Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1420.1 – Extracorporeal photopheresis for treatment of cutaneous T-cell lymphoma

Applicant: **Mallinckrodt Pharmaceuticals**

Date of MSAC consideration: **MSAC 78th Meeting, 3 April 2020**

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, visit the MSAC website

1. Purpose of application

A resubmission requesting Medicare Benefits Schedule (MBS) listing for integrated, closed system extracorporeal photopheresis (ECP) for patients with erythrodermic (stage T_4 M_0) cutaneous T-cell lymphoma (CTCL) who are refractory to one or more systemic therapies was received from Mallinckrodt by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to the safety, clinical effectiveness and cost-effectiveness MSAC supported public funding of extracorporeal photopheresis in the treatment of cutaneous T-cell lymphoma. However, MSAC noted that the proposed fee for service included items which are not typically reimbursed under the MBS, and that the Department should negotiate these with the applicant.

The MSAC-supported item descriptor is:

Extracorporeal photopheresis (ECP) delivered with an integrated, closed ECP system for the treatment of erythrodermic stage III-IVa T_4 M_0 cutaneous T-cell lymphoma (CTCL), if all the following criteria are met:

(a) the patient must be aged 18 years or over; and
(b) the patient must have received prior systemic treatment for this condition and experienced either disease progression or unacceptable toxicity while on this treatment; and
(c) the treatment must be in combination with use of ex-vivo injectable methoxsalen; and
(d) the treatment must be under the supervision of a specialist haematologist.

Benefit is claimable once per cycle of ECP treatment, regardless of the number of consecutive days over which each cycle is performed.

Consumer summary

Mallinckrodt Pharmaceuticals applied for public funding through the Medicare Benefits Schedule (MBS) for the use of extracorporeal photopheresis (ECP) to treat cutaneous T-cell lymphoma (CTCL).

CTCL is a rare type of cancer that affects T-cells (a type of white blood cell) and causes raised, rash-like or itchy patches of skin, skin lumps or ulcers. It is usually treated with chemotherapy (anticancer medicine) or immunotherapy (treatment that boosts the body's own immune response against the cancer).

ECP is a type of treatment that involves attaching a patient to a machine that removes some of their blood. The machine separates the white blood cells, and the red blood cells and plasma go back into the body. The white blood cells are mixed with a drug called methoxsalen, exposed to ultraviolet (UV) light, then put back into the patient. ECP activates the patient's immune system to fight the cancer.

MSAC accepted that ECP is safe and has fewer side effects than other CTCL treatments. There was little evidence to directly compare ECP with other treatments in terms of how well it works, but MSAC considered that ECP is probably as effective as other treatments. This evidence is unlikely to improve because CTCL is a rare condition, which makes it difficult to study. MSAC discussed the proposed cost of ECP and asked for a more detailed breakdown of costs and explanation of why each component is included. MSAC accepted that ECP was probably cost-effective, acknowledging the need for new treatments for CTCL and the small number of patients.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported MBS funding of ECP for CTCL. MSAC asked the Department to work with the applicant to review and negotiate the proposed fee for the service.

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

MSAC noted the codependent resubmission for extracorporeal photopheresis (ECP) for treatment of cutaneous T-cell lymphoma (CTCL). The application requests a Medicare Benefits Schedule (MBS) item to subsidise delivery of ECP treatment with an integrated closed system, and a Pharmaceutical Benefits Scheme (PBS) listing for methoxsalen (the substance used as part of the ECP service). MSAC noted the Pharmaceutical Benefits Advisory Committee (PBAC) deferred its recommendation on methoxsalen following the original submission in 2017 pending Therapeutic Goods Administration approval (which was granted in 2019) and MSAC support for ECP. MSAC also deferred its recommendation at that time and requested a revised economic model, inclusion of new comparators with accepted cost-effectiveness (vorinostat and brentuximab vedotin) and further justification of the proposed price.

MSAC noted the proposed MBS item descriptor had been revised to align with the revised PBS restriction for methoxsalen, and to limit to one fee per cycle of treatment. This limit would prevent double claiming if treatment is received over 2 days with an overnight stay. MSAC confirmed that treatment is intended to be delivered as an outpatient service, and overnight stay would only be required to manage any adverse events, if they arise. MSAC considered that limiting to once per cycle of treatment was appropriate. As suggested by ESC, MSAC discussed limiting the total number of cycles per patient per lifetime, but

considered that, if the treatment continues to be effective for a patient, there should not be an upper limit to the number of cycles. In response to another suggestion by ESC, MSAC did not think it necessary to require accreditation of the centre or health professionals supervising or delivering the service.

For consistency, MSAC also supported appropriate alignment of the MBS item descriptor with the following aspects proposed for the methoxsalen PBS restrictions:

- the criterion in the PBS restriction for continuing methoxsalen that "patient must demonstrate a response [defined as 'a greater than or equal to 50% skin score response from baseline for at least 4 weeks, within the first six months of treatment'] to PBS-subsidised treatment with this drug for this condition"; and
- the criterion in the PBS restrictions for both initiating and continuing methoxsalen that "the treatment must be the sole PBS-subsidised therapy for this condition".

MSAC accepted the residual high clinical need in patients with CTCL, given that none of the currently available treatment options are considered curative. MSAC noted that ECP is currently performed for CTCL in a single centre in Australia for a population of approximately 80 patients. MSAC noted the prevalence of cutaneous T-cell lymphoma in Australia has remained stable in the intervening period between the initial application and re-submission and that, given the low incidence, the evidence base for comparing therapies to treat this condition is unlikely to substantially improve.

MSAC noted that the nominated comparators had been revised as requested to include vorinostat and brentuximab vedotin, and to remove alemtuzumab (which is not PBS listed). Interferon-α remained as a comparator, as the applicant noted that peginterferon-α2a is used in CTCL and is unrestricted on the PBS. Together with methotrexate, MSAC accepted these comparators.

The clinical claims were that ECP has superior safety and at least non-inferior effectiveness compared with brentuximab vedotin and vorinostat. MSAC recalled that it had accepted the improved comparative safety of ECP over its accepted comparators in the original submission, and confirmed that ECP is associated with fewer adverse events than its comparators. Regarding comparative effectiveness, MSAC noted ESC's advice that the included studies (mainly non-randomised studies of small populations) preclude direct comparisons between the nominated pharmacological treatments and ECP, leading to continuing uncertainty about comparative effectiveness and safety. MSAC accepted ESC's advice that ECP is still likely safer than, and at least as effective as, all four identified comparators for stage T4, M0 CTCL, and also noted that the evidence is unlikely to improve because this is a rare condition.

MSAC discussed the proposed fee, noting that this covers personnel, consumables and other costs, but not any capital cost of the main device. MSAC suspected that the capital cost could be a limiting factor for implementation, noting that few centres currently provide this treatment for CTCL or for graft-versus host disease. MSAC noted the $**redacted** in the fee for consumables, which the applicant's pre-MSAC response stated includes a disposable single-use kit, manufacture, transport, research, development, clinical training, support, education, scientific consultation, customer service and access to online platforms. MSAC advised that, as not all these cost inputs are ordinarily reimbursed by the MBS, the applicant should supply a detailed breakdown and justification of each and all of these inputs, to inform a negotiation of the MBS fee with the Department in consideration of the small number of providers for this service. Similarly, MSAC also suggested that the PBAC may wish to negotiate the price of methoxsalen to lower the cost of the entire package.

In the economic model, MSAC noted the applicant's revisions to include multiple second-line agents with a 5-year time horizon, revised utilities and sensitivity analysis. MSAC noted the submission still had not included costs of treating adverse events. MSAC noted that the incremental cost-effectiveness ratio (ICER) is lower and more certain than in the original submission. MSAC also noted that the cost of brentuximab vedotin has a high impact on the ICER, and the applicant had included the published price of brentuximab vedotin, resulting in a claim that ECP is dominant, that is, it would increase the number of quality-adjusted life years (QALYs) gained and would reduce overall costs. However, the effective price of brentuximab vedotin (which the applicant does not have access to) is **redacted** lower than the published price; using the effective price results in an ICER of $**redacted** per QALY. MSAC advised that, acknowledging the small number of patients and high clinical need for this population, ECP is probably cost-effective.

MSAC discussed the weighted proportional use of the comparators (46% methotrexate, 32% interferon-α, 13% vorinostat, 9% brentuximab vedotin), particularly the split between vorinostat and brentuximab vedotin. The applicant's pre-MSAC response noted that these proportions were based on PBS item reports at the time of submission (covering April 2019 to June 2019). Since then, data have become available to January 2020, which show an increase in weighted proportional use of brentuximab vedotin to 11%, and reduction in vorinostat to 11% (both from April 2019 to January 2020). As such, the proportion of patients initiating brentuximab vedotin as a second-line treatment used in the weighted comparison in the submission (9%) is likely to be conservative. The Department confirmed that there had been a change in the proportional use of these treatments, and MSAC accepted that the initial weighted proportional use of the comparators was acceptable.

MSAC accepted the basis for the estimated financial costs to the MBS over 5 years.

MSAC accepted that equity of access for ECP is an issue, but that this would remain an issue whether ECP was listed on the MBS or not. MSAC recommended that the listing be reviewed in 2 years to monitor for usage beyond the estimated volumes.

4. Background

This is the first resubmission (applicant-developed assessment report; ADAR) of Application 1420.

At its July 2017 meeting, 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.

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 (Public Summary Document [PSD] Application No. 1420, 2017 p1).

The commentary provided a summary of outstanding matters of concern previously raised by MSAC in July 2017 and how the resubmission addressed those concerns (Table 1).

Table 1: Summary of outstanding matters of concern

Component	Matter of MSAC concern (July 2017)	How the resubmission addresses it
Comparators	Alemtuzumab inappropriate; interferon-α not acceptably cost-effective; vorinostat to be included (p3, 1420 PSD, July 2017).	Alemtuzumab removed; interferon-α retained (interferon-α2a is TGA approved for CTCL, *but not subsidised on PBS for CTCL; peg interferon-α2a is not TGA approved for CTCL, but is PBS-listed without restriction)*; vorinostat *and brentuximab vedotin (for CD30 positive patients only)* included. *Inclusion of interferon-α may not be appropriate.*
MBS descriptor and PBS restriction	Inconsistencies between proposed MBS descriptor and PBS restriction (p4, 1420 PSD, July 2017). Revisit MBS fee by reducing or providing stronger justification for costs (particularly consumables) (p4 and p12, 1420 PSD, July 2017).	Updated to improve consistency. *No statement included to limit consecutive day claiming.* *Not fully addressed.*
Primary evidence	Hughes 2015 considered to have high heterogeneity and likely to be at high risk of bias (p2 and p10, 1420 PSD, July 2017).	Updated analysis of Hughes cohort is presented in Gao *et al,* 2019; *Limited reporting necessitated sourcing of data from TGA report (Prince et al, 2019); likely to be at high risk of bias.*
Comparative efficacy	No direct comparative data available on the survival (or clinical response) of ECP treatment in patients with CTCL (T_4, M_0) (p7, 1420 PSD, July 2017).	Unchanged.
	Limited applicability of the three single-arm studies to likely benefit of ECP for the requested listing – including the provision of concomitant systematic therapy, proportion of patients with SS, and methoxsalen formulation (oral vs extracorporeal) (p8, 1420 PSD, July 2017).	*Same three single-arm studies in used to compare ECP response rates and survival in indirect treatment comparison with other studies using brentuximab vedotin and vorinostat. Heterogeneity between baseline demographics, disease stage/severity, definitions of key response and survival outcomes limited interpretation of results.*
Comparative safety	No comparative data on the safety of ECP in patients with refractory erythrodermic CTCL (p2, p10, 1420 PSD, July 2017).	Unchanged. Indirect comparison of adverse events and discontinuation rates between ECP, brentuximab vedotin and vorinostat across separate studies. *It was difficult to interpret this indirect comparison due to heterogeneity in patient populations and limited information presented.*
Circumstances of use	ECP treatment regimen not well standardised; The frequency and duration of treatment would impact on cost of providing the MBS service if payable per treatment session (p12, 1420 PSD, July 2017). Co-administration of systemic therapies and impact on outcomes was not addressed. Unclear whether primary study included use of oral methoxsalen.	Sensitivity analysis provided to account for more frequent regimen (Gao et al, 2019) in economic model. *Sensitivity analysis on financial implications shows costs may double using treatment regimen from Alfred* et al, *2017.* *Not considered/addressed* *Gao* et al, *2019 cohort likely included patients treated with oral methoxsalen, however this was not reported. Remains unclear.*
Trial population vs proposed MBS listing	Differences in severity of disease across comparator treatment subgroups in Hughes 2015.	*Not addressed.*

Component	Matter of MSAC concern (July 2017)	How the resubmission addresses it
Economic model	Overly simplistic structure and did not adequately capture cycling through multiple second line treatment options (p13, 1420 PSD, July 2017).	Revised model takes into account treatment cycling through multiple second-line treatments before progression to chemotherapy, *but did not consider disease health states as separate health states in the model.*
	Reconsider the application of utility and disutility weights in the model, with clear rationale (p11-12, 1420 PSD, July 2017).	Separate utility values (based on response rates for each treatment) and disutility values (based on adverse events experienced with each treatment) provided for most treatments. *Concerns remain over utilities/disutilities applied in the model (*i.e. *use of proxies, lack of utilities/disutilities applied to some health states).*
	Time horizon only captured costs for one year but not subsequent years (p3, 1420 PSD, July 2017)	Revised model used a 5-year time horizon to account for treatment cycling through second-line options*. This time horizon was adequate to account for cycling through the treatments included in the revised model.*
	Incorrect use of fees and lack of consideration for capital cost of ECP machine, costs of monitoring and treating adverse events. No sensitivity analysis provided.	*Correct fees used; some consideration of other costs but not all were considered in revised model (e.g. capital costs)* *Multiple sensitivity analysis provided.*

Source: Table 3, pp11-12 of the commentary
CTCL = cutaneous T-cell lymphoma; ECP = extracorporeal photophoresis; MBS = Medicare Benefits Schedule; MSAC = Medical Services Advisory Committee; PBS = Pharmaceutical Benefits Scheme; PSD = public summary document; SS = Sézary Syndrome; TGA = Therapeutic Goods Administration; vs = versus

5. Prerequisites to implementation of any funding advice

The ADAR stated that the original TGA application (Application PM-2016-023228-1-4) for methoxsalen was withdrawn prior to consideration by the TGA Advisory Committee on Medicines (ACM) in September 2017. The TGA delegate cited several concerns with the original TGA application not previously identified by the TGA Clinical Evaluator in relation to the outcomes presented and comparative effectiveness of ECP with other available therapies (outlined in Module 2.5 Clinical Overview Attachment A). The TGA application was subsequently resubmitted and addressed some of the limitations identified including justification for clinical end points and presenting updated data from patients treated at the Victorian Comprehensive Cancer Clinic (VCCC). The application received a positive recommendation by the TGA delegate on 3 September 2019 (Delegates overview, Attachment A).

The relevant part of the registered indication is:

> "UVADEX (methoxsalen) is indicated for use in conjunction with the THERAKOS CELLEX Photopheresis System for the … palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment."

The commentary stated that the system registered on the Australian Register of Therapeutic Goods (ARTG) was the Cellex® (ARTG numbers: 279305, 281849, and 279304).

6. Proposal for public funding

The ADAR updated proposed item descriptor for ECP is shown in Table 2. The updated restriction incorporates the advice of MSAC to: ensure consistent wording with the proposed PBS restriction for methoxsalen; and specify that methoxsalen is used alongside ECP

treatment (MSAC 1420 PSD, July 2017 p4).

Table 2: The proposed MBS restriction for integrated, closed ECP systems for patients with CTCL (in red includes the commentary's minor editing)

Category 3 – Therapeutic procedures
MBS 38xxx INTEGRATED, CLOSED- EXTRACORPOREAL PHOTOPHERESIS SYSTEMS for the ECP treatment of erythrodermic stage III-IVa T_4 M_0 cutaneous T-cell lymphoma (CTCL), if all the following criteria are met: (a) Patient must be aged 18 years and over (b) Patient must be refractory to prior systemic treatment for this condition. A refractory patient is defined as having had disease recurrence while on treatment or experienced intolerance to or toxicity from treatment (c) Treatment must be in combination with injectable methoxsalen (d) Treatment must be under supervision of a consultant haematologist. Caution: Patient must not be pregnant or breastfeeding. Patients and their partners must each be using an effective form of contraception if of child-bearing age. 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: Compiled from Table E2, p14 of ADAR; and Table 2, p10 of the commentary
Abbreviations: MBS = Medicare Benefits Schedule

The commentary stated that the proposed MBS or PBS listings included in the resubmission do not limit the frequency and duration of use for ECP or methoxsalen, and therefore does not preclude claiming of treatment on consecutive days, which would be within recommendations of current ECP treatment guidelines (Alfred et al, 2017; Knobler et al, 2014). The commentary stated there is potential for ECP/methoxsalen to be used twice every two weeks. While the resubmission notes that it is unlikely that clinicians will change their practice, this has potential to double the costs to government over the first five years; further, funding of ECP is likely to encourage use of ECP in more patients, and they may refer to international guidance on treatment regimens. MSAC may wish to consider if a statement regarding limitations to the frequency of claiming is required within the proposed MBS item descriptor.

The applicant's pre-MSAC response clarified that the proposed fee would cover both personnel costs and the cost of the single-use kit[1]:

- Personnel costs: A specialist consultation ($44.35) as it is recommended that ECP is supervised by a haematologist and ECP service supervision ($164). The ECP procedure takes approximately three hours and should be delivered by specially trained, experienced nursing staff.
- Cost of consumables ($**redacted**): The consumable for the ECP procedure is a disposable kit for single use with each procedure (i.e. a consumable). The disposable kit is necessary to perform each service and therefore is appropriate to include within the MBS item fee. The proposed cost of the kit is based on the following:
    - Manufacture and transport of the kit

[1] The applicant stated that the MBS item has been structured to include the cost of the proprietary procedural kit. This is similar to other MBS items with fee structures that include the cost of proprietary materials. For example, MBS fees for diagnostic procedures on the MBS frequently include costs for the use of proprietary single-use diagnostic kits. In addition, the Schedule fees for nuclear medicine imaging services incorporate the costs of proprietary radiopharmaceuticals. Therefore, it is reasonable to include the cost of the procedural kit as this is essential to help ensure patient access to ECP.

- Research and development costs of the ECP technology
- Importantly, the cost of the kit also covers clinical training and support, education and scientific consultation, comprehensive customer service and access to online platforms as outlined below.

The applicant also stated that the proposed item fee does not include: the cost of other consumables (e.g. cannulas, etc.), as it is anticipated that these costs would be covered by current activity-based hospital funding; and capital costs of the ECP machine.

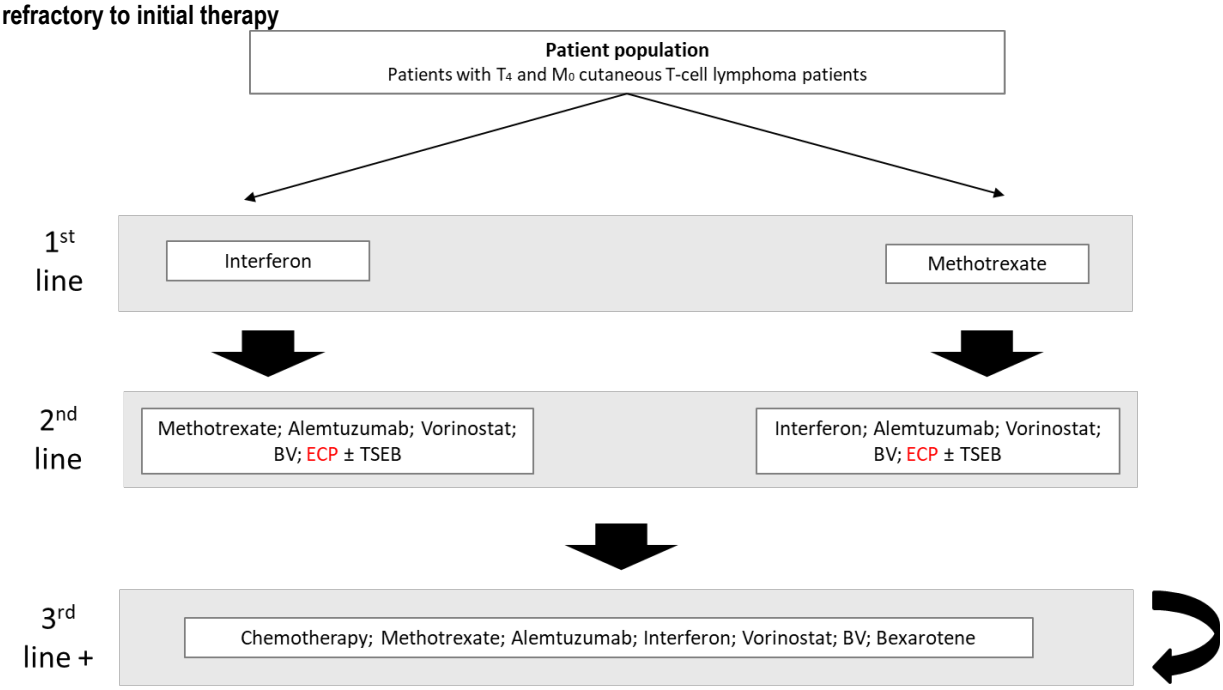
7. Summary of public consultation feedback/consumer Issues

This remained unchanged; see PSD Application No. 1420 2017, p5 for further detail.

8. Proposed intervention's place in clinical management

The ADAR stated that the proposed clinical treatment algorithm (Figure 1) was updated to include vorinostat and brentuximab vedotin as second- and third-line treatment options which is consistent with their PBS listings, and MSAC advice from July 2017.

Figure 1: Proposed clinical management algorithm in T4 and M0 cutaneous T-cell lymphoma patients that are refractory to initial therapy



Source: Figure E3, p20 of the ADAR
Abbreviations: BV = brentuximab vedotin; ECP = extracorporeal photopheresis; TSEB = total skin electron beam therapy

The commentary stated that the resubmission did not consider ECP given in combination with another systematic therapy, which might occur where patients have achieved small but inadequate response to ECP monotherapy. Combination systematic therapies are recommended in the 2017 National Comprehensive Cancer Network (NCCN) guidelines for MF/SS.

9. Comparator

The resubmission nominated second-line treatments methotrexate (46%), interferon-α (32%), vorinostat (13%) and brentuximab vedotin (9%) as comparators. The comparators had been revised since the July 2017 MSAC consideration; including removal of alemtuzumab (as

requested by MSAC), and addition of vorinostat (as requested by MSAC) and brentuximab vedotin (recently listed on PBS, for CD30-positive patients only given its mode of action).

ESC previously noted interferon-α2b is not considered to have established cost-effectiveness for treatment of patients with CTCL in the Australian setting. While the resubmission noted it is TGA approved for CTCL, it is not PBS listed for this indication; and in the absence of cost-effectiveness in the Australian setting, inclusion of interferon-α as a comparator in the resubmission may not be appropriate.

The applicant's pre-MSAC response noted that the estimated proportions for vorinostat and brentuximab vedotin were based on PBS utilisation data available at the time of submission (covering April 2019 to June 2019). Based on extending the period of data from April 2019 to January 2020, which the proportion of use of brentuximab vedotin would increase to 11%, and the proportion of use of vorinostat would reduce to 11% (see also Table 11).

10. Comparative safety

For primary evidence, the resubmission presented an updated analysis of the Victorian Comprehensive Cancer Centre (VCCC[2]) (Gao et al. 2019) data previously presented to MSAC (Hughes et al. 2015). The resubmission stated this updated retrospective analysis is considered to have high external validity, providing a comprehensive analysis comparing 65 patients with a diagnosis of MF or SS with blood involvement treated with ECP with other systemic treatment for CTCL over 21 years (1997 to January 2018). However, the resubmission acknowledged the study has low internal validity.

For supportive evidence for ECP, the resubmission included three other single-arm studies (Arulogun et al. 2008 [subpopulation with SS in VCCC database]; Knobler et al. 2012; Siakantaris et al. 2012), which were previously considered in the previous submission. However, the commentary highlighted that MSAC previously considered these studies to have several limitations regarding their applicability to estimating the likely benefit of ECP in the proposed population due to heterogeneity in study populations, the use of concomitant systemic therapy, and use of oral (not extracorporeal) methoxsalen (PSD Application No. 1420 2017, p8).

Due to a lack of direct evidence comparing ECP to vorinostat and brentuximab vedotin in the primary study (Gao et al. 2019), the resubmission included a naïve indirect treatment comparison with additional comparator studies.

Comparator studies consisted of one randomised controlled trial (RCT) (Prince et al. 2017) and two single-arm studies (Duvic et al. 2015; Kim et al. 2015) for brentuximab vedotin, and three single-arm studies for vorinostat (Duvic et al. 2009; Duvic et al. 2007; Olsen et al. 2007). Overall, the risk of bias in the studies was considered high by the commentary, due to single-arm design (most studies), heterogeneity in patient and disease characteristics (including CTCL subtype, stage and severity, CD30-positive disease), small sample sizes and lack of blinding. However, this high risk of bias should be contextualised in terms of the rarity of this condition, noting its TGA orphan drug designation and the challenges involved in conducting RCTs in patients with rare cancers.

The VCCC database **redacted.** From this, the resubmission considered ECP was **redacted**.

Table 3: redacted

[2] Two publications of the VCCC study were presented in the resubmission: Prince 2018 (is a pre-publication report used as primary evidence in the ECP TGA dossier); and publication by Gao et al 2019.

The resubmission stated that, compared with ECP, adverse events (AEs) for vorinostat and brentuximab vedotin were considerably more common and resulted in a greater number of treatment discontinuations. For vorinostat, discontinuations due to AEs were between 9-19% (Table 4). Notably, vorinostat was associated with pulmonary embolism, deep vein thrombosis and thrombocytopenia. In addition to these events being associated with considerable mortality and morbidity risk, the PBAC was concerned about the potential implications in patients receiving subsequent treatment agents that induce thrombocytopenia (Vorinostat PBAC PSD November 2016, para 6.20).

AEs with brentuximab vedotin were extremely common. Ninety-five percent of patients experienced an AE, 24% discontinued treatment due to an AE and 14% had a serious drug-related AE (see Table 4). The PBAC considered that brentuximab vedotin may have an inferior safety profile compared with methotrexate (Brentuximab vedotin PBAC PSD, July 2018, para 6.20).

Table 4: Summary of key adverse events in the comparator studies

Drug	Brentuximab vedotin	Vorinostat	
Study	Prince 2017 n/N (%)	Duvic 2007 n/N (%)	Olsen 2007 n/N (%)
Any adverse event	63/66 (95%)	NR	NR
Drug-related adverse event	57/66 (86%)	NR	NR
Drug-related serious adverse event	9/66 (14%)	NR	8/74 (11%)
Adverse event resulting in discontinuation	16/66 (24%)[ab]	7/37 (19%)	7/74 (9%)
On treatment deaths	4/66 (6%)[c]	2/37 (5%)[e]	3/74 (4%)[d]

Source: Prince 2017, Table S3, appendix page 19; Duvic 2007, in text page 35; Olsen 2007 in text page 3111

The resubmission did not present any new evidence relating to the safety of interferon-α or methotrexate, as MSAC has previously accepted that ECP "appears to be associated with fewer adverse events than interferon-α2b … 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" (PSD Application No. 1420, 2017, p2).

11. Comparative effectiveness

The key clinical outcome reported in Gao et al. 2019 was time to next treatment (TTNT), which was considered to be a proxy for quality of life. The resubmission stated that the median TTNT when ECP was used alone was 14 months; significantly greater than interferon-α (8 months, $p = 0.0067$), vorinostat (4 months, $p < 0.0011$), antibody/ ADC/FT/bexarotene vedotin therapy ($n = 20$; 6.5 months, $p = 0.028$), chemotherapy (3 months, $p < 0.0001$), and low-dose methotrexate ($n = 35$; 2.5 months, $p<0.0001$). Compared to biological agents including brentuximab vedotin (n=1 of 20), TTNT was also considerably greater ($n = 20$, 7 months, p-value not reported). Median overall time on treatment followed the same trend. ECP had the longest time on treatment compared to interferon-α (8 months), methotrexate (2.5 months), and vorinostat (4 months). However, the commentary noted TTNT data for ECP was provided across multiple treatment lines (e.g. lines 1-3 and above), including patients who received ECP monotherapy and in combination systemic therapies as first-line treatment, which are outside the requested ECP listing.

Table 5: redacted

Results for clinical response and survival outcomes are presented in Table 6. The results showed generally that the overall response rate was similar between those treated with ECP and brentuximab vedotin, and lower response rates were observed among the vorinostat studies. The resubmission noted that:

- median progression-free survival (PFS) was greater for ECP compared to brentuximab vedotin and vorinostat; however, the commentary considered this has similar issues as TTNT, in that it can take up to 10 months to receive a response so PFS would include this pre-response time); and
- brentuximab vedotin had superior OS (albeit reported in a phase II, unrandomised, single-centre trial).

However, the commentary considered it was difficult to compare response, PFS and overall survival OS across studies due to: heterogeneity in key patient baseline characteristics and prognostic factors (e.g. inclusion of LyP and pc-ALCL and requirement for CD30-positive disease in brentuximab vedotin studies); and heterogeneity in the outcome measures (e.g. OS from the date of diagnosis rather than the date of first dose; PFS *vs.* time to disease progression [TTP] in place of PFS). However, the commentary stated it should be noted that no therapies for CTCL have been demonstrated to have a survival benefit in isolation, and all long-term outcomes are confounded by multiple lines of treatment.

Table 6: Results of naïve comparison of ECP, brentuximab vedotin and vorinostat: clinical response and survival

	ECP n/N (%)				BV n/N (%)			Vorinostat n/N (%)		
	Gao *et al*, 2019	**Arulogun *et al*, 2008**	**Knobler *et al*, 2012**	**Siakantaris *et al*, 2012**	**Prince *et al*, 2017**	**Duvic *et al*, 2015**	**Kim *et al*, 2015**	**Olsen *et al*, 2007**	**Duvic *et al*, 2009**	**Duvic *et al*, 2007**
ORR	NR	8/13 (62%)[a,b]	29/39 (74%)[c]	11/18 (61%)	43/64 (67%)	All patients: 35/48 (73%) All CTCL: 26/39 (67%) MF only: 15/28 (54%)	21/30 (70%) Grade IV/SS: 4/10 (40%)	22/74 (30%)		8/33 (24%)
PFS	NR	28 m (med)	NR	28 m (med)	16.7 m (med)	13.2 m (med)[d]	6 m: 79% 12 m: (54%)	4.9 m (med TTP[e])		12.1 w (med TTP[e])
OS	80 or 120 m[f]	NR	NR	NR	NR	176 m[g]	NR	NR		NR

Source: Table 56, p127 and Table 58, p128 and Table 60, p129 and Table 63, p131 and Table 65, p134 of the resubmission
BV = brentuximab vedotin; CTCL = cutaneous T-cell lymphoma; m = months; med = median; MF = mycosis fungoides; NR = not reported; ORR = overall response rate; SS = Sézary Syndrome; TTP = time to disease progression; w = weeks
[a] Of the patients that responded (complete and partial), 88% were on concomitant systematic treatments
[b] 100% of patients had SS
[c] ORR for Knobler *et al,* 2012 includes near-complete response (defined as ≥90% skin response for at least 4 weeks duration) rather than complete (100%) response
[d] Includes whole cohort of patients, as subgroup analysis for patients with CTCL only was not presented in Duvic *et al,* 2015.
[e] PFS was not reported in any of the vorinostat trials, however, did report time to disease progression (TTP) defined as time from start of treatment until date of progressed disease. The resubmission considered TTP as a near equivalent measure to PFS, however it does not count patients who die from other causes
[f] Gao *et al, 2019* reported OS from first treatment (80 months) and OS from diagnosis (120 months)
[g] Duvic *et al,* 2015 reported OS from first dose was not reached, and OS from diagnosis as 176 months (14.7) years

The commentary also considered there is potential use for ECP in patients with relapsed/refractory CTCL who received brentuximab vedotin and subsequently lose expression of CD30 (Goyal et al, 2019), rendering them unable to receive either repeat treatment with brentuximab vedotin or experimental anti-CD30 treatments, including chimeric antigen receptor T cell (CAR-T) therapies directed against CD30.

Clinical claim

On the basis of the benefits and harms reported in the evidence base, the resubmission proposed that ECP has at least non-inferior efficacy and superior safety compared to

vorinostat or brentuximab vedotin for the treatment of refractory erythrodermic (Stage T_4 M_0) CTCL.

Translation issues
The commentary summarised the translation issues (Table 7).

Table 7: Summary of results of pre-modelling studies and their uses in the economic evaluation

Premodelling study	Results	Use in economic evaluation
Applicability		
Clinical trial data		
Comparability of trial population vs MBS/PBS listing	*The VCCC database* *Cohort: T_4 = 91%, M_0 = 97%* *Stage III or IVa = 86%* *Stage T_4M_0 per treatment group = unknown* *46% had prior use of systemic therapies* *Arulogan et al, 2008* *Cohort: SS only* *Stage/severity: Not reported*	*Individual monotherapy TTNT data for ECP and each treatment applied as transition probability and time in each health state.* *For ECP: A large proportion of the total cohort received ECP first-line (46%); only 3% of patients received ECP monotherapy at line 2.* *For comparators: Disease severity unclear in each treatment group.* *ECP response rates applied to ECP utilities within model. Only 23% of patients received ECP monotherapy and 77% of patients in this cohort received ECP in combination with another therapy.*
Circumstances of use *ECP regimen*	*ECP use in Australian practice:* *Once weekly for 6 weeks* *Fortnightly for 6 sessions* *Monthly thereafter*	*Not used. ECP regimen applied in model:* *2 sessions/month for 6 months* *Every 6 weeks thereafter* *SA: Australian regimen from Gao* et al, *2019*
Co-administered therapies	*77% of patients in Arulogun* et al, *2008 used co-administered therapies*	*The resubmission did not address whether the use of co-administered systemic therapies improved treatment outcomes.*
Usual therapy for CTCL		
2nd line	Australian survey (n-20) utilisation: Weighted utilisation [b] Methotrexate = 46% Interferon-α = 32% ~~Alemtuzumab = 22%~~ (*Alemtuzumab removed as a comparator in the resubmission; its proportion reassigned to brentuximab vedotin and vorinostat, based on PBS prescriptions in Apr-Jun 2019*)	*Base case: Weighting applied to 5-year CUA to generate a weighted ICER.*
TTNT as surrogate for progression free survival and QOL measure	*Decision to switch therapy is based on clinical basis. Methods used to assess skin response were not provided in Hughes et al, 2015.* TTNT can be used as a measure of treatment effectiveness and durability of response, indirectly effects QOL.	*The results of TTNT might not be applicable to the proposed population for ECP in Australia, due to continuing treatment with methoxsalen is based on skin response.* *Transition probabilities and time in each health state. Approach consistent with advice from MSAC in July 2017.*

Premodelling study	Results	Use in economic evaluation
Transformation		
Utility values for disease severity	Literature review performed. Values based on: Psoriasis utilities (TTO and SG) *(further justification provided for mapping psoriasis severity utilities to CTCL)* Weighted response rates [c] *(now calculated individually for each treatment based on response rates, as below)*	*Utilities: base case (TTO)* *ECP = 0.73 (0.06 monthly); vorinostat = 0.65 (0.05 monthly); brentuximab vedotin = 0.73 (0.06 monthly); interferon-α = 0.70 (0.06 monthly); methotrexate = 0.62 (0.05 monthly).* *Use of psoriasis health state utilities accepted by MSAC in July 2017. Psoriasis has similar disease manifestations, response rates associated with similar QOL vs CTCL.*
Finding appropriate utility values for each treatment	*Now presented using response rates (CR, PR, NR) for each treatment.* *Disutility assigned to each treatment based on selected AEs*	*Concerns regarding utilities assigned to interferon-α, methotrexate; disutilities applied to interferon-α, vorinostat and methotrexate.* *No disutility applied to ECP (not appropriate)* *No utility or disutility applied to gemcitabine or no treatment (assigned value for severe psoriasis = 0.59 (0.05 monthly). This was not appropriate.*
Other costs associated with treatment	*ECP: venous access*	*Not included. Expert opinion stated most patients treated with ECP would require venous catheter.*

Source: Table 81, p161 and pp149-161 of the resubmission
CR = complete response; CUA = cost utility analysis; ECP = extracorporeal photopheresis; HDACi = Histone deacetylase inhibitor; ICER = incremental cost effectiveness ratio; KM = Kaplan Meier; LOCF = last observation carried forward; MBS = Medicare Benefits Schedule; NR = no response; Pts = patients; PR = partial response; PBS = Pharmaceutical Benefits Scheme; QOL = quality of life; SA = sensitivity analysis; SG = standard gamble; SS = Sézary Syndrome; TSEB = total skin electron beam; TTNT = time to next treatment; TTO = time trade-off; Tx = treatment; vs = versus; VCCC = Victorian Comprehensive Cancer Clinic; Yr = year; Grey text = presented in submission to July 2017 MSAC

12. Economic evaluation

Brentuximab vedotin has a special pricing arrangement, and all analyses presented in this section are based on the published price of brentuximab vedotin. An alternative analysis using the effective price of brentuximab vedotin was presented in the Committee in Confidence section, which shifted the result from dominant to a moderately high ICER.

The stepped economic evaluation is summarised in Table 8; the base case is a cost-utility analysis (Step 3) now modelled over a five year time horizon to allow patients to cycle through multiple lines of therapy (including methotrexate, interferon-α, vorinostat and brentuximab vedotin), before switching to chemotherapy.

Table 8: Summary of the economic evaluation

	Step 1	Step 2	Step 3
Perspective	Australian Government	Australian Government	Australian Government
Comparators	Methotrexate Interferon-α Vorinostat Brentuximab vedotin	Methotrexate Interferon-α Vorinostat Brentuximab vedotin	Methotrexate Interferon-α Vorinostat Brentuximab vedotin
Type of economic evaluation	Cost per responder	Cost-utility analysis	Cost-utility analysis
Key sources of evidence	Responder analysis	TTNT analysis	TTNT analysis
Time horizon	6 months	6 months	5 years
Outcomes	Responder	QALYs	QALYs
Methods used to generate results	Markov model	Markov model	Markov model
Health states	Complete, partial and non-responder	ECP Methotrexate Interferon-α Vorinostat Brentuximab vedotin Dead	ECP Methotrexate Interferon-α Vorinostat Brentuximab vedotin Chemotherapy No treatment Dead
Cycle length	Not applicable	1 month	1 month
Discount rate	Not applicable	Not applicable	5% per annum costs and QALYs

Source: Table 84, p165 of the resubmission
ECP = extracorporeal photopheresis; QALY = quality-adjusted life year; TTNT = time to next treatment

For the base case (Step 3), including ECP as a second-line treatment option for CTCL dominated over other treatment strategies, including the weighted comparator (46% methotrexate; 32% interferon-α; 13% vorinostat; and 9% brentuximab vedotin) (Table 9).

Table 9: Incremental costs and effectiveness

	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
Step 1 (cost per responder – 6-month time horizon)					
ECP	$25,087.29	-	62%	-	-
Methotrexate	$74.02	$25,013.27	16%	45%	$55,324.49
Interferon-α	$6,924.96	$18,162.33	53%	8%	$215,232.68
Vorinostat	$23,843.56	$1,243.73	30%	32%	$3,910.02
Brentuximab vedotin	$109,048.53	-$83,961.24	40%	22%	Dominant
Step 2 (cost per QALY – no treatment cycling – 6-month time horizon)					
ECP	$25,087.29	-	0.37	-	-
Methotrexate	$74.02	$25,013.27	0.26	0.11	$233,061.36
Interferon-α	$6,924.96	$18,162.33	0.25	0.12	$152,320.32
Vorinostat	$23,843.56	$1,243.73	0.28	0.09	$14,536.16
Brentuximab vedotin	$109,048.53	-$83,961.24	0.26	0.11	Dominant
Step 3 (cost per QALY – cycling of treatments, 5-year time horizon)					
ECP	$145,514.36	-	2.33	-	-
Methotrexate	$166,738.81	-$21,224.45	2.12	0.21	Dominant
Interferon-α	$183,484.99	-$37,970.64	2.14	0.20	Dominant
Vorinostat	$181,277.88	-$35,763.52	2.14	0.20	Dominant
Brentuximab vedotin	$268,057.48	-$122,543.12	2.13	0.20	Dominant
Weighted comparator	$183,106.35	-$37,591.99	2.13	0.20	Dominant

Source: Stepped analyses sheet, CTCL_ECP model calculations.xlsx workbook
Abbreviations: ECP = extracorporeal photopheresis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year

The resubmission stated the dominance occurred as ECP displaced expensive pharmaceutical therapies (i.e. a greater proportion of patients avoided subsequent treatment with the high-cost treatment options vorinostat and brentuximab vedotin). In addition, ECP is associated with an incremental quality-adjusted life year (QALY) gain of between 0.20 and 0.21 due to ECP being associated with a longer TTNT compared with comparator treatments. Thus, the resubmission considered it is reasonable that patients treated with ECP can better tolerate treatment, remain in the ECP health state for a longer period and have a higher quality of life compared with comparator treatments.

Using the weighted comparator for the base case, the resubmission's sensitivity analyses indicated that most analyses were low impact and ECP remained the dominant strategy. However, the commentary stated the key driver of the dominance of ECP in the resubmission's sensitivity analyses was the cost of brentuximab vedotin, which was based on the published price of brentuximab vedotin. The commentary stated that the modelled results were also sensitive to use of a two consecutive-day treatment regimen (as per Alfred et al, 2017) which had a high impact on the ICER, with results indicating methotrexate was more cost effective than ECP (Table 10). However, in the pre-ESC response, the applicant stated that doubling the dosage regimen is not reflective of Australian or international practice and this assumption is incorrect.

Table 10: Key results of sensitivity analysis (italicised represents the commentary's additional sensitivity analyses)

Description	Incremental cost	Incremental QALY	ICER/QALY	Impact
1. Base case	**-$37,591.99**	**0.20**	**Dominant**	**-**
2. Discount rate 3.5%	-$37,892.89	0.21	Dominant	Low impact - favours comparator
3. The VCCC database ECP treatment regimen	-$31,642.42	0.20	Dominant	Low impact - favours ECP
4. Assume no disutility associated with treatment	-$37,591.99	0.17	Dominant	Low impact - favours ECP
5. Use vorinostat TTNT for brentuximab vedotin	-$27,506.72	0.21	Dominant	Low impact - favours ECP
6. Monthly cost of brentuximab vedotin discounted by 50%	-$3,644.89	0.20	Dominant	Moderate impact - favours ECP
7. ECP regimen: 2 consecutive episodes of ECP per treatment (Alfred 2017)[a] - ***methotrexate becomes most cost-effective***	*$42,870.73*	*0.20*	*$209,376.28*	**High impact** – favours ECP
8. Combining #6, #10, #12 - ***methotrexate becomes most cost-effective***	*-$3,644.88*	*0.01*	*Dominant*	*Moderate impact – favours* ECP
9. Combining #6, #10, #11, #12 - ***methotrexate becomes most cost-effective***	*-$1,263.16*	*0.01*	*Dominant*	*Moderate impact – favours* ECP
10. ECP utility adjusted for median time to response (10 months) [b]	*-$37,591.99*	*0.015*	*Dominant*	*Low impact - favours* ECP
11. ECP cost adjusted to include capital cost of machine (per patient, applied once) [c]	-$35,551.18	0.20	*Dominant*	*Low impact – favours* ECP
12. ECP disutility applied (for pulmonary embolism, applied for one month) [d]	*-$37,591.99*	*0.20*	*Dominant*	*Low impact – favours* ECP
13. Proportion of CD30+ patients reduced to 20% (base case = 80%) – ***methotrexate becomes most cost-effective***	*-$2,274.33*	*0.21*	*Dominant*	*Moderate impact – favours* ECP

ECP = extracorporeal photopheresis; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life year; TTNT = time to next treatment; VCCC = Victorian Comprehensive Cancer Clinic

Source: Table 118, p199 of the resubmission; CTCL_ECP model calculations.xlsx workbook; *and added during the evaluation.*

[a] Monthly cost of ECP adjusted to account for 2-consecutive day regimen as per Alfred *et al,* 2017 (consisting of two episodes of ECP treatment every 2-4 weeks (average = 3 weeks; which is 2.89 sessions per month) and continuing on same frequency for those with complete, partial or minimal response resulted in a monthly cost of $**redacted**.

[b] ECP utility recalculated to account for 10 month median time to response for ECP in Arulogan *et al,* 2008; Non-responder utility (0.59) applied for 10/12 months (0.83 of a year) plus the original ECP utility (0.73) accounting for CR/PR/NR applied for remaining 2/12 months (0.17 of a year) = 0.613 (yearly utility); applied to model per month (0.613/12 = 0.051).

[c] ECP monthly cost recalculated to include capital cost of ECP machine (additional cost of $**redacted** per patient, added as a one-off cost in the first cycle of treatment)

[d] ECP disutility adjusted to account for incidence of pulmonary embolism in VCCC cohort, following TGA warning regarding use of Therakos Cellex ECP device and the risk of thromboembolism in February 2018 (see Section B.7). Based on data in the resubmission, the incidence of PE on treatment with Therakos Cellex was 2.2% (1 patient experienced PE on treatment, out of a total of 46 patients treated with this device, as per Table 7, p11 in Prince *et al,* 2019). Combined with the PE disutility sourced from DeJong *et al,* 2017 (-0.32), provides a disutility of -0.007 over 1 year and 0.001 per month; applied for the first cycle of treatment only.

The applicant's pre-MSAC response provided updated PBS prescribing data (April 2019-January 2020) for the proportional use of vorinostat and brentuximab vedotin, indicating the proportion of patients initiating brentuximab vedotin as a second-line treatment used in the weighted comparison presented in the resubmission of 9% is likely conservative (Table 11).

Table 11: Updated proportional utilisation of vorinostat and brentuximab vedotin from April 2019 to January 2020, provided in the applicant's pre-MSAC response

Prescribing period	Medicine	PBS items	Scripts	Total scripts	%	Adjusted % [a]
April 2019–June 2019	Vorinostat	11138F, 11141J	39	67	58%	13%
	Brentuximab vedotin	11651F, 11660Q, 11661R, 11664X	28		42%	9%
April 2019–January 2020	Vorinostat	11138F, 11141J	128	267	48%	11%
	Brentuximab vedotin	11651F, 11660Q, 11661R, 11664X	139		52%	11%

Source: Table 1, p3 of pre-MSAC response
[a] adjusted for brentuximab vedotin and vorinostat having a total second-line treatment market share of 22%

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of listing ECP and methoxsalen on the MBS and PBS/RPBS, respectively (Table 12).

Table 12: Estimated use and financial implications

	2020	2021	2022	2023	2024
ECP					
Eligible population T_4 M_0 CTCL [a]	406	339	251	165	96
Patients treated [b]	81	102	100	83	58
MBS services [c]	1,458	1,836	1,800	1,494	1,044
Cost to MBS (85% rebate) [d]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Methoxsalen					
Number of doses	1,458	1,836	1,800	1,494	1,044
Net cost to PBS and RPBS [e]	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**
Net cost to governments	**$redacted**	**$redacted**	**$redacted**	**$redacted**	**$redacted**

Source: Section_E1420.1.xlsx workbook; Table 121, p204; Table 133, p208; Table 125, p205 and Table 129, p207 of the resubmission and *calculated during the evaluation*
CTCL = cutaneous T-cell lymphoma; ECP = extracorporeal photopheresis; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme; RPBS = Repatriation Pharmaceutical Benefits Scheme
[a] The resubmission subtracted the number of prevalent patients treated per year from the prevalent pool of patients with T_4M_0 CTCL.
[b] Uptake rate was assumed to be 20% in Year 1 increasing to 60% in Year 5
[c] The resubmission assumed that patients receiving ECP would only receive one year of treatment, using the modelled ECP regimen based on number of treatments in 14 months.
[d] Number of services x cost of ECP ($**redacted**)
[e] Number of doses x DPMQ of methoxsalen ($**redacted**)

The commentary stated that there was potential for the net cost per year to the MBS and PBS to be greater or less than estimated in the resubmission:

- uptake may be lower if there are delays in the provision of ECP (reduce net costs);
- uptake may be lower if ECP is not provided through many clinics (reduce net costs);
- utilisation may be higher or lower due to lack of robust prevalence data for CTCL (increase or decrease net costs);
- there is potential for ECP and methoxsalen to be used outside of the proposed restriction as a first line treatment (potential for this is high, based on the high proportion of patients in Gao et al, 2019 receiving ECP as first line treatment) (increase net costs); and
- there is potential for ECP and methoxsalen to be used as combination therapy with other systemic treatments (potential also high based on high proportion of patients receiving concomitant systemic treatments in Gao et al, 2019) (increased net costs).

14. Key issues from ESC for MSAC

Table 13: Summary of key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Limited evidence for ECP and comparators	The resubmission includes new comparators – vorinostat and brentuximab vedotin. ESC advised that the studies included are predominately non-randomised studies of small populations such that ESC could not make direct comparisons, leading to continuing uncertainty about comparative effectiveness and safety. ESC considered that ECP is still likely safer than, and at least as effective as, other treatments for stage T4, M0 CTCL. ESC also noted that the evidence is unlikely to improve because this is a rare condition. The stated proportional use of vorinostat and brentuximab vedotin at 13% and 9% respectively, should be confirmed by the applicant as reflecting current usage estimates.
The proposed item fee has not been justified in the resubmission or the pre-ESC response	ESC suggested that the fee needs to be categorised and justified in defining both the personnel costs, as well as the cost of any consumables. ESC noted that what is described by the applicant as 'consumables' is in fact the medical device (i.e. the proprietary procedural kit supplied by the sponsor). Clarity regarding the cost of the procedural kit versus other consumables would be helpful.
MBS descriptor now aligns with the PBS restriction of methoxsalen	ESC suggested that the Department's changes be accepted, which is to address the frequency of treatment issue (i.e. limit the ECP claim to once per cycle of therapy, which may occur over consecutive days). ESC also considered it appropriate to limit the service to hospital only. However, given the anticipated use of ECP to be only delivered in public hospital settings due to the initial expense of the equipment and expertise required, the PBS is then not the appropriate funding mechanism for methoxsalen if patients are admitted for treatment. Rather, medicines used for treatment of public inpatients are funded under the National Health Reform Agreement.
Revised ICERs in the resubmission	ESC considered that the modelled ICER in the resubmission is lower and more certain than the previous submission. Even when the effective price of brentuximab vedotin is used, the weighted ICER is lower than in the previous submission. Given the impact of the brentuximab vedotin price, greater justification for the proposed weighting of brentuximab vedotin and other therapies in the group of comparators is warranted.
Uncertainty about the ECP treatment regimen (number of cycles per patient)	This has not been addressed in the ADAR or in the pre-ESC response. ESC queried whether the risk of higher-than-expected patient use could be mitigated by limiting the total number of cycles permitted per patient (either in the MBS item descriptor or in the PBS restriction for methoxsalen).

ESC discussion

ESC noted that MSAC previously deferred its advice regarding ECP to treat CTCL patients, and recommended that a new economic model be submitted including vorinostat as a comparator. The resubmission included both vorinostat and brentuximab vedotin as comparators.

ESC noted that the new proposed item descriptor addressed the following requests from MSAC from the previous submission:

- The item descriptor now aligns with the proposed PBS restriction of methoxsalen.
- A mechanism is now in place to restrict ECP to second-line use.
- Wording is included in the descriptor to limit use to trained professionals.

- ECP is to be used with methoxsalen.

However, ESC noted the following changes to the item descriptor have not been included in the resubmission:

- no statement that ECP is not to be used concurrently with other systemic CTCL treatments
- no information on the source of referral and accreditation of specialists providing the service
- no reduction in fee.

ESC discussed the practicality of limiting each cycle of ECP to a single treatment, as ECP is a 1–2 day treatment, and other systemic treatments can start afterwards or between cycles. The current PBS listings prevent concurrent use with other PBS-listed treatments, which ESC considered to be a reasonable option to prevent concurrent use with other medicines. However, ECP is often used with concurrent therapies in trials, in clinical practice and as recommended by the NCCN guidelines, as are many of the comparators. ESC was concerned that the ADAR and pre-ESC response did not address this.

ESC supported the Department's suggested wording changes to the descriptor, but recommended that the frequency be limited to once per cycle which addresses the commentary's concern regarding the potential for double claiming of the MBS item if treatment is administered over 2 days. ESC agreed that the procedure should be an overnight procedure (type A). This also addresses the commentary's concern regarding the item number being billed twice per week. ESC noted the lack of consensus regarding the optimal ECP protocol in the literature (which affects costing), but the literature does support the claim that ECP will not be billed more than once per week in any case.

ESC queried including the cost of consumables ($**redacted**) and considered that this was actually the cost of the device, which is a procedural kit. ESC considered this to be unacceptable. ESC also queried whether the $**redacted** included initial training costs, and requested that the applicant present a detailed cost breakdown of the proposed service. The associated PBS listing of methoxsalen would enable subsidised treatment of patients in the community (out of scope of ECP), private hospital inpatients (very likely out of scope of ECP) and public hospital outpatients - likely in scope for ECP for some, but not all patients, as some will require management of adverse effects of the procedure or require overnight monitoring.

ESC expressed some concern about using ECP as a second-line treatment in the clinical algorithm, as the NCCN guidelines recommend using it as a first-line treatment option. ESC queried how using ECP as first-line treatment would affect the economic outcomes.

ESC noted the addition of the Gao et al. (2018) study in the resubmission, which reflects a more contemporary cohort, but still comprises few patients. Comparator studies also comprise case series data, and ESC considered that the limitations and differences among all the study data make it difficult to assess comparative safety.

ESC accepted the use of TTNT as a primary outcome measure, but noted that ECP is given for at least 6 months before clinicians decide whether to continue. Consequently, the TTNT endpoint inherently favours ECP. ESC acknowledged that using TTNT to derive survival curves for each treatment is not ideal, but it is preferable to the method used in the previous submission (describing median TTNT). Due to this 6-month lead time, ESC considered it

may be more appropriate to have two MBS items: one for initial treatment and one for continued use after confirmed response to initial treatment. This would be consistent with the proposed PBS listing for methoxsalen.

ESC considered that the weighted comparators (46% methotrexate, 32% interferon-α, 13% vorinostat, 9% brentuximab vedotin) were mostly valid, but noted there was no justification for the vorinostat/brentuximab vedotin split. Justification of the vorinostat/brentuximab vedotin proportional split is required given that inclusion of the relatively higher cost brentuximab vedotin in the comparator arms favours ECP. ESC agreed with the pre-ESC response that vorinostat and brentuximab vedotin should be included, and that it was acceptable to include interferon-α (as previously advised by MSAC).

ESC noted the commentary's query regarding the ADAR using health states that are not based on disease status, but agreed with the pre-ESC response that defining health states by treatment allows modelling of multiple pathways of care in the comparator arm and displacement of therapies by ECP, which aligns with previous MSAC advice. However, ESC considered that the applicant needs to better justify the choice of specific treatment sequences in each comparator arm.

ESC noted the commentary's discussion regarding sources and derivation of utility weights, and considered that the higher utility weight for ECP (0.73) compared with the other treatments (0.59–0.68) is driving the modelled QALY gain. However, given the limited evidence for other CTCL treatments, ESC considered it reasonable to test the model with additional sensitivity analyses to glean more information regarding the robustness of the ICERs.

ESC noted that the applicant used the effective price (not published price) of brentuximab vedotin, which impacts the ICER for each modelled arm, as the applicant does not have access to the effective price. The weighted ICER with the brentuximab vedotin effective price is $**redacted** per QALY, compared with ~$150,000 per QALY in the previous submission.

ESC noted the differing treatment regimens proposed in the previous submission and the resubmission, and recognised the risk of the total cost per patient being higher than $**redacted**. The recommended regimen in the National Comprehensive Cancer Network guidelines would result in 21 cycles over 14 months (see Table 7 in the commentary). Increasing costs per patient could be mitigated by limiting the number of cycles permitted (either in the MBS item descriptor or in the PBS restriction for methoxsalen). However, ESC queried the rationale for stopping a treatment after 18 cycles if it is continuing to be effective, and noted that the potential for patients receiving more than 18 cycles has not been accounted for in the financial impacts.

ESC noted that the pre-ESC response stated that peginterferon-α2a now has an unrestricted PBS listing, which could affect the economic model (which includes the non-pegylated cost). ESC recommended that the equi-effective dose of non-pegylated interferon-α2a versus peginterferon-α2a be investigated and incorporated in the economic model.

The commentary expressed concern about leakage to the graft-versus-host disease (GVHD) population, but ESC considered that the detailed MBS item descriptor will mitigate this. ESC noted that the applicant has stated it will be submitting a separate MSAC application for ECP in the GVHD population.

ESC noted some uncertainty in the financial impact, in that all services are attributable to the one year of treatment. ESC considered that, in reality, patients will be staggered for treatment over >12 months and that treatment duration will be longer than 12 months.

ESC noted the applicant proposed a sponsor-led support program to ensure quality, system installation, repair and training for new services. However, the applicant included few details about such a program, and ESC requested that more detail be sought about this.

ESC discussed the general issue of funding ECP through the MBS, as the service already has an AR-DRG code. ECP is currently delivered for CTCL at one centre in Melbourne, which the Victorian Government partially funds. ESC noted it was unlikely that this service would be available in private hospitals. ESC also noted the likely ongoing access issue for patients, as this service would only be available in major cities if approved for listing on the MBS.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

Mallinckrodt pharmaceuticals welcomes the decision of MSAC. We will continue our efforts to help with Australia's unmet medical needs for ECP treatment.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website:
visit the MSAC website