including status epilepticus, mortality (i.e. SUDEP), impact on cognitive impairment, quality of life, impact on all seizures (not only GCTC seizures). A lower response threshold such as a 25% reduction in seizure frequency may also be relevant considering the refractory and severe nature of the condition.

6.13 In addition to the STICLO trials, the submission also referenced a large number of non-comparative studies. The studies were of STP (20 studies), TOP (seven studies) and LEV (three studies) as adjuvant therapy with other AEDs for SMEI. The submission did not rely on efficacy data from any of these studies for the clinical claim, and only presented a brief summary of results.

6.14 The non-comparative studies found 22% to 80% of patients treated with STP (reported by five studies), 20% to 78% of patients treated with TOP (seven studies) and 11% to 64% of patients treated with LEV (three studies) had >50% reduction in seizure frequency from baseline at different durations of follow-up. The differences across

study findings could be attributed to numerous differences in study design, population, AED doses and follow-up. The results from the non-comparative studies were consistent with the treatment arm in the STICLO trials, which demonstrated 72% to 75% of patients had >50% reduction in seizure frequency from baseline at two months (see Comparative effectiveness).

6.15 The submission did not present any formal comparison between STP and the nominated appropriate comparator of "standard care" (other AEDs and treatments), including TOP and LEV. A naïve comparison across a large number of non-comparative studies indicated a similar proportion of patients achieved a >50% reduction in seizure frequency from baseline with STP, TOP and LEV when used as adjuvant treatment for SMEI.

Comparative harms

6.16 Significantly more patients in the STP arm experienced at least one adverse event (AE) compared with placebo (see Table 6). The most common AEs included drowsiness/sleepiness, appetite loss and weight loss. One patient on STP in STICLO-France withdrew due to status epilepticus, though this likely relates to lack of efficacy rather than a treatment related AE. Evidence for an assessment of comparative harms between STP versus "standard care" (other AEDs and treatments) was not presented in the submission.

6.17 The ESC noted that, as per trial protocol, patients received dose reductions if they experienced AEs such as sleepiness and anorexia during the first month of treatment. The ESC considered that this made interpreting adverse events data difficult as it was unclear whether an adverse event was related to the use of STP or CLB (due to the increased plasma level effect of STP on CLB).

Benefits/harms

6.18 A summary of the comparative benefits and harms for STP (plus VAL and CLB) versus placebo (plus VAL and CLB), adjusted for the meta-analysis, is presented in Table 6 below.

Table 6: Summary of comparative benefits and harms for STP (plus VAL and CLB) and placebo (plus VAL and CLB)

Trial	STP	Placebo	RR (95% CI)	Events/100 patients*		RD (95% CI)
				STP	Placebo	
Benefits						
Percentage of Responders^						
STICLO-France	15/22	1/20	13.64 (1.98, 94.09)	68.2	5.0	0.63 (0.42, 0.85)
STICLO-Italy	8/12	1/11	7.33 (1.08, 49.58)	66.7	9.1	0.58 (0.26, 0.89)
Meta-analysis	23/34	2/31	10.5 (2.7, 40.8)	67.4	6.5	0.61 (0.43, 0.79)
Harms						
Any AE						
STICLO-France	21/21	9/20	2.22 (1.37, 3.61)	100	45	0.55 (0.33, 0.77)
STICLO-Italy	10/12	3/11	3.05 (1.13, 8.29)	83	27	0.56 (0.22, 0.90)
Meta-analysis	31/33	12/31	2.43 (1.55, 3.81)	94	39	0.55 (0.36, 0.74)
Drowsiness or sleepiness						
STICLO-France	15/21	2/20	7.14 (1.87, 27.34)	71.4	10	0.61 (0.38, 0.85)
STICLO-Italy	7/12	1/11	6.42 (0.93, 44.16)	58.3	9.1	0.49 (0.17, 0.82)
Meta-analysis	22/33	3/31	6.89 (2.29, 20.74)	66.7	9.7	0.57 (0.38, 0.76)
Appetite loss						
STICLO-France	7/21	1/20	6.67 (0.90, 49.45)	33.3	5	0.28 (0.06, 0.51)
STICLO-Italy	6/12	1/11	5.50 (0.78, 38.76)	50	9.1	0.41 (0.08, 0.74)
Meta-analysis	13/33	2/31	6.11 (1.50, 24.90)	39.4	6.5	0.33 (0.14, 0.52)
Weight loss						
STICLO-France	6/21	0/20	12.41(0.74, 206.86)	28.6	0	0.28 (0.09, 0.48)
STICLO-Italy	2/12	0/11	4.62 (0.25, 86.72)	16.7	0	0.17 (-0.04, 0.38)
Meta-analysis	8/33	0/31	7.73 (1.01, 58.85)	23.7	0	0.24 (0.10, 0.39)

Abbreviations: RD = risk difference; RR = risk ratio; STP=stiripentol

* Maximum duration of follow-up: STICLO-France/STICLO-Italy= 2 months. Only GCTC seizures were included for the efficacy outcomes in the STICLO trials despite several seizure types at baseline (e.g., myoclonic seizures, atypical absences, focal seizures) (paragraph 5.6).

^ Percentage of "responder" defined as: ≥50% decrease in GCTC seizures (on a 30-day basis) at 2 months vs baseline; Not dropped out due to status epilepticus; Seizures had not increased by ≥50% within 20 days compared to baseline and not having seizure increased by ≥50% at baseline compared to pre-inclusion and not returning to pre-inclusion level at Month 1.

estimated during the evaluation using STATA 14 and RevMan version 5.

Source: Compiled during the evaluation

6.19 The submission did not provide evidence to enable the comparison of benefits and harms for STP to other AEDs and treatments as adjuvant treatment.

6.20 On the basis of direct evidence presented by the submission, for every 100 patients treated with STP (plus VAL and CLB) in comparison to placebo (plus VAL and CLB, noting this is not likely to be the comparator or therapy that will be replaced in practice) and followed up for a maximum duration of two months:

- Approximately 61 additional patients would be classified as a responder or achieve a ≥50% reduction in seizure frequency, however the additional number in practice may be slightly lower because patients in the placebo arm may have received sub-therapeutic doses of AEDs;
- Approximately 57 more patients would experience drowsiness or sleepiness;
- Approximately 33 more patients would experience appetite loss;
- Approximately 24 more patients would experience weight loss.

Clinical claim

6.21 The submission described STP (as adjunctive treatment to VAL plus CLB) as superior in terms of efficacy but inferior in terms of safety compared to placebo (plus VAL and CLB), based on results in the STICLO trials. Despite its concerns over STP's clinical place in therapy and the appropriate comparator for the submission, the ESC considered that the clinical claim versus placebo was reasonably supported by the clinical evidence presented in the submission, noting the following caveats:

- Both trials were small and of short duration. The reduction in seizure frequency is a clinically relevant end point but its relationship with longer-term outcomes such as developmental delay, cognitive impairment, and behavioural disorders has not been clearly established. Any potential reduction in status epilepticus (and corresponding survival benefit) was not assessed.
- CLB was limited to a maximum of 20mg/day in the trial (0.5mg/kg/day), which is at the lower end of the maintenance dosing range of 0.3-1mg/kg/day as recommended in the TGA approved PI. The limit on CLB dosage could have led to heavier patients receiving sub-therapeutic levels of CLB. The potentiating effect of STP with CLB was found to have elevated the CLB/norCLB towards therapeutic levels in the STP group only, favouring STP (plus VAL and CLB) over placebo (plus VAL and CLB). Thus at least some of the reduction in seizure frequency observed during STP treatment could be attributed to the increase in the concentration of CLB/norCLB. The submission did not present any data or estimates with respect to this issue.
- With respect to safety, significantly more patients treated with STP (plus VAL and CLB) experienced AEs compared to placebo (plus VAL and CLB). AEs can be severe leading to withdrawals however appeared to be reversible upon dose adjustments of concomitant AEDs. The ESC considered that further evidence is required on the relationship between AEs, doses of AEDs and potential risk factors (age, weight, type of add-on AEDs, and co-morbidities).

6.22 The ESC noted that the submission did not present evidence or make any clinical claim for STP compared to standard care informed by other AEDs and treatments. Based on the best available evidence from non-comparative studies, the proportion of patients with >50% reduction in seizure frequency from baseline appeared to be generally comparable for STP, TOP and LEV, as adjuvant therapy for SMEI. Results were not reported for other relevant outcomes, such as status epilepticus.

Economic analysis

6.23 The submission presented a stepped economic evaluation based on the direct randomised trials (STICLO-France and STICLO-Italy). The type of economic evaluation was a cost-utility analysis to estimate the incremental costs and benefits of STP (plus VAL and CLB), versus placebo (plus VAL and CLB). Given the proposed listing of STP may replace or displace other AEDs for SMEI including TOP and LEV, the ESC

considered that the submission's modelled economic evaluation does not capture the most likely costs and consequences in practice. The PSCR argued that STP will not replace or displace other AEDs in practice as they are not specifically indicated for SMEI. However, the ESC noted that a specific indication for SMEI is not necessary for other PBS listed AEDs to be used in this indication.

6.24 Table 7 summarises the key component of the economic evaluation.

Table 7: Summary of model structure and rationale

Component	Summary
Time horizon	5 years in the model versus 2 months in the trials. The ESC noted a potential translation issue regarding the extrapolated duration of response, and considered the results to be highly uncertain in favour of STP as the model assumed the treatment effect to continue at the same rate over 5 years based on only 2 months of trial data.
Outcomes	Quality-adjusted life years
Methods used to generate results	Markov cohort model using cohort expected value analysis.
Health states	i) Seizure free: 100% reduction (SF) ii) Not seizure free: ≥50% to <100% reduction (NSF) iii) Not adequately controlled: <50% reduction (NAC) iv) Death: absorbing state The health states may not adequately reflect all of the clinically relevant outcomes for patients with SMEI, including status epilepticus or smaller seizure response thresholds. A sensitivity analysis was presented which assumed: i) patients in both arms who were not in the seizure free health state experienced the same rate of status epilepticus; ii) status epilepticus was associated with increased hospitalisation costs; and iii) status epilepticus did not affect survival or quality of life. While these assumptions were conservative, the value of this sensitivity analysis was low. Patients commenced in the model (cycle 0) in one of four health states and then remained in these states for the duration of the model. It was noted that 6.5% of patients commenced the model as "Dead" due to an adjustment to account for "mortality by age 4". At the end of each cycle, patients either i) remained in their current health state or ii) transitioned to dead; no other transitions were permitted, which the ESC considered to be potentially problematic given that current clinical practice indicates that patients cycle around different treatments over time, indicating fluctuations in health state. The ESC also questioned whether health states based on percentage reduction from baseline frequency, as opposed to absolute number of seizures, is clinically meaningful over the 5 year time horizon.
Utilities	Health state utilities were based on Verdian et al 2008 (available as abstract only), which elicited preferences from the general public (N=119) for health states associated with Lennox-Gastaut-Syndrome. The assumed utility values were: SF (0.648), NSF (0.553), NAC (0.244), dead (0). Verdian et al 2008 reported utility scores for four seizure health states using the TTO and EQ-5D. The submission applied the average of both the TTO and EQ-5D scores in the model, and assumed that HS-1 ("21-28 seizures / week") and HS-2 ("<50% decrease") in Verdian et al 2008 informed quality of life in the NAC health state of the model. The submission's approach was poorly justified and averaging across the TTO and EQ-5D was not reasonable. The ESC considered that the TTO results were preferable to the EQ-5D, given they were more consistent with published utilities for SMEI patients, as well as other published utilities for epilepsy by absolute seizure frequencies. The ESC also considered that the absolute number of seizures and seizures avoided would be a more accurate measure upon which to consider quality of life outcomes than the percentage change.
Cycle length	1 year. The cycle length is only reasonable if the assumed perfect maintenance of response is accepted. A half cycle correction was applied to adjust for mortality every 6 months.

Component	Summary
Transition probabilities	Seizure reduction categories (100%, 50-99% and <50% reductions) reported in STICLO-France and STICLO-Italy. The proportion of patients who commenced in each health state was based on 2-month trial data; patients who achieved <50% reduction in seizures in the trials were assumed to discontinue treatment after two months; there were no transitions assumed thereafter aside from annual mortality. This may not be appropriate because the model does not capture any changes in seizure response over time, such as waning to treatment or patient discontinuations due to adverse events. The ESC considered that a reduction in seizure frequency of approximately 25-30% (less than the required 50% in the model) would be significant and thus potentially improve quality of life.
Costs	Drug costs were calculated using Australian unit costs multiplied by the average weight and dosage of patients in STICLO-France and Italy, by arm. The ESC noted that the model was sensitive to the assumed weight of the patients given the cost of STP accounts for most of the incremental difference between arms; an increase in the patient weight of 25% in both arms of the model (to 39.8kg and 37.5kg respectively) increased the ICER by [redacted]% (to $15,000 - $45,000/QALY). No data was provided to inform the likely weight of the proposed PBS population. No allowance was made in the model to account for the likely increase in weight of the cohort over time which favours STP. The ESC considered that increasing weight with age should be incorporated into the model. The ESC also considered that there may be additional costs associated with increased levels of monitoring associated with STP use compared to other treatment options which had not been accounted for.

Abbreviations: SMEI=severe myoclonic epilepsy in infancy; STP=stiripentol;
Source: Table 39, p69 of the submission

6.25 The ESC considered that the economic model was not informative for PBAC decision making given the following issues:

- placebo (plus VAL and CLB) as the main comparator is not reflective of standard care;
- the unadjusted trial results potentially favour STP (plus VAL and CLB);
- the structure of the model does not take into account all of the clinically relevant outcomes for STP in SMEI, including status epilepticus and other disease sequelae;
- the assumption that patients will cease STP if response rate is <50% after two months was not adequately supported given additional therapies can be added onto existing therapies; current practice does not support ceasing; and the proposed restriction did not include response criteria. The PSCR accepted that the NAC state should ideally be split into two categories, 0 to <25% and 25 to <50%, as it was probable that patients achieving at least a 25% reduction in seizure frequency would continue on STP. However, the PSCR added that as there were so few patients in each category of seizure reduction the results would not be able to be extrapolated;
- the lack of transitions (aside from mortality) in the model does not capture potential changes in seizure response over time associated with waning or subsequent discontinuations; an assumption that patients will maintain the same level of seizure response for the duration of the model was not adequately supported;
- the cost of STP was likely underestimated given the model does not account for the expected weight changes of the cohort over time, which potentially favours

STP. The PSCR argued that as weight based dosing levels lower with age, there is minimal effect on the ICER with increasing weight of patients over time; and

- the nominated utilities (weighted TTO/EQ-5D results) were not adequately supported and potentially favours STP given the utilities for HS-1 and HS-2 from the EQ-5D are much lower than the corresponding TTO estimates. The PSCR stated that using only one method would bias results either for or against STP. However, the ESC were concerned about the large differences in utility scores elicited using the TTO and EQ-5D particularly for the worse health states (see Table 8).

Table 8: Published utility scores

Health state	Description	TTO	EQ-5D	Model state
HS-1	Uncontrolled seizures with a frequency of 21-28 per week	0.393	0.020	Not adequately controlled = 0.244
HS-2	Reduction in seizure frequency of <50%	0.461	0.100	
HS-3	Reduction in seizure frequency of between 50% and 75%	0.605	0.500	Not seizure free = 0.553
HS-4	Reduction in seizure frequency of over 75%	0.699	0.596	Seizure free = 0.648

Source: Table 45, p78 of the resubmission

6.26 The ESC noted that other utility studies identified during the evaluation which reported utilities by seizure frequencies, albeit in adult populations, are summarised in Table 9 below. Based on absolute seizure frequencies, the TTO estimates from Verdian et al 2008 were generally closer to the estimates of refractory epilepsy of adults in the literature. However, the ESC still expressed concerns over the age of the data, and the fact that it does not take into account current standard care.

Table 9: Summary of utilities in the literature for refractory epilepsy in adults, by seizure frequency

Study	Instrument	Population	Estimates
Messori et al 1998	TTO	Patients with refractory epilepsy in Italy (N=81)	• Presence of AEs (N=9): 0.40 • ≥10 seizures per month (N=12): 0.66 • 2-9 seizures per month (N=30): 0.79 • ≤1 seizure per month (N=15): 0.91 • Seizure freedom (N=15): 0.96
Selei et al 2002	EQ-5D	Patients with refractory epilepsy in the UK (N=125)	• Baseline >10 seizures per month (N=NR): 0.798 • Baseline 2-9 seizures per month (N=NR): 0.902 • Baseline ≤1 seizure per month, (N=NR): 0.934 • No response: 0.824 • Seizure free (N=NR): 0.923
Langfitt et al 2006	EQ-5D (UK/US), HUI-2, HUI-3, SF-6D	Patients with refractory epilepsy ≥1 seizure per month on 2 or more AEDs in the US (N=64)	• Baseline: range 0.610 to 0.816 • Seizure free (N=33): +0.01 to 0.12 • SF-6D: baseline=0.702, seizure free=+0.07

Source: Table 3.5.2, March 2020 Commentary

Abbreviations: AED=anti-epileptic drug; AE=adverse event; NR=not reports; TTO=time trade off;

Source: constructed during the evaluation; Messori et al 1998, Adjuvant lamotrigine therapy in patients with refractory seizures: a lifetime cost-utility analysis, Eur J Clin Pharmacol 53:421-427; Selei et al 2002, Evaluation of the relationship between epilepsy severity and utility, Value in health 5(6):512-513; Langfitt et al 2006, Validity and Responsiveness of Generic Preference-based HRQOL Instruments in Chronic Epilepsy, Quality of Life Research 15(5):899-914

6.27 Table 10 summarises the key drivers of the model.

Table 10: Key drivers of the model

Description	Method/Value	Impact Base case: $15,000/QALY - $45,000 / QALY
Discontinuation rate	The model assumed that patients classified as NAC will discontinue STP after 2 months. The ESC considered that patients with a greater than 25% reduction in seizure frequency would likely continue on treatment.	High, favours STP. (The ICER increased by 47.3% to $45,000/QALY-$75,000/ QALY assuming all patients continue STP).
Utilities	The model used the average of TTO and EQ-5D scores in Verdian et al 2008 across 4 health states to inform quality of life across 3 health states in the model. The health state descriptions in the publication and the model do not match perfectly, and it is not valid to average across different elicitation methods.	High, favours STP. (The ICER increased by 56.7% to $45,000/QALY-$75,000 / QALY assuming TTO scores in Verdian et al 2008).
Response rate	The main difference in incremental QALYs comes from the greater proportion of patients in the NSF and SF health states in the STP arm. The trial results used in the model were not adjusted for differences in CLB levels (which were lower in the placebo arm), potentially favouring STP.	Low to moderate, favours STP. (The ICER increased by 10.6% to $15,000/QALY-$45,000/ QALY assuming 2 fewer patients in NAC (27/31) and 2 additional patients in SF (4/31) in placebo arm of the trials.
Patient weight (associated with the cost of STP)	Patients' body weight for the likely PBS population were not provided to justify dosages of STP assumed for the modelled population. The cost of STP is also likely underestimated given the model does not account for the expected weight changes of the cohort over the five years.	Low to moderate, favours STP. (The ICER increased by 12.1% to $15,000/QALY-$45,000/ QALY assuming average cohort weight increased by 2kg per year). The PSCR cited a recent article (Chiron et al, 2018) in support of the argument that total dose may not increase with age and associated weight gain.

Abbreviations: ICER=incremental cost-effectiveness ratio; NAC=not adequately controlled; NSF=not seizure free; QALY=quality adjusted life year; SF=seizure free; STP=stiripentol; TTO=time trade off;
Source: compiled during the evaluation

6.28 Table 11 provides the results of the stepped economic evaluation. Steps 3, 4 and 5 were added during the evaluation to illustrate the stepped impact of each assumption (i.e. extrapolation, half-cycle correct, background costs, and then discounting) on the ICER.

Table 11: Presentation of the stepped derivation of the base case economic evaluation from the clinical study data

Step and component	STP	PBO	Increment
STEP 1: trial based; drug costs and outcomes to 2 months			
Costs	$	$93	$
Seizure free patients		0	0.35
Incremental cost / extra seizure free patient			**$ / seizure free patient**
STEP 2: QALYs introduced; drug costs and QALYs to 2 months			
Costs	$	$	$
QALYs			0.04
Incremental cost / QALY			**$ / QALY**
STEP 3: Extrapolation introduced; drug costs and QALYs to 5 years (no half-cycle correction and undiscounted)			
Costs	$	$	$
QALYs			1.00
Incremental cost / QALY			**$ / QALY**
STEP 4: Half-cycle correction introduced; drug costs and QALYs to 5 years (half-cycle correction and undiscounted)			
Costs	$	$	$
QALYs			1.01
Incremental cost / QALY			**$ / QALY**
STEP 5: Background costs introduced; all costs and QALYs to 5 years (half-cycle correction and undiscounted)			
Costs	$	$	$
QALYs			1.01
Incremental cost / QALY			**$ / QALY**
STEP 6: Discounting introduced; all costs and QALYs to 5 years (half-cycle correction and discounted)			
Costs	$	$	$
QALYs			0.92
Incremental cost / QALY			**$ / QALY**

Abbreviations: ICER=incremental cost-effectiveness ratio; QALY=quality adjusted life year; SF=seizure free; STP=stiripentol; PBO=placebo;
Source: Tables 57 to 59 and Table 61, pp89-91 and Diacomit Cost-effectiveness Model 2019.xlsm

The redacted table shows ICERs in the range of less $15,000/QALY - $75,000/QALY.

6.29 Table 12 summarises the results of key sensitivity analyses presented in the submission and additional analyses conducted during the evaluation. The results illustrate that the model was very sensitive to the assumed utilities, assumed discontinuation of patients with <50% reduction in seizures at two months, and increase in patient weight over time. The ESC noted a scenario using utility scores from TTO response (i.e. not pooling TTO and EQ-5D), continuation on STP even after loss of response, and assuming an increase in the weight of patients (i.e. growing children) resulted in an ICER of $75,000 - $105,000 per QALY gained, compared with $15,000 - $45,000 per QALY gained in the base case.

Table 12: Results of sensitivity analyses

Univariate analyses	Incremental costs	Incremental effectiveness	Incremental cost-effectiveness
Base case	$[redacted]	0.92	$[redacted] / QALY
Sensitivity analyses conducted by the submission			
Increase proportion in NAC, NSF and SF of STP arm by 25%	$[redacted]	1.17	$[redacted] / QALY
Decrease proportion in NAC, NSF and SF of STP arm by 25%	$[redacted]	0.67	$[redacted] / QALY
Switching AED cost increased by 25%	$[redacted]	0.92	$[redacted] / QALY
Switching AED cost decreased by 25%	$[redacted]	0.92	$[redacted] / QALY
Background cost NSF increased by 25%	$[redacted]	0.92	$[redacted] / QALY
Background cost NSF decreased by 25%	$[redacted]	0.92	$[redacted] / QALY
Background cost SF increased by 25%	$[redacted]	0.92	$[redacted] / QALY
Background cost SF decreased by 25%	$[redacted]	0.92	$[redacted] / QALY
Status epilepticus per patient per year (corrected*)	$[redacted]	0.92	$[redacted] / QALY
Sensitivity analyses conducted during the evaluation			
No change in AED, (i.e., continue STP regardless of response)	$[redacted]	0.92	$[redacted] / QALY
Utility - Verdian et al 2008 TTO, NAC:0.461[a], NSF:0.605, SF:0.699	$[redacted]	0.50	$[redacted] / QALY
Utility - Verdian et al 2008 TTO, NAC:0.393[b], NSF:0.605, SF:0.699	$[redacted]	0.67	$[redacted] / QALY
Utility - Verdian et al 2008 TTO, NAC:0.427[c], NSF:0.605, SF:0.699	$[redacted]	0.59	$[redacted] / QALY
Mortality rate = 0	$[redacted]	1.01	$[redacted] / QALY
No 'mortality by age 4' adjustment	$[redacted]	0.98	$[redacted] / QALY
25% transition from SF to NSF after 2 years	$[redacted]	0.90	$[redacted] / QALY
Increase cohort weight by 2kg per year	$[redacted]	0.92	$[redacted] / QALY
Response rate assuming 2 fewer patients in NAC (27/31) and 2 additional patients in SF (4/31) in placebo arm of the trials	$[redacted]	0.84	$[redacted] / QALY
Multivariate sensitivity analyses conducted during the evaluation			
Assume: utility - Verdian et al 2008 TTO, NAC:0.427[c], NSF:0.605, SF:0.699 and no change in AED	$[redacted]	0.59	$[redacted] / QALY
Assume: utility - Verdian et al 2008 TTO, NAC:0.427[c], NSF:0.605, SF:0.699 and increase cohort weight by 2kg per year	$[redacted]	0.59	$[redacted] / QALY
Assume: no change in AED and increase in cohort weight by 2kg per year	$[redacted]	0.92	$[redacted] / QALY
Assume: utility - Verdian et al 2008 TTO, NAC:0.427[c], NSF:0.605, SF:0.699, no change in AED and increase in cohort weight by 2kg per year	$[redacted]	0.59	$[redacted] / QALY

Abbreviations: AED=anti-epileptic drug; NAC=not adequately controlled; NSF=not seizure free; PBO=placebo; QALY=quality adjusted life year; SF=seizure free; STP=stiripentol; TTO=time trade off;

* Annual probability of status epilepticus event per patient was adjusted to include patients from the STICLO trials and corrected median follow-up durations as reported in the TGA evaluation report and study reports.

[a] utility for NAC health state in the model assumed from TTO for 'HS-2' health state in Verdian et al 2008

[b] utility for NAC health state in the model assumed from TTO for 'HS-1' health state in Verdian et al 2008

[c] utility for NAC health state in the model assumed from the average TTO for 'HS-1' and 'HS-2' health states in Verdian et al 2008

Source: Table 63, p93 of the submission and Diacomit Cost-effectiveness Model 2019.xlsm

The redacted table shows ICERs in the range of $15,000/QALY - $45,000/QALY for sensitivity analyses conducted by the submission; ICERs in the range of $15,000/QALY - $65,000/QALY for sensitivity analyses conducted during the evaluation; and ICERs in the range of $75,000/QALY - $105,000/QALY for multivariate sensitivity analyses conducted during the evaluation.

6.30 The ESC considered that an alternative reasonable approach would be a cost-minimisation analysis to other AEDs. The ESC noted that based on current PBS prices, the daily cost (at the approved ex-manufacturer price level, AEMP) for a 31.8kg patient

treated with TOP or LEV as adjuvant therapy ranges from $[redacted] to $[redacted] per day, compared with the requested price for STP of $[redacted] per day.

Drug cost/patient/year

6.31 The cost per patient per year of STP (excluding the cost of VAL and CLB) is $[redacted] (365 days) assuming the average trial weight (31.84kg), recommended daily dose (50mg/kg/day) and requested DPMQ (250mg (120): $[redacted]). The cost of treating a patient increases by $[redacted] per year assuming an average weight increase of 2kg per year.

6.32 Table 13 presents the cost per patient of STP and VAL/CLB (placebo) in the trial, modelled evaluation and financial estimates.

Table 13: Drug cost per patient for STP (plus VAL and CLB) and placebo (plus VAL and CLB)

	STP			Placebo		
	Trial^	**Model[b]**	**Financial estimates**	**Trial^**	**Model[b]**	**Financial estimates**
Mean dose (mg/kg/day)				-		-
STP	49.6	[redacted]	50	-	-	-
VAL (pre-enrolment)	25.3	25.3	-	25.1	25.1	-
CLB (pre-enrolment)	0.55	0.55	-	0.55	0.55	-
Mean duration (days)	STP / VAL / CLB = 57.3#	STP = 1140 VAL = 1658 CLB = 1658	365.25	50.3	STP = - VAL = 1658 CLB = 1658	-
Cost/patient/day	$[redacted] ‡	$[redacted] ‡	$[redacted] ¥	$1.55[a]	$1.55[a]	-
Cost/patient/year	$[redacted]	$[redacted]	$[redacted]	$565.54	$565.54	-

Abbreviations: CLB=clobazam; NAC=not adequately controlled; NSF=not seizure free; SF=seizure free; STP=stiripentol; VAL=valproate;

‡ Based on requested DPMQ (250mg) $[redacted]

¥ Based on the requested DPMQ (250mg) $[redacted] and (500mg) $[redacted] updated during the evaluation based on the requested AEMP, and assuming 25%STP pack split across strength (250mg / 500mg) and formulation (capsule / powder).

Average duration of exposure for STICLO-France (not reported for STICLO-Italy)

^ Based on the average dose at pre-enrolment of VAL and CLB pooled from STICLO-France and STICLO-Italy. This differed to the pooled average dose at baseline of VAL and CLB in the respective treatment arms STP (23.9 and 0.53) and placebo (22.3 and 0.49).

[a] Based on the submission's average cost of VAL on the PBS (2289L and 2293Q) of $23.23 and $39.45 and cost of CLB 10mg (50) $21.69.

[b] The modelled mean duration was calculated as the proportion receiving treatment in each health states over 5 cycles. Of note, the submission assumed that 30.26% of patients initiated STP would cease after 2 months due to lack of response,

Source: Compiled during the evaluation from Tables 8, 9, and 19 of STICLO-France and Tables 5 and 6 of STICLO-Italy trial reports, Diacomit Cost-effectiveness Model 2019.xlsm and utilisation-and-cost-model-v77_stiripentol_FINAL.xlsm

Estimated PBS usage & financial implications

6.33 This submission was not considered by DUSC. An epidemiological approach was used to estimate the prevalence of SMEI in Australia, the utilisation of STP and the associated financial implications to the PBS. It was assumed that STP would be prescribed as adjuvant therapy to VAL and CLB, all patients will continue treatment with STP irrespective of response and there will be no change to VAL, CLB or any other AEDs. It was also assumed there would be a small net cost to the MBS associated with initiation of STP, but a net savings to State and Territory hospital budgets associated with fewer seizures.

6.34 Table 14 summarises the key inputs used in the financial estimates. The ESC noted that the submission did not consider the impact that listing STP may have on the utilisation of other AEDs (used in addition to STP, or being displaced by STP).

Table 14: Key inputs for financial estimates

Parameter	Value applied and source	Comment
% population with SMEI (including deaths)	1 in 45,700 (0.0022%), Rosander 2014	Reasonable given lack of Australian data.
% SMEI eligible for STP (i.e., ≥4 GCTC/mth)	77%, Sponsor commissioned survey of Australian neurologists (n=4)[a]	Although the requested PBS restriction did not propose any definition for not adequately controlled or severe disease (i.e. baseline seizure frequency), the ESC considered 77% was likely reasonable. Strzelczyk et al 2014 reported 9/13 (69.2%) of patients included in the study had refractory seizures on conventional AEDs resulting in initiation of STP/CLB.
Uptake rate of STP	83% in Year 1 increasing to 97% in Year 6, assumption	The ESC considered this was reasonable given the high clinical need in this population.
Discontinuation rate	0%, assumption	The ESC considered this was reasonable and conservative, but noted that this assumption was inconsistent with the economic evaluation, which inappropriately assumed patients discontinued STP after two months if they achieved <50% seizure reduction.
Patient weight	31.8kg[b], STICLO-France and STICLO-Italy	The use of mean patient weight, assumed % pack split and packs per year to estimate the distribution and number of packs required was poorly justified. The PSCR argued that weight gain with age had minimal impact on costs or the ICER due to decreasing dosage (per kg) with age. The ESC considered that a static weight of 31.8kg was unlikely to occur in practice, and the ESC noted there was no consideration in the financials or economics of the impact of weight changes in the treated population. Overall, the ESC considered that the recommended daily dose of 50mg/kg/day was reasonable and conservative. Given considerable variation across the daily dose and required number of packs and strengths, and given STP doses for heavier patients cost more, an alternative approach may have been to estimate the breakdown of strengths and packs required for the estimated distribution of patients by daily dose on the PBS. The mean weight of the PBS population (or distribution of patient weight) would also change over time as the prevalent patient cohort ages and younger incident patients are added.
% STP packs (60) split / patient	250mg cap/powder: 25%/25%, 500mg cap/powder: 25%/25%, assumption	
STP 250mg (120) scripts / patient / y	19.38 (assuming no 500mg scripts)	
STP 500mg (240) scripts / patient / y	4.85 (assuming no 250mg scripts)	
% Seizure free (SF)	STP: 35.29% and PBO: 0.00%, STICLO-France and STICLO-Italy	May be an overestimate due to the potential of a sub-therapeutic control arm. However, given the submission conservatively assumed 0% discontinuation rate, the only resource implications associated with seizure control were background monitoring costs to the MBS and hospital budgets which were negligible.
MBS item	GP: MBS 3 (100%) Neurology initial: MBS 132 (85%) Neurology follow up: MBS 119 (85%)	Reasonable.
Inpatient admission	B76A, B76B (weighted), NHCDC round 21, 2016-17	Reasonable.
Emergency room	B76A, B76B (ED cost, weighted), NHCDC round 21, 2016-17	The ED cost assumed does not include the "ED pro" cost buckets, which increases average costs for emergency room visits from $61.36 to $945.53. The financial implication of this cost however is minimal due to the low proportional use of services per year.

Abbreviations: AED=anti-epileptic drug; CLB=clobazam; ED=emergency department; PBO=placebo; SMEI=severe myoclonic epilepsy in infancy; STP=stiripentol; VAL=valproate; mth=month; y=year

[a] Clinician survey questions: 4. Of the Dravet syndrome patients you currently treat with the combination of valproate and clobazam, what percentage do not have their seizures adequately controlled (experience ≥4 seizures per month) by this treatment strategy?

[b] 31.8kg is representative of children aged 6-12 years according to the Clinical growth chart (sourced from Centers for Disease Control and Prevention http://www.cdc.gov/growthcharts)

Source: Tables 67-79, pp99-108 and utilisation-and-cost-model-v77_stiripentol_FINAL.xlsm

6.35 Table 15 summarises the estimated use and financial implications of the PBS listing for the proposed STP.

Table 15: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Number of scripts dispensed[a]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Estimated financial implications of STP						
Cost to PBS#	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]
Net financial implications						
Net cost to PBS#	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]	$[redacted]

Abbreviations: STP=stiripentol;

a Assuming around 12 scripts per patient per year as estimated by the submission.

DPMQ for 500mg formulation was updated during the evaluation based on the requested AEMPs.

Source: constructed during the evaluation from Tables 77-82, pp103-106 and utilisation-and-cost-model-v77_stiripentol_FINAL.xlsm

The redacted table shows that at Year 6, the estimated number of patients was less than 10,000.

6.36 The total cost to the PBS of listing STP was estimated to be less than $10 million in Year 6, and a total of less than $10 million in the first 6 years of listing. The results presented in the submission were updated during the evaluation to account for the corrected DPMQs.

6.37 The financial estimates were uncertain given the lack of Australian data on which to base the eligible population and other issues with the assumptions outlined in Table 14.

For more detail on PBAC's view, see section 7 PBAC outcome.

7 PBAC Outcome

7.1 The PBAC recommended the Authority Required (Streamlined) listing of stiripentol (STP) for the treatment of patients with generalised tonic-clonic and clonic seizures associated with severe myoclonic epilepsy of infancy (SMEI, also known as Dravet syndrome) who are not adequately controlled by prior lines of therapy. The PBAC recognised the clinical need for additional treatment options for this small group of patients who continue to experience seizures despite treatment with multiple anti-epileptic drugs (AEDs), and considered, among other matters, that the cost-effectiveness of STP would be acceptable at the price proposed in the submission.

7.2 The PBAC was satisfied that STP provides, for some patients, an improvement in efficacy over the current standard of care, consisting of a range of other AEDs and treatments as adjuvant therapy to valproate (VAL) and a benzodiazepine.

7.3 The PBAC recommended the following changes to the requested restriction:

- The requested maximum quantity (240 capsules/sachets) for the highest strength (500 mg) was considered excessive as it provides 1 month of treatment for a patient weighing 80 kg. The PBAC therefore considered that a maximum quantity of 2 packs (120 units) and a maximum of 3 repeats for all dosage forms would be appropriate;
- GP and paediatrician prescribing should be in consultation with a neurologist and should be for continuing therapy only;
- Noting that clobazam (CLB) is not currently listed on the PBS, the PBAC considered it more appropriate that prior therapy should be with valproate and any benzodiazepine;
- Due to the small adult population living with SMEI, it would not be clinically appropriate to restrict use to patients under the age of 18 and therefore that the restriction should be silent on age.

7.4 The PBAC considered that standard care, consisting of a range of AEDs and treatments including topiramate and levetiracetam, was the appropriate main comparator, but that due to the limited evidence evaluating the efficacy of these treatments in SMEI patients, placebo (plus VAL and CLB) was used as the comparator in the clinical comparison and economic model. Noting the variable and individualised nature of standard care in SMEI, the PBAC agreed with the ESC that the evidence presented compared to placebo was still informative in demonstrating the incremental benefit of STP against a standardised trial comparator.

7.5 The PBAC noted that, despite limitations in the STILCO trials including that some patients in the placebo arm received sub-therapeutic doses of CLB and that only generalised clonic and tonic-clonic seizures were included as the primary outcome measure, after adjustment for plasma concentrations of CLB and its active metabolite (norCLB), pooled data still demonstrated the benefit of STP over placebo. While the adjustment resulted in the odds ratio decreasing from 34.5 to 18.2, the PBAC still considered that the clinical claim of superior comparative effectiveness versus placebo was reasonable.

7.6 The PBAC also noted the non-comparative studies presented in the submission for STP, TOP and LEV, and considered that these results were consistent with the treatment arm in the STICLO trials, which demonstrated 72% to 75% of patients had >50% reduction in seizure frequency from baseline at two months. The PBAC considered this data also supported the proposed listing.

7.7 The PBAC noted that significantly more patients treated with STP (plus VAL and CLB) experienced adverse events compared to placebo (plus VAL and CLB), consistent with the claim of inferior comparative safety. Given the short follow-up of the trials, the PBAC agreed with the ESC that further evidence is required on the relationship between adverse events, doses of AEDs, and potential risk factors.

7.8 The PBAC acknowledged the issues raised by ESC (outlined in paragraph 6.25) with respect to the economic model, but noted that due to the difficulties associated with modelling the range of clinically relevant outcomes in SMEI based on the currently available data, a revised model would be unlikely to address the uncertainty any further. On that basis, and considering the high clinical need in this rare and refractory population, the PBAC considered that the cost-effectiveness of STP was acceptable.

7.9 The PBAC accepted the estimated use of STP as presented in the submission, and considered that the discontinuation rate would likely be low in practice as additional lines of treatment would be added on to STP, rather than substituted, if patients achieve any level of seizure reduction from STP treatment.

7.10 The PBAC advised that STP is not suitable for prescribing by nurse practitioners.

7.11 The PBAC advised that the Early Supply Rule should not apply to STP.

7.12 Under Section 101(3BA) of the *National Health Act 1953*, the PBAC advised that STP should not be treated as interchangeable with any other drugs on an individual patient basis.

7.13 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically the PBAC found that:

a) While STP provides a clinically relevant improvement in efficacy over alternative therapies, the magnitude of benefit was not considered to be substantial;

b) Treatment with STP is expected to address an unmet clinical need, but this need was not considered to be urgent, as other AEDs, while not specifically indicated for SMEI, are available treatment options;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.14 The PBAC advised that this submission would not meet the criteria for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new items:

Name, Restriction, Manner of administration and form	PBS item code	Max. Qty (Packs)	Max. Qty (units)	№.of Rpts	Proprietary Name and Manufacturer	
STIRIPENTOL stiripentol 250 mg capsule, 60	NEW	2	120	3	Diacomit®	Emerge Health Pty Ltd
stiripentol 500 mg capsule, 60	NEW	2	120	3	Diacomit®	Emerge Health Pty Ltd
stiripentol 250 mg powder for oral liquid, 60 sachets	NEW	2	120	3	Diacomit®	Emerge Health Pty Ltd
stiripentol 500 mg powder for oral liquid, 60 sachets	NEW	2	120	3	Diacomit®	Emerge Health Pty Ltd

Category / Program: GENERAL – General Schedule (Code GE)
Prescriber type: ☐Dental ☒ Medical Practitioners ☐Nurse practitioners ☐Optometrists ☐Midwives
Restriction Level / Method: ☒ Authority Required – Streamlined
Indication: Severe myoclonic epilepsy of infancy (Dravet syndrome) **Clinical criteria:** ▪ Patient must have, or have had, generalised tonic-clonic seizures or generalised clonic seizures that are not adequately controlled with a benzodiazepine and valproate. **AND** ▪ The treatment must be as adjunctive therapy to a benzodiazepine and valproate. **Treatment criteria:** ▪ Must be treated by a neurologist if treatment is being initiated; or ▪ Must be treated by a neurologist if treatment is being continued/re-initiated; or ▪ Must be treated by a paediatrician in consultation with a neurologist if treatment is being continued; or ▪ Must be treated by a general practitioner in consultation with a neurologist if treatment is being continued

This restriction may be subject to further review. Should there be any changes made to the restriction the Sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Emerge Health welcomes the PBAC's prompt positive recommendation for the Pharmaceutical Benefits Scheme listing of Diacomit (stiripentol) for Australian patients living with Dravet syndrome.