



**Australian Government**  

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**Medical Services Advisory Committee**

## **Public Summary Document**

### ***Application No. 1420 – Extracorporeal photopheresis for cutaneous T-cell lymphoma***

**Applicant:** Optum Consulting, on behalf of Mallinckrodt Pharmaceuticals

**Date of MSAC consideration:** MSAC 70<sup>th</sup> Meeting, 27 July 2017

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

#### **1. Purpose of application**

The codependent application requested:

- Medicare Benefits Schedule (MBS) listing for extracorporeal photopheresis (ECP) for erythrodermic (stage T<sub>4</sub>, M<sub>0</sub>) cutaneous T-cell lymphoma (CTCL); *and*
- Pharmaceutical Benefits Schedule (PBS) listing for methoxsalen (UVADEX®).

#### **2. MSAC's advice to the Minister**

After considering the available evidence presented in relation to safety, clinical effectiveness and cost-effectiveness of extracorporeal photopheresis (ECP) with methoxsalen for treatment of refractory erythrodermic (stage T<sub>4</sub>M<sub>0</sub>) cutaneous T-cell lymphoma (CTCL), MSAC deferred its advice on public funding pending a revision of the economic model.

MSAC accepted there was a high unmet clinical need and established clinical place for ECP. While MSAC noted that the condition was a rare disease and would have a limited budgetary impact, the evidence base was weak with a high and uncertain incremental cost-effectiveness ratio (ICER).

MSAC noted that the PBS listing of vorinostat had substantially changed the treatment pathway for refractory erythrodermic CTCL and requested that the revised economic model only include comparators with accepted cost-effectiveness (methotrexate and vorinostat). MSAC also considered that there was a need to revisit the proposed MBS fee and align the MBS item descriptor and the proposed PBS restriction.

Any resubmission would need to be considered via ESC.

### 3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this was a new submission to list a service to use integrated, closed ECP systems on the MBS for patients with refractory erythrodermic CTCL who had failed one or more systemic treatments. MSAC noted that this application was an integrated codependent submission with the PBAC to consider the active agent used in ECP, methoxsalen (UVADEX), which is a TGA-designated orphan drug for the treatment of CTCL. MSAC noted that methoxsalen was considered at the July 2017 PBAC meeting, and the PBAC is awaiting MSAC's decision, with intent to expedite reconsideration consistent with the TGA outcome for methoxsalen if MSAC supports MBS listing.

CTCL is a rare type of non-Hodgkin lymphoma that affects the skin resulting in raised, rash-like or itchy patches of skin, skin lumps or ulcers and swollen lymph nodes. It is an incurable condition and, in its later stages more than 80% of the skin is involved, with intractable pruritus and a high risk of infection secondary to scratching. It has an annual incidence of 0.23–0.75 per 100,000 people in Australia. MSAC acknowledged the high clinical need for an effective treatment in this population.

ECP is a systemic treatment for refractory erythrodermic CTCL during which whole blood is processed outside the body in a closed system. The white blood cells are separated out, mixed with methoxsalen and then exposed to ultraviolet light, before being returned to the patient. MSAC acknowledged that there is an established clinical place for ECP in advanced CTCL.

MSAC noted that the comparators for ECP used in the submission were methotrexate, interferon- $\alpha$ 2b and alemtuzumab. MSAC noted since the protocol had been finalised, vorinostat had also been recommended by the PBAC for the treatment of refractory CTCL and is now listed on the PBS for this indication.

MSAC noted that no comparative data is available on the safety of ECP in patients with refractory erythrodermic CTCL. MSAC noted that ECP appears to be associated with fewer adverse events than interferon- $\alpha$ 2b or alemtuzumab and appears to have a similar safety profile to methotrexate. MSAC noted that most described adverse events from ECP and methoxsalen were mild and transient.

MSAC considered evidence from the primary study (n = 198; Hughes C et al 2015), which was a retrospective database analysis of Australian patients with CTCL requiring systemic therapy. MSAC noted that the primary efficacy outcome used in this trial, time to next (systemic) treatment (TTNT), was used as a proxy for quality of life. However, MSAC noted that TTNT was not directly interchangeable with other quality of life measures as it may be impacted by prior treatments used, the order/timing of treatments over the long-term, and the availability, adverse effect profile and expected efficacy of the various treatments. MSAC noted that this study reported no significant difference in TTNT between ECP and comparators, but had high heterogeneity. MSAC noted that, although the evidence supporting ECP for CTCL was limited, the rarity of the condition makes it unlikely that the evidence base will improve substantially.

MSAC voiced a number of concerns with the economic evaluation. MSAC noted in particular that alemtuzumab was listed as a second line comparator, and although it has been approved for multiple sclerosis, it has not been evaluated or approved for CTCL. As a result, MSAC noted that the clinical effectiveness and cost-effectiveness of alemtuzumab for the treatment of CTCL has not been established in the Australian setting, which would be a prerequisite for establishing the cost-effectiveness of ECP against alemtuzumab. MSAC noted that there is a large difference between fortnightly treatment costs for each of the second line comparators -

methotrexate (\$6.04), interferon (\$1,018) and alemtuzumab (\$68,364) - and the difference in these costs has a significant impact on the economic model. Specifically, the inclusion of alemtuzumab significantly favours ECP. MSAC also considered that the costs of methoxsalen were inappropriately reduced by assuming that a single vial could be shared across different patients, whereas this is not accepted practice.

MSAC noted that gemcitabine monotherapy was the only third line treatment included in the model, and vorinostat and combination therapies with ECP were not included in the model. MSAC also noted that the economic model omitted a number of factors that could influence treatment costs: the capital cost of the ECP machine, central lines for venous access, infection prophylaxis for alemtuzumab, monitoring costs, and the cost of managing adverse events. MSAC further noted that the sponsor followed ESC's advice to remodel the economic analyses to show the impact of treatment displacement. MSAC observed that no sensitivity analyses were included, and suggested that the new model needed to be tested more thoroughly to ensure that all of ESC's concerns had been met. MSAC voiced concern that the incremental cost-effectiveness ratio (ICER) shifted from ECP being dominant (less costly and more effective) in the original model to ECP costing nearly \$150,000 per QALY. MSAC noted this was indicative of a high level of uncertainty in the modelling.

Since vorinostat has been recommended for use in CTCL by the PBAC and thus has been demonstrated to be acceptably cost effective, while alemtuzumab has not, MSAC advised removing alemtuzumab from the model and including vorinostat, but cautioned that this was likely to increase the ICER above the current \$150,000 estimate. MSAC noted that methotrexate, which is PBS listed and therefore presumed to be acceptably cost-effective, should still be included in the model. MSAC also noted that interferon has also not been demonstrated to be acceptably cost-effective, but considered that its removal from the model would have less impact on the resulting ICER.

MSAC noted that the economic model included costs for one year but not subsequent years. MSAC noted that, since CTCL is a chronic condition, patients may require treatment over a number of years and consequently, the current values are likely to underestimate the true costs of ongoing treatment. MSAC noted that since CTCL is a rare condition with fewer than 100 patients estimated to be eligible for ECP treatment each year, the MBS cost was estimated to be \$1.5–2 million per year.

MSAC noted that the proposed MBS fee for the service was **\$redacted** with the price of the consumables used during the procedure (**\$redacted**) accounting for most of the fee. MSAC queried whether this price was appropriate. However, MSAC also noted that any reduction in the price paid for the consumables could result in a transference of the payment of these costs to patients.

MSAC considered that patients with refractory erythrodermic CTCL are a high clinical need group and ECP has an established place in therapy. MSAC noted that ECP for CTCL is currently only provided at a single Australian centre (the Peter MacCallum Cancer Centre), and considered that inequity of access is unlikely to be resolved by MBS funding of ECP services. MSAC also noted that the MBS cannot be used to cover the costs of travel and accommodation.

MSAC noted that ESC had suggested consideration of sources funding other than the MBS, such as through a Nationally Funded Centre (NFC). MSAC noted that recent advice from the NFC Reference Group indicated that a number of factors make ECP unsuitable for funding using this approach: the procedure is not viewed as complex or low volume (in the context of the NFC); it is used to treat a broader range of indications than proposed by MSAC (i.e. graft

versus host disease); it is provided as an outpatient procedure; and it requires ongoing treatment rather than a single episode of treatment (as required by the NFC). MSAC noted that, while no clear alternatives to MBS funding were evident, the Department should still continue to investigate the possibility of alternative sources of funding.

MSAC noted that the item descriptor and proposed PBS restriction both needed to be edited to correct the following inconsistencies: the inclusion of statements within the proposed MBS item descriptor that are not within the PBS restriction; the inclusion of criteria within the proposed PBS restriction that are not within the proposed MBS item descriptor; and specification of methoxsalen used alongside ECP treatment in the MBS item descriptor.

MSAC noted that refractory erythrodermic CTCL is associated with a high level of morbidity that leads to significant, ongoing quality of life impairments. However, MSAC indicated that the PBS listing of vorinostat since the protocol was approved had substantially changed the clinical treatment pathway. After considering the evidence presented in relation to the safety, clinical effectiveness and cost-effectiveness, and recognising the high clinical need of this group, MSAC deferred its advice on funding pending an updated economic model which includes comparators with accepted cost-effectiveness (methotrexate and vorinostat). MSAC also considered that there was a need to revisit the proposed fee by either reducing it or providing a stronger justification for each of its components.

#### **4. Background**

This application has not previously been considered by MSAC.

#### **5. Prerequisites to implementation of any funding advice**

Three device components are used to deliver ECP: the photopheresis system, the photopheresis system lamp assembly and the photopheresis system blood set. All three device components are listed on the Australian Register for Therapeutic Goods (ARTG) as Class IIa or Class IIb devices.

Methoxsalen is a TGA-designated orphan drug for the treatment of CTCL and graft-versus-host disease (GVHD) following allogeneic haemopoietic stem cell transplant.

#### **6. Proposal for public funding**

An MBS item number was sought to subsidise delivery of treatment with an integrated, closed ECP system, and a PBS listing of methoxsalen was sought to reimburse the cost of the medicine as part of the service.

##### MBS listing

Table 1 outlines the proposed MBS restriction. This listing does not include multi-step procedures.

**Table 1: Proposed MBS item**

<b>Category 3 – Therapeutic procedures</b>
MBS 38xxx INTEGRATED, CLOSED EXTRACORPOREAL PHOTOPHERESIS SYSTEMS for the ECP treatment of erythrodermic (Stage T <sub>4</sub> and M <sub>0</sub> ) cutaneous T-cell lymphoma patients above 18 years of age, who are refractory <sup>β</sup> to one or more systemic treatments. Treatment includes a specialist consultation and continuous monitoring with nurse attendance under the supervision of a consultant physician. Fee: \$redacted Benefit: 75% = \$redacted 85% = \$redacted

Source: Protocol 1420 [Submitted April 2016], β: Refractory implies patient has had either disease recurrence while on treatment or has experienced intolerance/toxicity to treatment

## **7. Summary of Public Consultation Feedback/Consumer Issues**

As part of the public consultation feedback, seven responses were received from specialists, three from consumers/care givers, three from organisations, two from peak bodies, and two from clinical nurse specialists.

Responses consistently highlighted the high clinical need for the reimbursement of integrated, closed ECP systems for erythrodermic (stage T<sub>4</sub>, M<sub>0</sub>) CTCL, which is considered part of ‘standard of care’. Responses also highlighted the safety and efficacy of ECP treatment within the proposed indication, noting access is not currently equitable due to *ad hoc* funding arrangements across the jurisdictions.

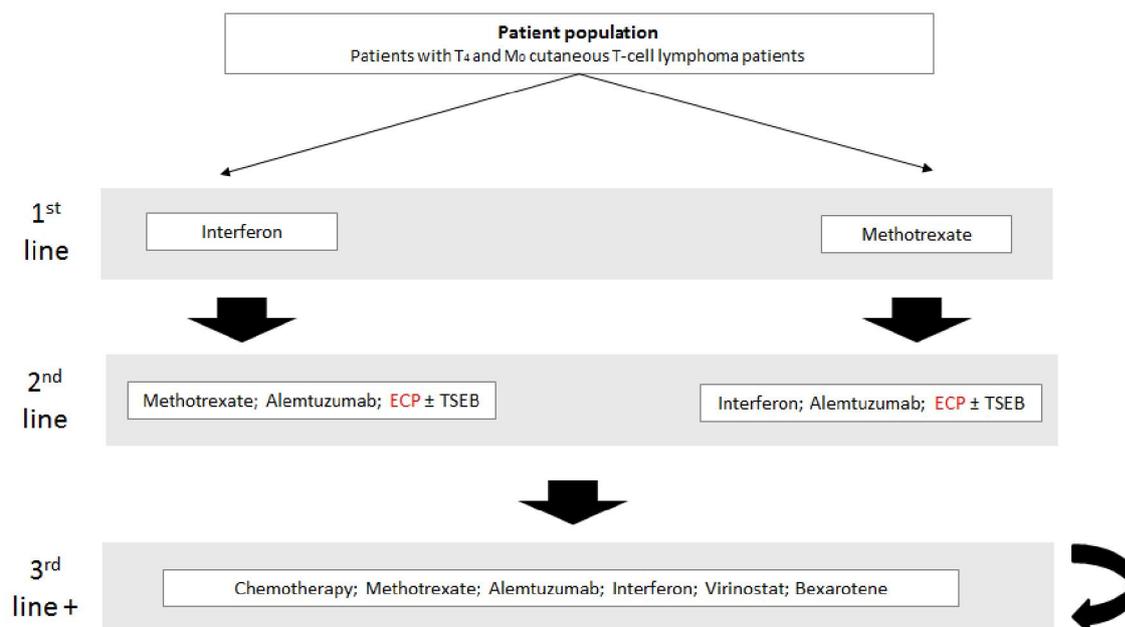
## **8. Proposed intervention’s place in clinical management**

Cutaneous T-cell lymphoma (CTCL) is a rare group of non-Hodgkin’s lymphoma in which malignant T-cell clones accumulate in the skin leading to disfiguring plaques and patches. CTCL mostly impacts men aged between 40 and 60 and the estimated prevalence in Australia is less than 1200 patients in total. The two most common CTCL variants are mycosis fungoides (MF) and Sézary syndrome (SS).

When patients present with symptoms of CTCL, they are classified into stages of disease severity. Patients with early stage disease often only have localised skin disease, while advanced disease may have extensive skin involvement and may have disseminated into lymph nodes and other organs. Advanced stages can involve multiple immune derangements and require systemic therapy.

The proposed patient population that would benefit most from ECP therapy delivered with an integrated, closed system are patients with extensive skin disease (T<sub>4</sub>: *erythroderma* [involvement of ≥ 80% body surface area]), variable blood and lymph node involvement, but no disease in visceral organs (M<sub>0</sub>), and who have failed one or more systemic treatments.

**Figure 1 Proposed clinical algorithm**



## 9. Comparator

The submission stated that, irrespective of first line treatment, the most commonly used second line treatments for patients with erythrodermic (stage T<sub>4</sub>, M<sub>0</sub>) CTCL are methotrexate, interferon- $\alpha$ 2b and alemtuzumab. The submission therefore proposed that the appropriate comparators for treatment with an integrated, closed ECP system in patients with erythrodermic (stage T<sub>4</sub>, M<sub>0</sub>) CTCL, who are refractory to one or more systemic treatments, are methotrexate, interferon- $\alpha$ 2b and alemtuzumab.

The critique included an additional comparator, vorinostat due to its recommendation for listing by the March 2017 Pharmaceutical Benefits Advisory Committee meeting. The critique compared the clinical effectiveness of ECP with vorinostat using progression-free survival. The critique questioned the inclusion of alemtuzumab as a comparator.

## 10. Comparative safety

No comparative data were available on the safety of ECP in patients with refractory erythrodermic (stage T<sub>4</sub>M<sub>0</sub>) CTCL. The clinical evidence used to support the claim of superior safety was from a naïve comparison of safety data from differing patient groups which included early-stage CTCL (ECP and interferon- $\alpha$ 2b), advanced CTCL (alemtuzumab and methotrexate) and rheumatoid arthritis (methotrexate).

This comparison indicated that ECP had fewer, relatively transient adverse events compared with alemtuzumab and interferon- $\alpha$ 2b. ECP might have a safety profile similar to or better than methotrexate; however, it was difficult to make a strong conclusion, given the variation in methotrexate dosing and the applicability of this analysis.

In its pre-MSAC response, the applicant provided further limited safety data from the Peter MacCallum Cancer Centre in Victoria.

## 11. Comparative effectiveness

The available data do not show that ECP results in a statistically significant improvement in the primary clinical outcome of time to next treatment (TTNT) compared to its comparators. However, this may be due to insufficient sample sizes in the studies, which may be traced back to the rarity of the disease.

Based on a naïve comparison of treatment effectiveness from Hughes et al 2015, ECP treatment did not result in a statistically significantly longer median duration of TTNT than methotrexate, interferon- $\alpha$ 2b or alemtuzumab (Table 2).

**Table 2: TTNT cohort results (all patients with various disease stages of MF/SS) from Hughes et al 2015**

Study	Intervention	Main comparator		
	ECP	Methotrexate	Interferon- $\alpha$ 2b	Alemtuzumab
n	n=53	n=84	n=68	n=16
Median line of therapy	2	2	2	3.5
Median TTNT (95% CI)	9.2 (5.9, 21.8)	5.0 (3.6, 6.5)	8.7 (6.0, 18.0)	4.1 (2.7, 6.5)
1 yr free from further tx (%)	39.1%	25%	41.7%	27.8%
2 yr free from further tx (%)	25.7%	21.2%	29.1%	27.8%

No comparative data were available on the survival (or clinical response) of ECP treatment in patients with refractory erythrodermic (stage T<sub>4</sub>M<sub>0</sub>) CTCL. Table 3 summarises the results for overall survival and progression free survival for ECP treatment from three other single arm studies.

**Table 3: Results of clinically relevant outcomes (OS and PFS) from single-arm studies of ECP treatment**

Study	Arulogun et al 2008	Knobler et al 2012	Siakantaris et al 2012
n	13	39	18
Median follow-up, months (SD)	16 months (range: 83-64)	46 months (0-94)	34 months ( $\pm$ 25)
Median PFS	28 months	—	28 months <sup>a</sup>
PFS at 2 years (predicted)	55%	—	—
Median OS (cohort)	—	79.2 months	51 months
Median OS (subgroup: stage T <sub>4</sub> )	—	64.6 months <sup>b</sup>	—
OS at 4 years (predicted)	82%	—	—

ECP = extracorporeal photopheresis; OS = overall survival; PFS = progression free survival; SD = standard deviation

<sup>a</sup> ECP was combined with other systematic treatments in 17 (94%) patients

<sup>b</sup> From 31/39 (79%) patients with generalised erythroderma

From Knobler et al 2012, the results for overall survival with ECP treatment showed that the subgroup with advanced skin disease (T<sub>4</sub>) had worse survival than cohort population (65 vs. 79 months). The results from the Australian study, Arulogun et al 2008, show that the median progression free survival was 28 months. However, no comparative data were available on the survival of patients treated with ECP with CTCL (T<sub>4</sub>M<sub>0</sub>). Compared to vorinostat, these results may suggest that ECP results in a longer median duration of progression-free survival (28 months) than vorinostat (2.8 - 4.9 months from two different small single-arm studies of vorinostat) although the statistical significance across these results has not been assessed.

Table 4 summarises outcomes related to clinical response, for ECP treatment.

**Table 4: Results for clinical response from single-arm studies of ECP treatment**

Study	Arulogun <i>et al</i> 2008	Knobler <i>et al</i> 2012	Siakantaris <i>et al</i> 2012
n	13	39	18
Time to response	—	—	—
Median (range)	10 months <sup>a</sup>	—	—
≥ 90% response (range)	—	20 months (7,63)	—
≥ 50–90% response (range)	—	7 months (4,29)	—
≥ 25–50% response (range)	—	5 months (2,7)	—
Response duration n (%)	—	—	—
Median	—	—	29 ± 24 months
Overall response rate n (%)	8 <sup>b,c</sup> (62%)	29 (74%)	11 (61%)
Complete response n (%)	2 (15%)	16 (41%)	5 (28%)
Partial response n (%)	6 (46%)	13 (33%)	6 (33%)
Non-responders n (%)	5 (38%)	10 (26%)	7 (39%)

a After 12 months, 60% of patients continued to respond to ECP treatment

b Of the patients that responded (complete and partial), 88% were on concomitant systematic treatments

c 100% of patients had Sezary syndrome

The results showed that the median time to respond to ECP treatment was 10 months (Arulogun *et al* 2008) and time to response was longer for patients with ≥ 90% response compared with patients with 50-90% response (20 months vs. 7 months respectively). The median duration of response to ECP treatment was 29 months (Siakantaris *et al* 2012). Additionally, ECP treatment resulted in 61-74% of patients achieving overall response.

MSAC considered that these other three single-arm studies had several limitations regarding their applicability to estimating the likely extent of benefit of ECP in the requested MBS listing:

- Arulogun *et al* 2008: all patients had SS, and 7/8 patients who responded received concomitant systemic therapy (Table 4, footnote b)
- Siakantaris *et al* 2012: 17/18 patients received concomitant systemic therapy (Table 3, footnote a)
- Knobler *et al* 2012: used oral (not extracorporeal) methoxsalen.

### Clinical claim

Acknowledging limitations in the evidence base for ECP, the submission claimed that the integrated, closed ECP system has at least non-inferior efficacy and superior safety relative to methotrexate, IFN- $\alpha$ 2b and alemtuzumab – for the treatment of refractory erythrodermic (Stage T<sub>4</sub> and M<sub>0</sub>) CTCL.

## 12. Economic evaluation

Due to limited evidence, a simple model design was used to calculate the costs and benefits of an integrated, closed ECP system when compared with either interferon- $\alpha$ 2b, methotrexate or alemtuzumab.

The economic model has two core health states for patients who receive usual second line treatment and usual third line treatment. Second line treatments include patients receiving integrated, closed ECP, interferon- $\alpha$ 2b, methotrexate or alemtuzumab. Subsequently all patients who fail second line treatment are assumed to receive gemcitabine monotherapy as a usual third line treatment.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, with the base case assumptions, are shown in Table 5.

**Table 5: ICER results (discounted) including third line treatments**

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER per QALY
Integrated, closed ECP system	\$redacted		1.79		
Methotrexate	\$22,639	\$redacted	1.04	0.72	\$redacted
Interferon- $\alpha$ 2b	\$51,022	\$redacted	1.64	0.14	\$redacted
Alemtuzumab	\$1,790,509	\$redacted	1.16	0.60	Dominant
Weighted	\$417,691	\$redacted	1.34	0.43	Dominant

ICER = Incremental Cost Effectiveness Ratio, note difference due to rounding

The critique stated that the submission’s base case economic comparator was not appropriate (weighted comparator: 46% methotrexate; 32% interferon- $\alpha$ 2b; and 22% alemtuzumab). Specifically, the weighting of alemtuzumab was overestimated (significantly favoured ECP).

The model structure was overly simplified and did not align with the proposed treatment algorithm where ECP would add to the list of treatment options for patients with refractory erythrodermic (T<sub>4</sub>, M<sub>0</sub>) CTCL. Specifically, the inclusion of gemcitabine as the only third-line treatment option was not appropriate (and favoured ECP).

The unit of measure used in the critique for estimating the cost of treatment with ECP was treatment cost/patient/course. This value was estimated at \$redacted for a treatment regimen of 16 ECP sessions. However, the critique noted that the submission did not validate the assumption of 16 ECP sessions per treatment regimen. Based on a 21 month median duration of ECP treatment, the treatment cost per patient course was estimated at \$redacted.

In its pre-MSAC response, the applicant provided a revised incremental cost-effectiveness ratio of \$148,871.39 per QALY. This was calculated using incremental costs of \$redacted and incremental QALY gains of 0.153. The applicant considered that the recalculated ICER was not unreasonable in the context of a rare, debilitating disease with high clinical need and no curative treatment options.

### **13. Financial/budgetary impacts**

An epidemiological approach was taken to develop the utilisation and financial estimates for the proposed listing of an integrated, closed ECP system. The financial impact to both the PBS and the MBS is outlined in Table 6. The net financial impact to the Government in 2017 was estimated as \$redacted, comprised of a net cost to the PBS of \$redacted and a net cost to the MBS of \$redacted.

This net cost to the Government is expected to increase initially then reduce to \$redacted by 2021. The costs associated with other treatments were not incorporated into this financial analysis as the applicant claimed that integrated, closed ECP systems would not be expected to replace any other funded treatments for patients with T<sub>4</sub>M<sub>0</sub> CTCL.

**Table 6: Net cost to Government**

	2017	2018	2019	2020	2021
Total patients with CTCL (Both incident and prevalent populations)	388	324	241	159	93
Proportion of patients treated per year	20%	30%	40%	50%	60%
Prevalent patients treated per year	78	97	96	79	56
Net cost to the PBS of the proposed listing	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to the MBS of the proposed listing	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted
Net cost to the Government of the proposed listing	\$redacted	\$redacted	\$redacted	\$redacted	\$redacted

#### 14. Key issues from ESC for MSAC

ESC noted that cutaneous T-cell lymphoma (CTCL) was a rare disease affecting a small number of patients and as such, the evidence base for the submission was limited.

ESC noted that the submission relied upon Hughes et al 2015 as the primary study. This Australian study was a retrospective analysis of data collected from 198 patients with CTCL who underwent systemic therapies between 1975 and 2014. The various systemic therapies included, among others, extracorporeal photopheresis (ECP) and use of interferon- $\alpha$ 2b, methotrexate, alemtuzumab and histone deacetylase inhibitors (which include vorinostat). ESC noted that this study was likely to be at high risk of bias because:

- it included a highly heterogeneous mix of patients in terms of their baseline and prognostic factors;
- it compared patients who had failed many different types of treatment with those who had failed only one or two types of treatment; and
- data were collected over a long period of time and treatment pathways were likely to have changed during that time.

ESC noted that there were no comparative safety data on the use of ECP in refractory stage CTCL and the safety data were taken from studies that enrolled patients with early stage CTCL, advanced CTCL and rheumatoid arthritis. This evidence suggested that ECP may be associated with fewer adverse events than interferon- $\alpha$ 2b or alemtuzumab, and may have a safety profile similar to or better than methotrexate.

ESC noted that a procedural outcome, time to next systemic treatment (TTNT) measured in the Hughes study, was used as the primary measure of comparative effectiveness. The submission asserted that TTNT is a good proxy measure for patient quality of life. However, ESC considered that TTNT is influenced by a variety of factors that may have had little to do with the efficacy of treatment. These factors included the availability of other treatments, patient treatment preferences, and the order in which other treatments have been used. ESC also considered that the use of a procedural outcome to measure effectiveness in an unblinded study increased the risk of bias.

ESC noted that the Hughes study reported no significant difference in TTNT between ECP and comparators other than chemotherapy, which was likely to be used as third line or later treatment.

The committee noted that the comparator included in the economic model was a weighted basket of second line treatments including methotrexate (46%), interferon- $\alpha$ 2b (32%) and

alemtuzumab (22%) and that the relative weight of each treatment was based upon the responses of 20 Australian clinicians to a survey rather than the published literature.

ESC considered that the economic model was simplistic and based upon implausible clinical assumptions. ESC noted that the Hughes study had concluded that chemotherapy should only be used once all other treatment options had been exhausted. However, despite the availability of a range of different second line treatments, the model assumed all patients only tried one type of second line therapy before moving immediately on to third line chemotherapy. As a result, the majority of people in the model had progressed to chemotherapy within one year. ESC also noted that the model did not consider the possibility that ECP and/or other treatment options may be used together as combination therapy. ESC noted that the applicant asserted that ECP would replace other second-line treatments, but ESC considered it was more likely that ECP would *displace* other treatments and this scenario was not captured in the economic model.

ESC questioned the appropriateness of generating an exponential survival curve to model 'time on treatment' using median TTNT and the proportion of patients free from further treatment at one and two years. ESC noted that this inappropriately combined different measures and combined three point estimates to generate continuous measures over time. ESC noted that there were relevant Kaplan Meier survival curves presented in the Hughes study and suggested that using these to inform the model more would be more appropriate.

ESC questioned whether including alemtuzumab in the basket of second line comparators was appropriate and noted that, in the Hughes study, alemtuzumab was indicated to be a later line therapy (median line of therapy 3.5). In contrast, the Hughes study indicated that interferon- $\alpha$ 2b, methotrexate and ECP were all second line therapies (median line of therapy 2). The committee noted that inclusion of alemtuzumab in the basket of comparators significantly favoured ECP due its high cost. The cost of a fortnight's supply of alemtuzumab was ~\$68,000 compared with ~\$2,200 for ECP, ~\$1,000 for interferon- $\alpha$ 2b and \$6 for methotrexate.

In addition, ESC noted that the effectiveness and cost-effectiveness of alemtuzumab or interferon- $\alpha$ 2b have not been established in the Australian context for the treatment of CTCL, given that neither is TGA registered nor PBS listed for this indication. If MSAC were to agree that either were a relevant comparator, then MSAC would also need a basis to establish the cost-effectiveness of these alternatives before using them as a basis for considering the cost-effectiveness of ECP. For example, asserting dominance of ECP over alemtuzumab is not a compelling argument for an MBS listing of ECP if alemtuzumab is not itself acceptably cost-effective in treating CTCL.

By contrast, methotrexate is PBS-listed without restriction, and so there is an implicit acceptance of its cost-effectiveness for this therapeutic use.

ESC considered that the March 2017 recommendation by the PBAC to list vorinostat on the PBS for the treatment of CTCL would impact upon the clinical algorithm and economic model included in the submission.

ESC considered that the way utility and disutility values had been derived was inadequately described and/or justified. ESC accepted that using utility values for psoriasis (Zug et al 1995) as a proxy appeared to be reasonable, but questioned the way they had been applied. Health states corresponding to having mild, moderate and severe psoriasis had been mapped to response to ECP treatment (complete/partial/non-response; Arulogun et al 2008) without justifying this approach. The application of the resulting utility weight (0.71) to all patients

on the basis that the response profile for each type of second line treatment would be identical was also questioned by ESC.

ESC noted that disutility due to the adverse effects associated with the comparators was derived from a study of interferon- $\alpha$ 2b treatment in Stage III cutaneous melanoma (Crott et al 2004), but considered its use has not been adequately justified. In addition, ESC noted that the disutility value (0.13) calculated from this study was applied identically to all three of the comparators in the economic model. ESC questioned the assumption that the disutility caused by adverse effects as a result of treatment with interferon- $\alpha$ 2b, methotrexate and alemtuzumab would be of similar magnitude given the likely differences in safety profile of the three agents.

Other issues with the economic model included the incorrect use of specialist fees (MBS items 104 and 105) instead of consultant physician fees (MBS items 110 and 116); a lack of consideration of capital costs for the ECP machine; the cost of consumables, the need for vascular access (e.g. PICC/central line); the costs of infection prophylaxis in patients receiving alemtuzumab; monitoring costs; and the cost of treating adverse events.

Given these issues with the economic modelling, ESC considered the economic model to be unreliable and the claim that ECP dominated other second line treatments to be highly uncertain. ESC considered the economic model did not adequately reflect clinical practice or the impact of listing the service upon the MBS. ESC suggested that the economic model be redesigned to:

- allow use of multiple second line treatments before the use of vorinostat (PBAC approved) or alemtuzumab (not approved) followed by chemotherapy (i.e., allowing for displacement of other therapies);
- use the true survival analyses of TTNT presented in the Hughes study to inform estimates of time on treatment; and
- reconsider the utility (and disutility) values used in the model and provide adequate justification of any values subsequently used in the modelling.

ESC noted that there is a strong possibility of unintended utilisation if ECP is used as first line therapy. ESC noted that in the Hughes study, ECP was used first line in 29.9% of patients with T<sub>4</sub> disease and that it is listed as a first line treatment option in the 2005 [Australian Clinical Practice Guidelines for the Diagnosis and Management of Lymphoma](#).

ESC noted that the ECP treatment regimen is not well-standardised. The treatment regimen (number, frequency and duration of treatment sessions) set out in the submission differed from the Journal of the European Academy of Dermatology and Venereology (JEADV) guidelines (Knobler et al 2014). ESC noted that if the proposed MBS fee were payable per treatment session, the frequency and duration of treatment would impact upon the cost of providing the service.

ESC noted that the cost of the consumables for the ECP service were high (~\$redacted). ESC noted that, while the applicant had provided a diagram of the procedural kit used during the service in the pre-ESC response, there was still no justification or breakdown of the costs associated with this kit.

ESC considered that listing ECP on the MBS would not address all access and equity issues. ESC noted that the small patient population, high capital costs and specialist training to deliver the procedure of ECP meant that the service would likely remain limited to major metropolitan settings, even if the application were successful. ESC noted that centralised treatment in a specialised facility is best in situations where there is a small patient volume

and a high level of treatment complexity. Moreover, ESC noted that MBS funding cannot be used to reimburse administrative and travel costs and therefore could not be used to subsidise patient travel costs. ESC suggested that considering alternative methods of funding, such as a Nationally Funded Centre (NFC), would be worthwhile.

ESC noted that there were a number of issues with the MBS item descriptor including:

- the need for the MBS and PBS listings to be consistent; (e.g. “above 18 years of age” should also be included in the PBS restriction);
- inclusion of wording to prevent use of ECP as a first line treatment;
- inclusion of information about the frequency of use and duration of use (including restricting ongoing use to patients responding to treatment);
- a statement that ECP is to be used with methoxsalen;
- a statement that when ECP is subsidised for CTCL, it is not to be used concurrently with any other systemic treatment for CTCL; and
- information on the source of referral and accreditation of specialists and treatment centres providing the service.

From a consumer perspective, ESC noted that there was likely to be considerable uncertainty around out of pocket costs for patients and carers, particularly if they were required to travel to access treatment.

ESC Key ISSUES	ESC ADVICE
Safety	<p>ECP likely to be safer than, and at least as effective as, alternative Rx for T<sub>4</sub>, M<sub>0</sub> CTCL:</p> <ul style="list-style-type: none"> <li>• Limited evidence base for safety &amp; effectiveness c. high risk of bias, but unlikely to improve.</li> <li>• Small no. of patients with debilitating disease &amp; few effective alternatives</li> </ul>
MBS Item Descriptor	<p>Proposed descriptor inadequate to capture pertinent requirements.</p> <p>MBS item descriptor needs a mechanism to ensure second line use, given that in the primary clinical study 30% of ECP use was first line in CTCL T<sub>4</sub> patients</p> <p>Reinstate wording in the proposed descriptor that limits use to appropriately trained professionals, in an appropriate setting, following demonstration of failure of 1<sup>st</sup> line therapy</p>
MBS Funding	<p>Proposed fee may not adequately capture costs.</p> <p>Delivery of Rx of high complexity to a small no. of patients not well suited to public funding <i>via</i> MBS – may be more suitable for a NFC-type funding model</p>
The modelled ICERs submitted by the applicant are unreliable due to the structure and inputs used (see below) and rather than ECP being dominant, it is more likely to be associated with an ICER of ~\$150k/QALY	<p>Re-design model to allow multiple second line treatments to be trialled before the use of alemtuzumab followed by chemotherapy. R-specify the monthly probabilities of TTNT using the survival analyses in Hughes 2015 (not the % free of treatment at 1 and 2 years)</p> <p>Reconsider the application of utility and disutility weights in the model, with a clear rationale</p>
The economic model has an overly simplistic structure which does not adequately capture cycling through second line Rx options before progression to vorinostat/alemtuzumab then	

chemotherapy	
The basket of second line comparators inappropriately includes alemtuzumab, and this significantly favours ECP.	
The applications of utility and disutility weights in the model is not adequately justified, and the quantification of the superior safety profile of ECP is not well supported, or tested in the model	
The selective use of TTNT data from Hughes 2015 is not adequately supported, or appropriately applied in the economic model.	

## 15. Other significant factors

Nil

## 16. Applicant's comments on MSAC's Public Summary Document

Mallinckrodt Pharmaceuticals are disappointed with MSAC's decision to defer its recommendation for ECP in patients with CTCL. Mallinckrodt Pharmaceuticals reiterate alemtuzumab is considered an appropriate treatment comparator for ECP, acknowledging it is not TGA approved or registered for this indication. Also, Roferon-A® (interferon- $\alpha$ -2a) is TGA approved<sup>[1]</sup> for CTCL, although it has not been assessed by PBAC. Mallinckrodt Pharmaceuticals agree with MSAC's view there is a high unmet clinical need for ECP. ECP is a rare disease and will have a limited budget impact. Mallinckrodt Pharmaceuticals will continue to work with the Department of Health and MSAC to ensure patients can access safe and effective treatment with ECP.

## 17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)

<sup>[1]</sup> <https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2010-PI-04073-3>