



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application 1651 – Integrated, closed-system, extracorporeal photopheresis systems for the treatment of chronic graft-versus-host disease

Applicant: Mallinckrodt Pharmaceuticals and Terumo BCT Australia Pty Limited

Date of MSAC consideration: 82nd MSAC Meeting, 29-30 July 2021

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

1. Purpose of application

A codependent application requesting Medicare Benefits Schedule (MBS) listing of the integrated, closed extracorporeal photopheresis (ECP) system and Pharmaceutical Benefits Scheme (PBS) listing of the drug methoxsalen (UVADEX®) to treat patients with chronic graft versus host disease (cGVHD) who are steroid-dependent and/or steroid-intolerant and/or steroid-refractory (herein referred to as treatment refractory cGVHD) was received from Mallinckrodt by the Department of Health in February 2021.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to comparative safety, clinical effectiveness and cost-effectiveness, MSAC supported the creation of new Medicare Benefits Schedule (MBS) items for integrated, closed-system, extracorporeal photopheresis (ECP) systems in the treatment of chronic graft-versus-host disease (cGVHD). MSAC considered the uncertainties in the clinical evidence, however advised that ECP plus methoxsalen has acceptable safety, superior effectiveness and acceptable cost-effectiveness in the treatment of cGVHD compared with the current standard of care alone for the proposed patient population. MSAC also advised that there was a high unmet clinical need for effective treatments for cGVHD, given that it is not well managed by existing therapies.

MSAC supported the following MBS item descriptors and fees:

Item XXXX: initial treatment

Extracorporeal photopheresis for the treatment of chronic graft-versus-host disease (cGVHD) following allogeneic haematopoietic stem cell transplantation; if

- a. the service is provided in the initial 12 weeks of treatment; and*
- b. the service is delivered using an integrated, closed extracorporeal photopheresis system; and*
- c. the patient has received prior systemic steroid treatment for this condition and has experienced refractory disease or is dependent or intolerant to steroid treatment; and*
- d. the service is provided in combination with the use of Pharmaceutical Benefits Scheme-subsidised methoxsalen; and*
- e. the service is supervised by a specialist or consultant haematologist or oncologist with allogeneic bone marrow transplantation experience.*

Applicable once per treatment cycle

Steroid-refractory or steroid-dependent disease is defined as one of the following:

- A lack of response or disease progression after a minimum of prednisone 1 mg/kg/day or equivalent for at least 1 week, OR*
- Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg every day or equivalent other day for at least 4 weeks, OR*
- Increase to prednisolone dose to > 0.25 mg/kg/day or equivalent after 2 unsuccessful attempts to taper the dose.*

Fee: \$1,908.35 Benefit: 75% = \$1,431.30 85% = \$1,823.65

Item YYYY: continuing treatment

Extracorporeal photopheresis for the continuing treatment of chronic graft-versus-host disease (cGVHD) in adults following allogeneic haematopoietic stem cell transplantation; if in the preceding 12 weeks:

- a. (i) a service to which item XXXX applies has been provided; and*
(ii) the patient has demonstrated a response to this service; and
(iii) the patient requires further treatment; and
- b. the service is delivered using an integrated, closed extracorporeal photopheresis system; and*
- c. the service is provided in combination with the use of Pharmaceutical Benefits Scheme-subsidised methoxsalen; and*
- d. the service is supervised by a specialist or consultant haematologist or oncologist with allogeneic bone marrow transplantation experience.*

Applicable once per treatment cycle

A response, for the purposes of administering MBS item XXXX, is defined as attaining a complete or partial response in at least one organ according to NIH criteria. Response only needs to be demonstrated after the first 12 weeks of treatment.

Fee: \$1,908.35 Benefit: 75% = \$1,431.30 85% = \$1,823.65

Consumer summary

This application is from Mallinckrodt Pharmaceuticals and Terumo BCT Australia Pty Limited to list integrated, closed-system, extracorporeal photopheresis (ECP) systems on the Medicare Benefits Schedule (MBS) and methoxsalen on the Pharmaceutical Benefits Scheme (PBS) for the treatment of chronic graft-versus-host disease (cGVHD).

cGVHD is a common side effect in people who receive a bone marrow transplant (also called a haematopoietic stem cell transplant, or HSCT) from a donor. Immune cells from the HSCT start recognising the patient's own cells as foreign and attacks them. This causes lots of damage in the body, especially to the liver, skin and gut. It can be fatal.

cGVHD is usually treated with steroids to settle down the immune system. Some patients do not get better after taking steroids, and the side effects of using steroids for a long period of time are sometimes very severe.

During ECP treatment, the patient is connected to an ECP machine, which takes the patient's blood, runs it through the machine and returns the blood to the patient. Inside the machine, the patient's white blood cells are separated out, treated with a drug called methoxsalen and exposed to UV (ultraviolet) light. This is thought to reprogram the immune system to stop attacking the patient.

MSAC concluded that ECP was safe and more effective in cGVHD than ongoing steroids or other medicines that dampen the immune system. MSAC also concluded that ECP was good value for money because patients with cGVHD have limited options for treatment and they have received HSCT with the intent to cure them of their disease.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported funding for ECP for cGVHD because it is safe and more effective than current treatment. ECP is also good value for money for patients with cGVHD, who have limited options for treatment.

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

MSAC noted this codependent application requesting MBS listing of an integrated, closed loop ECP system and Pharmaceutical Benefits Scheme (PBS) listing of the drug methoxsalen to treat steroid-dependent, steroid-intolerant or steroid-refractory cGVHD. MSAC noted the Pharmaceutical Benefits Advisory Committee (PBAC) is scheduled to consider the submission at its next available meeting if MSAC supported public subsidy of ECP.

MSAC recalled its previous decision to support ECP for treatment of end-stage cutaneous T-cell lymphoma (CTCL, [Public Summary Document \[PSD\] Application No. 1420.1, p1](#)).

MSAC noted initial treatment with ECP for cGVHD consisted of 12 weeks initial treatment. This included three ECP treatments in the first week followed by two ECP treatments per week for at least 12 weeks for a total of 25 ECP sessions. Following response to the initial 12-week treatment course, patients may receive a further 12 weeks of ECP where ECP is performed twice per month, for approximately six further ECP sessions. MSAC noted that this differed from the six-month initial treatment period for CTCL, followed by ongoing ECP while patients maintain a response to therapy.

MSAC noted the consultation feedback from clinical organisations, a consumer organisation and a medical practitioner, all of which were supportive of the application. Feedback noted that patients have limited treatment options and reducing the dose of immunosuppressant medications improves long-term outcomes. MSAC also noted the high clinical need in the proposed population.

MSAC noted that, although there are several sites in Australia performing allogenic HSCTs, ECP is currently only available in two centres in Australia. Many patients will need to travel to access treatment. MSAC noted that one of the potential outcomes of MBS listing would be to make ECP more widely available, although it was unclear whether or how quickly this would occur in practice. MSAC requested that the Department seek further information from the applicant on how it would increase geographical access if ECP was listed on the MBS.

The application described the comparator of standard of care as typically involving the continued use of systemic steroids from first-line treatment, which may be combined with mycophenolate or calcineurin inhibitors to reduce and/or substitute for chronic high-dose systemic steroids. MSAC considered this to be appropriate for the steroid-refractory and steroid-dependent populations, but not the relatively small steroid-intolerant population.

MSAC accepted that ECP has non-inferior safety compared with standard of care. MSAC considered that reducing or substituting long-term steroids and immunosuppressant medication was also an important outcome for alleviating their cumulative adverse effects for patients. MSAC considered that this long-term consequence would not be captured in the short-term evidence presented in the ADAR.

MSAC accepted that ECP had likely superior clinical effectiveness compared with standard of care, although the clinical studies presented involved small numbers of participants and short follow-up times. MSAC considered that the NIH global response was the most clinically relevant outcome measure as it considers treatment response in many of the organs likely to be affected by cGVHD. MSAC noted that the MBS item descriptor requires patients attain a complete or partial response in at least one organ according to National Institutes of Health (NIH) criteria for continuing therapy. However, response according to NIH criteria was not reported in the included studies. MSAC noted that the key randomised trial, Flowers (2008)¹, reported statistically significant improvements in the unblinded assessment of skin response rate, ocular response, and reduction in corticosteroid dose with ECP. However, Flowers (2008) did not find a statistically significant improvement in the blinded assessment of its primary outcome, the median percentage change in total skin score (TTS) after 12 weeks. MSAC noted that oral, joints and gastrointestinal tract responses were not significantly different in Flowers (2008) but trended towards improvement with ECP. The open-label, single arm studies presented in the ADAR showed similar rates of response.

MSAC noted the concerns from ESC that the literature search in the applicant-developed assessment report (ADAR) was unsatisfactory and did not include sufficient paediatric data. MSAC noted that additional paediatric studies were included in the ESC report. MSAC noted the pre-MSAC response's contention that these additional studies used two-step, open ECP systems rather than integrated, closed ECP systems. The pre-MSAC response highlighted that open systems are no longer used in Australia in part due to the increased risk of reinfusion error, infection, and cross contamination. MSAC agreed with the pre-MSAC response that the additional paediatric data aligned with the clinical evidence presented in the ADAR and is

¹ Flowers ME *et al.* A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease. *Blood*. 2008;112(7):2667-2674.

unlikely to change the overall conclusion of comparative effectiveness. MSAC considered paediatric patients appeared to have similar response outcomes to adults, however Australian data from the Victorian Comprehensive Cancer Centre suggested there may be more difficulties with venous access in children.

MSAC reviewed the economic evaluation, which was a cost-utility analysis with a 10-year time horizon. MSAC noted the base case, which showed that ECP was dominant, but noted that this was uncertain due to the extrapolation of 12-week outcomes to 10 years, the uncertain effect of treatment response on mortality, and uncertainty as to whether the benefits are similar in all three populations (model inputs included the steroid-refractory population only). Model inputs included a response rate to ECP of 80%, informed by Australian single-arm studies. MSAC noted ESC's concerns that this was twice as high as the skin response rate seen in the ECP arm in the randomised controlled trial (40%). MSAC considered that using skin response alone in the economic model would bias against ECP. MSAC accepted the applicant's rationale that a higher response rate was justified as it would capture response in other organs which is consistent with the NIH criteria for response. MSAC also accepted the assumption that the same relative risk would apply to both ECP response rate estimates to estimate the response rate to standard of care (and thereby increasing the incremental improvement in response rates from 30% in the trial to 60% in the model), noting that this was consistent with other relative risk reductions from clinical studies of ECP in cGVHD assessing more global outcomes, including studies involving the less preferred open ECP systems as well as the requested closed ECP system.

MSAC noted that the model included the assumption that response or not at 12 weeks was generally maintained for the rest of the model (10 years). This affected the modelled results for cost offsets, utility gains and overall survival gains. The pre-MSAC response clarified that the risk of disease progression in responders in the model was estimated to be 4.1% per year based on data from the Royal Prince Alfred Hospital Special Access Scheme. This was applied to responders in both the ECP and standard of care arms. MSAC also noted that the model did not capture the utility benefits of reduced steroid or other immunosuppressant use. MSAC noted that the pre-MSAC response cited an economic model, Mohammad (2014)², showing improved survival and cost savings to the health system for patients who had undergone paediatric liver transplantation and were able to taper off immunosuppressant medication.

MSAC noted that the economic model did not include the cost of concomitant immunosuppressants for the ECP arm, however the model was not very sensitive to its inclusion. Instead, MSAC noted a key driver of the economic model was the increased cost in non-responders of post-progression treatments such as rituximab and intravenous immunoglobulin (IVIg). MSAC noted although there may be hospital funding of rituximab, its cost-effectiveness in this setting has not been assessed by the PBAC. MSAC further recalled that it had advised that immunoglobulin is not a cost effective therapy to manage infections in all patients who have acquired hypogammaglobulinaemia secondary to haematological malignancies or post-haemopoietic stem cell transplantation at the current price ([PSD Application 1565](#), p1).

MSAC therefore relied on the respecified base case in the Commentary with a 5-year time horizon and costs of rituximab removed, resulting in an incremental cost-effectiveness ratio (ICER) of \$48,754/QALY. MSAC considered that the shorter time horizon in the revised

² Mohammad S *et al.* Withdrawal of immunosuppression following pediatric liver transplantation: a Markov analysis. *J Pediatr Gastroenterol Nutr.* 2014;59(2):182-189.

base case adequately addressed the uncertainty relating to the duration of response as response in cGVHD is generally durable. MSAC considered that also reducing the associated cost offsets adequately addressed the uncertainty relating to the duration of non-response and associated modelled utility and overall survival gains. MSAC noted that this ICER was similar to the previously accepted ICER/QALY for ECP in CTCL. In addition, MSAC noted that ECP for CTCL is a palliative therapy whereas allogeneic HSCT is performed with curative intent and considered that this strengthened the rationale for subsidising ECP in the cGVHD population.

MSAC noted the financial impact of ECP, including corrections to costs to include the Greatest Permissible Gap and Original Medicare Safety Net, and considered this to be acceptable. As noted above in relation to only two centres currently providing ECP, MSAC advised that the uptake of ECP was uncertain as it would be dependent on expanding service provision. MSAC also advised that as more allogeneic HSCTs are performed, particularly in older patients, there will be a greater clinical need for ECP. MSAC considered that the cost estimates should have included the cost of central venous access and flushing of central lines. The financial estimates also did not account for reductions in the use of corticosteroids and other immunosuppressants.

MSAC advised that the MBS item should be reviewed after 2 years.

MSAC advised that co-claiming restrictions should be enforced to ensure that additional supervision items are not claimed as the proposed fee covers the cost of specialist supervision of nursing staff involved with ECP service delivery.

MSAC supported item descriptors that did not limit the proposed use of ECP to adults. MSAC noted that around 20% of allogeneic haematopoietic stem cell transplant recipients are for children under 16 years of age, and these people would not be eligible for ECP if the MBS item descriptors limited the service to adults. MSAC noted that the item descriptor specified that it was for use in adults to align with the TGA-approved product information for methoxsalen, which is restricted to adults. MSAC noted that PASC had advised that the item descriptor and codependent PBS restriction for methoxsalen should omit reference to the age of the patient rather than specifying an age (1651 ratified PICO Confirmation, p8). MSAC noted the ECP was being used treat children in Australia. MSAC advised that PBAC should consider aligning the PBS restriction for methoxsalen to align with this aspect of the MBS item descriptor.

4. Background

At its April 2020 meeting, MSAC supported public funding of ECP in the treatment of cutaneous T-cell lymphoma (CTCL). 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 (p2, [Public Summary Document \[PSD\] Application 1420](#)).

On 1 November 2020, two new MBS items were introduced for the treatment of CTCL with ECP:

- Item 14247: ECP for the first six months of treatment for cutaneous T-cell lymphoma administered under the supervision of a specialist or consultant physician in the speciality of haematology, with a schedule fee of \$1,908.35.
- Item 14249: ECP for after the first six months of treatment for cutaneous T-cell lymphoma administered under the supervision of a specialist or consultant physician in the speciality of haematology, with a schedule fee of \$1,908.35.

In November 2019, MSAC considered a Post-Market Review of on the Government funded supply of replacement human gamma immunoglobulin therapy via the National Blood Authority. In relation to arrangements for the treatment of acquired hypogammaglobulinaemia secondary to haematological malignancies, or post-haemopoietic stem cell transplantation, MSAC advised that immunoglobulin is not a cost-effective therapy to manage infections in all patients who have acquired hypogammaglobulinaemia secondary to haematological malignancies or post-haemopoietic stem cell transplantation at the current price. MSAC considered that immunoglobulin could be cost-effective in some patients currently eligible for immunoglobulin under the Criteria (version 3) for this indication, however the variation in the underlying patient conditions and treatments causing hypogammaglobulinaemia in this population made an overall conclusion about the cost-effectiveness difficult (p1, [PSD Application 1565](#)).

5. Prerequisites to implementation of any funding advice

The Therakos®, Integrated, Closed CellEx® Photopheresis System and its drug counterpart, methoxsalen (UVADEX®), are approved by the TGA and registered on the Australian Register of Therapeutic Goods (ARTG) for the treatment of cGVHD.

6. Proposal for public funding

The ADAR sought public funding via:

- (a) two MBS items (initial and continuing treatment) to subsidise delivery of the ECP treatment with an integrated, closed ECP system for patients with treatment refractory cGVHD (Table 1), and
- (b) the PBS listing of methoxsalen (UVADEX®) to reimburse the cost of the drug as part of the service.

Table 1: Proposed MBS items for integrated, closed ECP systems for patients with cGVHD

<p>Initial treatment</p> <p>xxxxx</p> <p>Extracorporeal photopheresis for the treatment of chronic graft-versus-host disease (cGVHD) in adults following allogeneic haematopoietic stem cell transplantation; if</p> <ol style="list-style-type: none">the service is provided in the initial 12 weeks of treatment; andthe service is delivered using an integrated, closed extracorporeal photopheresis system; andthe patient has received prior systemic steroid treatment for this condition and has experienced refractory disease or is dependent or intolerant to steroid treatment; andthe service is provided in combination with the use of Pharmaceutical Benefits Scheme-subsidised methoxsalen; andthe service is supervised by a specialist or consultant haematologist or oncologist with allogeneic bone marrow transplantation experience. <p>Applicable once per treatment cycle</p> <p>Steroid-refractory or steroid-dependent disease is defined as one of the following:</p> <ul style="list-style-type: none">-A lack of response or disease progression after a minimum of prednisone 1 mg/kg/day or equivalent for at least 1 week, OR-Disease persistence without improvement despite continued treatment with prednisone at > 0.5 mg/kg/day or 1 mg/kg every day or equivalent other day for at least 4 weeks, OR-Increase to prednisolone dose to > 0.25 mg/kg/day or equivalent after 2 unsuccessful attempts to taper the dose <p>Fee: \$1,908.35 Benefit: 75% = \$1,431.30 85% = \$1,823.65</p> <p>Continuing treatment</p> <p>xxxxx</p> <p>Extracorporeal photopheresis for the continuing treatment of chronic graft-versus-host disease (cGVHD) in adults following allogeneic haematopoietic stem cell transplantation; if in the preceding 12 weeks:</p> <ol style="list-style-type: none">(i) a service to which item xxxx applies has been provided; and(ii) the patient has demonstrated a response to this service; and(iii) the patient requires further treatment; andthe service is delivered using an integrated, closed extracorporeal photopheresis system; andthe service is provided in combination with the use of Pharmaceutical Benefits Scheme-subsidised methoxsalen; andthe service is supervised by a specialist or consultant haematologist or oncologist with allogeneic bone marrow transplantation experience. <p>Applicable once per treatment cycle</p> <p>A response, for the purposes of administering MBS item XXXX, is defined as attaining a complete or partial response in at least one organ according to NIH criteria. Response only needs to be demonstrated after the first 12 weeks of treatment.</p> <p>Fee: \$1,908.35 Benefit: 75% = \$1,431.30 85% = \$1,823.65</p>

Source: Table A.4, p40 of the ADAR.

cGVHD, chronic graft versus host disease; ECP, extracorporeal photopheresis; MBS, Medicare Benefits Schedule

The proposed MBS item descriptors are within the TGA indications and consistent with the proposed PBS restrictions for methoxsalen, with the exception that for initial treatment, unlike the MBS item descriptor, the PBS restriction specifies that “Patient must not have previously received PBS-subsidised treatment with this drug for this PBS indication”.

PASC advised that the item descriptor and codependent PBS restriction for methoxsalen should omit reference to the age of the patient rather than specifying an age or using a term such as “adolescent” (p8, [ratified PICO](#)).

The Commentary noted the following with respect to the applicant's justification for the requested MBS fee (consisting of \$44.35 for a specialist consultation, \$164 for ECP service supervision of nursing staff and **\$redacted** for consumables):

- If supervision by a specialist consultant is required for this service then a separate MBS item may be charged. For example, MBS item 116 can be co-claimed. The cost of this item is \$79.05.
- As noted in the ADAR, one of the intended outcomes of listing of ECP on the MBS was that it would become more widely available compared to the two centres that currently provide the service.
- The requested MBS fee is the same as that of the current listing of ECP albeit that this is for an active treatment purpose whereas ECP for CTCL is for palliative care purposes.

Only patients showing a response to initial therapy are eligible for continued therapy. "Response", for both the MBS item and PBS restriction, is defined as attaining a complete or partial response in at least one organ according to NIH criteria (i.e. limited to an improvement in cGVHD symptoms). PASC advised that for the steroid-dependent population, the definition of "response" might also appropriately include a reduction in use of concomitant therapy (with a reduction of steroid dose being the most expected response, p20, [ratified PICO](#)). The Commentary suggested that MSAC may wish to consider whether the definition of response in the MBS item descriptor should be amended to include a reduction in use of concomitant therapy, with consistent changes then also relevant to the PBS restriction.

7. Summary of public consultation feedback/consumer issues

Consultation feedback from three clinical organisations, one consumer organisation and one medical practitioner was received. The feedback was supportive of ECP systems for the treatment for patients with cGVHD.

The Peter MacCallum Cancer Centre/Victorian Comprehensive Cancer Centre and the Royal Prince Alfred Hospital both provided positive written statements about the use of ECP for steroid refractory/steroid-dependent/steroid-intolerant cGVHD. The RPAH noted that this is a group of patients who usually progress to requiring increasing doses of immunosuppressant medications. Their mortality rate is very high, often due to life-threatening infections from their medications. Being able to reduce the dose of immunosuppressant medications significantly improves the long-term outcome of these patients. These are severe patients where treatment options are limited.

The Leukaemia Foundation highlighted that currently ECP is difficult to access as only two centres currently provide ECP and only one centre provides ECP for children. The Leukaemia Foundation highlighted the difficulties patients experience travelling for treatment while seriously unwell and immunocompromised. The Leukaemia Foundation supported MBS listing of ECP for both paediatric and adult patients.

In its consideration of consultation feedback, PASC noted that some current problems with equity of access will persist even if the item is listed and the potential for substantial residual out-of-pocket costs beyond MBS funding associated with travel to the few centres capable of providing the service.

8. Proposed intervention's place in clinical management

Description of proposed intervention

ECP is a leukapheresis-based, immunomodulatory therapy in which a patient's leukocytes are collected and treated *ex vivo* with methoxsalen and UVA light and then returned to the patient. Integrated, closed ECP systems (such as the THERAKOS CELLEX system) complete the processes of cell separation, photo activation of methoxsalen, and reinfusion of the treated cells back into the patient within an automated and fully integrated process. All components of the treatment are validated for use together.

Description of medical condition

cGVHD can occur in patients undergoing allogeneic transplant procedures. This event originates from donated bone marrow or peripheral blood stem cells that view the recipient's body as foreign, before mounting an attack against the host's body cells. cGVHD can appear immediately or any time after a patient's allogeneic transplant. Despite prophylactic immunosuppression, there is an increased risk of developing the disease from Hematopoietic Stem Cell Transplantation. This may contribute to 17-20% of transplant-related deaths regardless of donor-relatedness.

The mainstay of treatment for cGVHD is systemic steroid therapy, however, the most effective approach to steroid-refractory/intolerant/dependent GVHD remains controversial. ECP is recommended by international guidelines and consensus documents for steroid-refractory and dependent cGVHD patients.

Clinical place

The current and proposed clinical management algorithms are presented in Figure 1 and Figure 2 and are consistent with those developed for the ratified PICO Confirmation.

It was proposed that ECP plus methoxsalen treatment would initially be used as an adjunct treatment with the nominated comparators, and that sustained ECP treatment would reduce the daily dosage of these comparator treatments and their associated toxicities. The Commentary highlighted that, consistent with comments made regarding the comparators, only currently subsidised treatments are represented in the clinical management algorithms. Thus, the inclusion of rituximab costs (as a third-line treatment) and in the model was inappropriate.

The Commentary also questioned the inclusion of IVIg (for the 'progressed' health state) in the model. The pre-ESC response included feedback from two clinical haematologists who advised that many of their patients with cGVHD require multiple immunosuppressant therapies, experience recurrent infections and develop hypogammaglobulinaemia and therefore qualify for funded IVIg via the national blood arrangements. The clinical haematologists further advised that, as the cGVHD responds to treatment, the immunosuppressant therapy can be weaned resulting in a reduced need for IVIg including the possibility of ceasing IVIg.

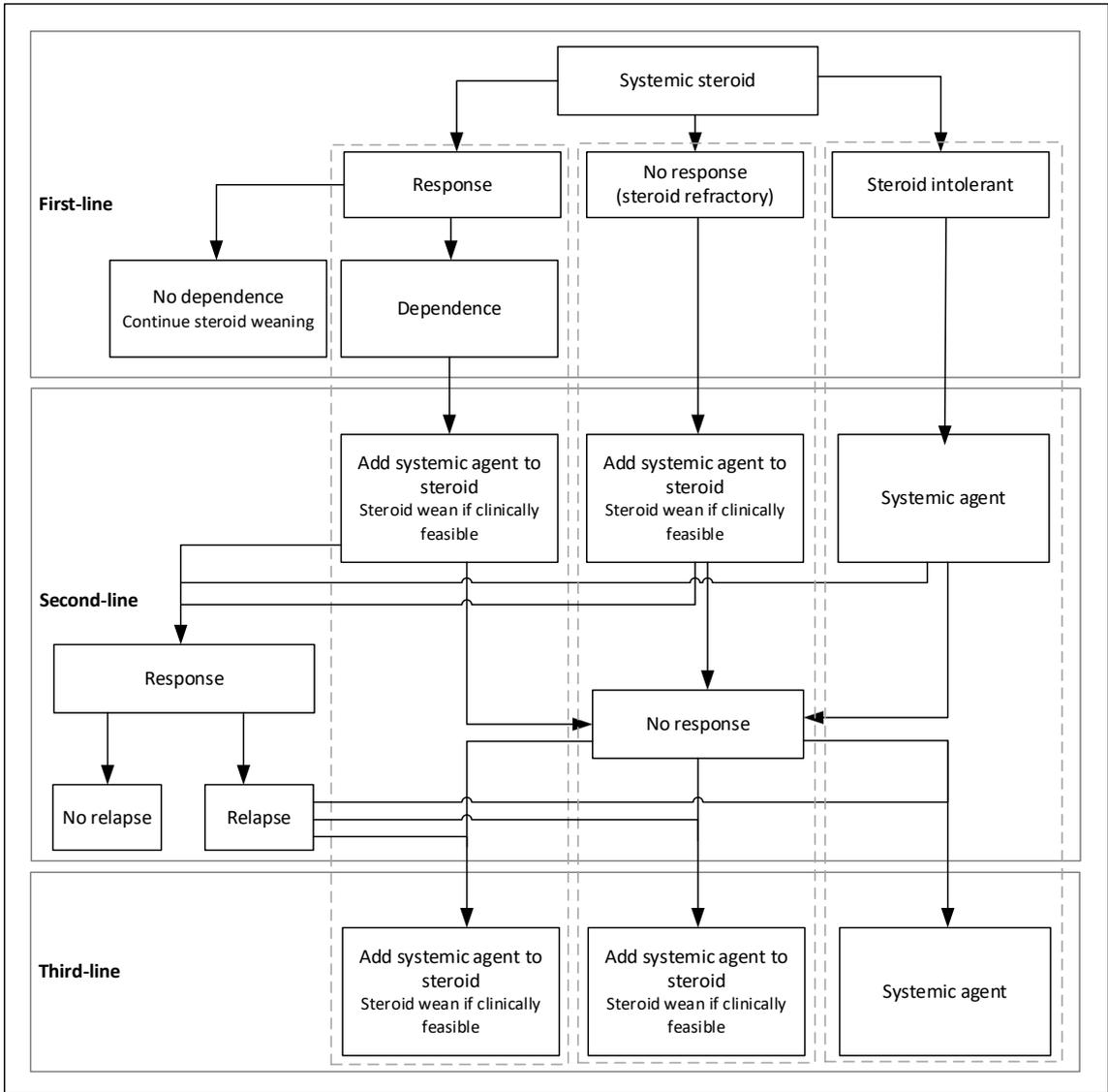


Figure 1: Current management algorithm

Source: Figure A.5, p54 of the ADAR.

Note: systemic agent denoted in diagram refers to the use of calcineurin inhibitors (e.g. tacrolimus and ciclosporin) and/or mycophenolate mofetil.

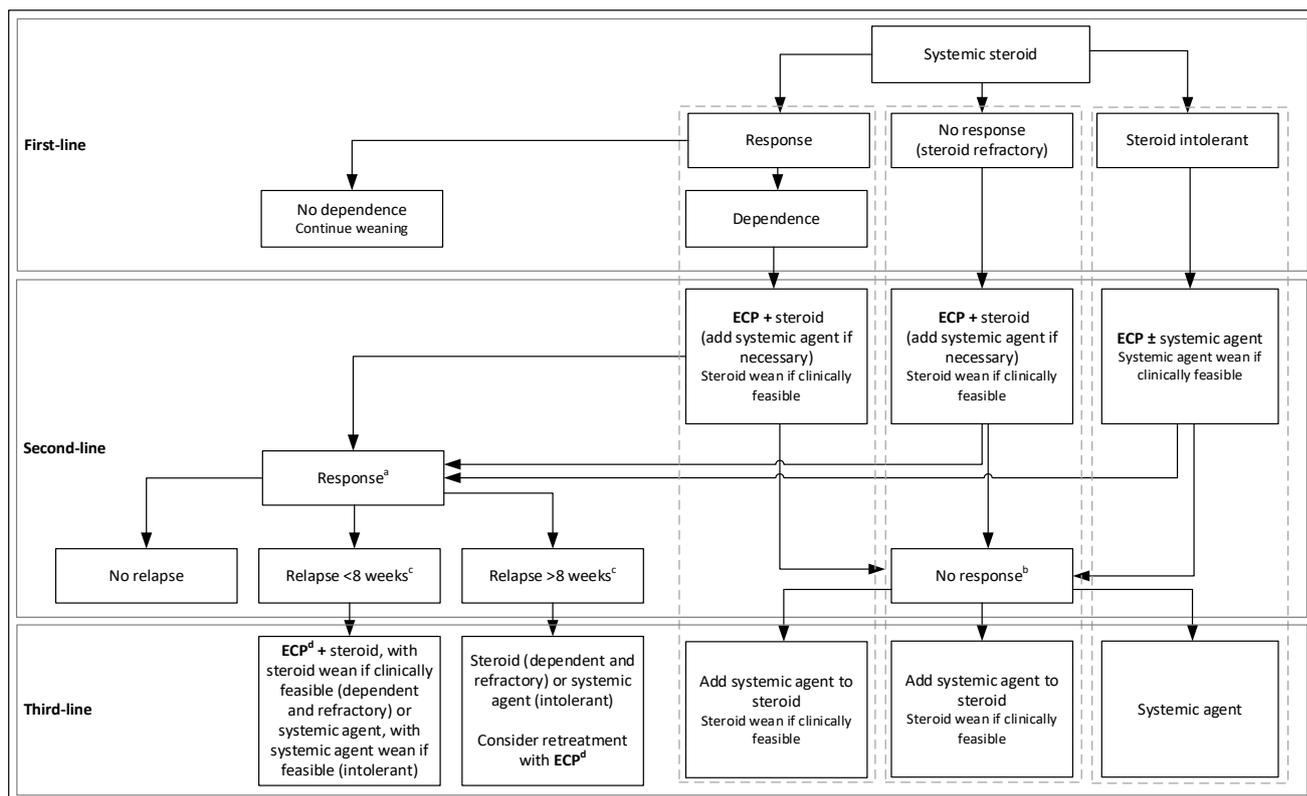


Figure 2: Proposed management algorithm

Source: Figure A.6, p56 of the ADAR.

Note: For some patients starting ECP as third-line and later-line, ECP may also be added to systemic steroids and/or other treatment, with the aim of weaning both steroids and other therapy.

^a Response: the initial treatment cycle would be 12 weeks, then review and continue with another 12-week treatment cycle if the patient is responding. PASC noted that clinicians review the treatment every 12 weeks before continuing. PASC noted that the initial 12-week treatment cycle is twice per week, and the second 12-week cycle is twice per month. PASC noted that the definition of “response” was limited to an improvement in cGVHD symptoms. PASC advised that for the steroid-dependent population, the definition of “response” might also appropriately include a reduction in use of concomitant therapy (with a reduction of steroid dose being the most expected response)

^b No response: patients who do not respond sufficiently to ECP after the initial 12-week cycle should not continue with the treatment

^c From cessation of ECP

^d Re-using the initiation regimen for ECP (12-week treatment cycle, twice per week)

Systemic agent: calcineurin inhibitor (e.g. tacrolimus and ciclosporin) or mycophenolate mofetil

9. Comparator

Based on the current International Guidelines on the treatment of cGVHD and the Australian clinician interviews presented in the ADAR, the nominated comparator for the second-line treatment of treatment refractory cGVHD was the best available standard of care (SOC). In Australia, SOC typically involves the continued use of steroids from first-line treatment, in combination with mycophenolate or calcineurin inhibitors with the view of reducing and/or displacing chronic high dose systemic steroidal treatment.

ECP with methoxsalen is expected to be delivered over 3 hours of outpatient time with specialist nurses compared with the comparators being administered orally.

The Commentary highlighted the following from the ratified PICO Confirmation:

- PASC noted that the comparators listed in the PICO Confirmation (and nominated in the ADAR) are appropriate for populations a [steroid-refractory] and b [steroid-dependent]. ECP is mostly expected to add to and then partially replace systemic steroids.

- PASC noted that the comparators listed in the PICO Confirmation (and nominated in the ADAR) are not appropriate for the relatively small population c [steroid-intolerant] because ‘steroid-intolerant’ should not be able to continue steroids; further clarity is needed around the current standard of care in Australia for this group. For example, to ascertain whether mycophenolate or a calcineurin inhibitor would be used without steroids.

PASC also noted that currently subsidised treatments would be the most appropriate comparators because they are more likely to be used currently than non-subsidised treatments. PASC noted that many of the treatments listed in Figure 3 [of the PICO Confirmation] are not subsidised in Australia and that the applicant had accepted that ruxolitinib and ibrutinib were not PBS-listed for the proposed population. Therefore, the PICO [and subsequently, the ADAR] should not retain any implication that non-subsidised treatments are also appropriate comparators. While not nominating non-subsidised treatments as comparators, the ADAR included rituximab as a third-line treatment option in its stepped economic evaluation, which was inappropriate because rituximab is not PBS-subsidised for cGVHD.

10. Comparative safety

Clinical claim

The ADAR proposed that, in addition to the standard of care, ECP plus methoxsalen has superior efficacy and non-inferior safety in the treatment of treatment refractory cGVHD than the current standard of care alone. Moreover, it was proposed that, after a period of sustained treatment, ECP plus methoxsalen treatment may reduce or displace corticosteroids, calcineurin inhibitors and mycophenolate mofetil in the second line treatment of cGVHD, thereby reducing comorbidities associated with the chronic use of immunosuppressant medication.

Characteristics of the evidence base

The ADAR was based on:

- One randomised controlled trial (RCT) enrolling patients with cGVHD, comparing ECP with SOC (Flowers 2008);
- Two observational Australian registry studies, the Royal Prince Alfred Hospital Special Access Scheme (RPAH SAS) and the Victorian Comprehensive Cancer Centre Special Access Scheme (VCCC SAS); and
- Six prospective single-arm studies (Greinix 2011, Dignan 2014, Foss 2005, Gandelman 2018, Okamoto 2018, Seaton 2003). The Commentary noted that the ADAR did not treat the Greinix (2011) study as a single-arm study, most likely due to Greinix (2011) reporting on 29 patients initially enrolled and randomised to SOC in the Flowers (2008) RCT. However, as this publication reports only on the open-label cross-over phase and does not provide any comparative evidence, it should have been considered and assessed as a single-arm study.

The ADAR appeared to have specifically excluded studies enrolling paediatric and/or adolescent patients. As ECP is being used in children, the Commentary considered this was inappropriate as it did not allow MSAC a basis to consider whether the proposed MBS item should preclude use in children. The pre-ESC response noted that Flowers (2008), the only RCT that has assessed the safety and efficacy of ECP in the treatment of treatment refractory cGVHD, had included patients as young as 13 years of age, and there was paediatric data from the VCCC SAS.

Paediatric data reported in the meta-analysis by Malik (2014)³ and the study by Flinn (2020) were extracted for inclusion in the ESC Report (Table 3, Table 6 and the paragraph following Table 6).

The ADAR assessed that the overall risk of bias for Flowers (2008) was ‘moderate’. The Commentary considered that, given two domains (lack of blinding of participants) and ‘other’ (trial was supported by the device developer) were ‘high’ risk and a further two domains were ‘unclear’ (allocation concealment) and ‘moderate’ (incomplete outcome data addressed by last observation carried forward; LOCF), a more reasonable assessment may be an overall high risk of bias.

The Commentary considered that the ADAR had reasonably assessed the overall risk of bias as high for the two prospective Australian registry studies (RPAH SAS and VCCC SAS) and five single-arm nonrandomised prospective studies (Dignan 2014, Foss 2005, Gandelman 2018, Okamoto 2018 and Seaton 2003), owing to their single-arm study design. The Commentary considered that Greinix (2011) similarly had a high risk of bias.

Of the adverse events reported in the Flowers (2008) RCT, only anaemia occurred more frequently in the ECP treatment group than the control group (24.5% vs 6.0%, $p < 0.05$).

Common adverse events reported in the studies included infection (catheter-related and other), and catheter-related thrombosis.

The VCCC paediatric data reported that there had been challenges in maintaining vascular access for ECP. Of 13 patients, 8 experienced line infections and three 3 patients required multiple central access devices.

Across the trial and studies, no deaths were attributed to ECP plus methoxsalen treatment.

11. Comparative effectiveness

Cutaneous cGVHD outcomes

The results for the outcome of total skin score (TSS), reported in three studies (Flowers 2008, Greinix 2011, Seaton 2003) are summarised in Table 2.

The primary end point of the Flowers (2008) RCT was the median percentage change in TSS after 12 weeks of treatment compared with the baseline (pre-treatment) value using a validated ordinal 50-point whole body scoring system. The authors stated that the TSS was assessed by a medical professional who was trained in the skin evaluation scoring system, not otherwise involved with the care of the patient, and not informed of the patient’s study arm assignment (i.e., blinded). The fraction of each of 10 topographic areas involved with 1 or more of 5 types of skin lesions was estimated and recorded as follows: 0 = normal; 1 = discoloured (hyperpigmentation, hypopigmentation, erythematous) or alopecia; 2 = lichenoid plaque, thickening, able to move; 3 = thickened, able to move and pinch; 4 = hidebound, unable to move or pinch. No statistically significant difference in TSS at 12 weeks was observed between the treatment arms in Flowers (2008). Patients in Greinix (2011) had a baseline TSS of 8.5 (range: 1.0-18.5). Following 12 and 24 weeks of ECP treatment, TSS declined by -7.9% and -25.8, respectively. Similarly, Seaton (2003) reported decreasing skin

³ Malik MI et al. Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. *Blood Res.* 2014;49(2):100-106.

scores over time. The Commentary highlighted that it appears that the ‘skin score’ measured in Seaton (2003) is not the same as that used in Flowers (2008) and Greinix (2011).

Table 2: Total Skin Score outcome results across the included studies

Total skin score % change from baseline at	Flowers 2008		Greinix 2011 Flowers 2008	Seaton 2003 ^a
	ECP, n = 48	SOC, n = 47	N = 29	N = 28
Week 4	NR	NR	NR	0.76%
Week 8	NR	NR	NR	-29.0%
Week 12	-14.5%	-8.5%	-7.9%	-48.5%
	P=0.48			
Week 24	-31.4%	NR	-25.8%	-53.4%

Source: Table B.25, p113 of the ADAR.

Bold typography indicates statistically significant differences between groups or between baseline and outcome measurement.

^a The authors stated that quantitative assessment of cutaneous cGVHD disease was assessed during treatment by combining surface area involvement and severity of disease in each area of skin assessed. The measuring technique was adapted from the modified Rodman scleroderma skin scoring method, where total skin score = [(percentage of body surface area containing erythematous or lichenoid lesions × grade of erythema)] + [percentage body surface area containing sclerodermoid lesions × grade of sclerodermoid change].

Complete or partial cutaneous response reported in the studies are summarised in Table 4.

Flowers (2008) reported that a statistically significantly greater proportion of those treated with ECP reported complete or partial skin responses compared to those treated with SOC at 12 weeks. However, the authors also stated this was “[a]n unblinded assessment of skin involvement ... performed by the experienced clinical investigator who was aware of the treatment assignment”. Each of the single-arm studies reported that some patients reported complete or partial cutaneous responses. Unlike other studies, Seaton (2003) defined clinical response as more than 25% reduction in initial skin score for patients who had stable or reduced levels of systemic immunosuppression; any patient requiring increased immunosuppression was deemed to be a non-responder, notwithstanding any clinical improvement in skin disease.

A systematic review by Malik (2014)⁴ that was not included in the ADAR presented additional data on paediatric patients with steroid refractory cGVHD treated with ECP.

Table 3: Response rates for steroid refractory cGVHD in paediatric patients

Study	Design	N	ECP cycles (median)	Age (median)	Skin response
Berger (2007)	Prospective	10	22	11.2 years	90%
Perotti (2010)	Retrospective	23	34	11.8 years	83%
Kanold (2007)	Retrospective	15	24	14 years	80%
Gonzalez Vicent (2010)	Retrospective	6	6	10 years	NR
Messina (2003)	Retrospective	44	NR	8.2 years	55%

Source: Table 1-2, p102 of Malik (2014)

cGVHD = chronic graft versus host disease; CR = complete response; ECP = extracorporeal photopheresis; N = number of participants; NR = not reported; ORR = overall response rate

Extracutaneous cGVHD outcomes

Table 4 also reports complete or partial extracutaneous response reported in the studies. Flowers (2008) reported that a statistically significantly greater proportion of those treated with ECP reported complete or partial ocular responses compared to those treated with SOC

⁴ Malik MI et al. Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. *Blood Res.* 2014;49(2):100-106.

at 12 weeks; no statistically significant differences were observed for any other organ system. Each of the single-arm studies reported that some patients reported complete or partial responses in various affected organs. As for skin responses above, Seaton (2003) defined clinical response as more than 25% reduction in initial skin score for patients who had stable or reduced levels of systemic immunosuppression.

Table 4: Complete and partial clinical response in cutaneous and extracutaneous cGVHD affected organs in the included studies

Complete and partial clinical response n/N, (%) at	Flowers 2008		Greinix 2011 Flowers 2008	RPAH SAS	Dignan 2014	Foss 2005 ^a	Okamoto 2018	Seaton 2003
	ECP, n = 48	SOC, n = 47	N = 29	N = 42	N = 38	N = 25	N = 15	N = 28
Skin								
Week 12	17/43 (40)	4/40 (10)	7/27 (26)	NR	NR	NR	3/11 (27)	8/21 (38)
Week 24	NR	NR	9/29 (31)	NR	10/14 (71) ^a 8/10 (80) ^b	NR	3/11 (27)	10/21 (48)
Week 36	NR	NR	NR	NR	NR	NR	4/11 (36)	NR
Final visit	NR	NR	NR	30/38 (79)	NR	20/25 (80)	NR	NR
Ocular								
Week 12	8/27 (30)	2/28 (7)	4/15 (27)	NR	NR	NR	4/13 (31)	NR
Week 24	7/26 (26)	NR	7/15 (47)	NR	NR	NR	4/13 (31)	NR
Week 36	NR	NR	NR	NR	NR	NR	3/13 (31)	NR
Final visit	NR	NR	NR	6/15 (40)	6/11 (71)	3/3 (100)	NR	NR
Oral								
Week 12	16/30 (53)	8/30 (27)	13/20 (65)	NR	NR	NR	5/13 (38)	NR
Week 24	13/30 (43)	NR	14/20 (70)	NR	NR	NR	5/13 (38)	NR
Week 36	NR	NR	NR	NR	NR	NR	6/13 (46)	NR
Final visit	NR	NR	NR	14/22 (64)	4/11 (36)	6/13 (46)	NR	3/14 (21)
Joints								
Week 12	4/18 (22)	2/16 (12)	4/11 (36)	NR	NR	NR	4/8 (50)	NR
Week 24	9/18 (50)	NR	5/12 (42)	NR	NR	NR	3/8 (38)	NR
Week 36	NR	NR	NR	NR	NR	NR	3/8 (38)	NR
Final visit	NR	NR	NR	0/1 (0)	3/5 (60)	3/6 (50)	NR	NR
Gastrointestinal tract								
Week 12	1/2 (50)	3/9 (33)	1/2 (50)	NR	NR	NR	1/3 (33)	NR
Week 24	1/2 (50)	NR	2/2 (100)	NR	NR	NR	1/3 (33)	NR
Week 36	NR	NR	NR	NR	NR	NR	1/3 (33)	NR
Final visit	NR	NR	NR	0/2 (0)	5/5 (100)	1/1 (100)	NR	NR

Source: Table B.27, pp120-121 of the ADAR.

^a patients with lichenoid disease

^b patients with non-movable sclerodermoid disease

Bold typography indicates statistically significant differences between groups or between baseline and outcome measurement

Table 5 summarises the global complete and partial clinical responses reported in the studies. Somewhat consistent proportions of patients in the Dignan 2014, Gandelman 2018 and Okamoto 2018 studies reported a global complete and partial clinical response in cGVHD affected organs as assessed by the NIH cGVHD Guideline (range: 43.5%-66.7%). This was somewhat aligned with the proportions of patients in the Australian RPAH SAS, VCCC SAS and Gandelman 2018 studies who reported a global complete and partial clinical response in cGVHD affected organs as assessed by providers (79%, 82% and 62% respectively). The 79% cited for RPAH SAS could not be independently verified. In the VCCC SAS paediatric

cohort, 4 patients experienced a complete response, 6 patients experienced a partial response, 3 patients experienced stable disease and 4 patients experienced disease progression.

Table 5: Global complete and partial clinical response cGVHD affected organs in the included studies

Study	RPAH SAS	VCCC SAS Adult population	VCCC SAS Paediatric population	Dignan 2014	Gandelman 2018	Okamoto 2018
Proportion of patients with NIH cGVHD Guideline-defined global complete and partial clinical response n, (%)	NR	NR	NR	19/38 (50)	(43.5)	8/15 (53.5) ITT 8/12 (66.7) PP
Proportion of patients with provider-assessed global complete and partial clinical response n, (%)	33/42 (79) ^a	27/33 (82)	10/13 (77)	NR	(62.3)	NR

Source: Table B.28, p122 of the ADAR

^a Calculated using raw patient data (source: RPAH SAS Appendix 1a)

ITT: intention-to-treat; PP: per protocol

Table 6 presents the overall response rates and organ specific response rates from the paediatric ECP studies presented in Malik (2014). Malik (2014) reported that the pooled complete response rate for the paediatric population was 39% (95% CI: 29%, 51%; P=0.17). The overall response rate in paediatric patients was 69% (95% CI: 58%, 78%; P=0.24). The difference between adults and paediatric CR and ORR was not statistically significant.

Table 6: Overall and organ-specific response rates in paediatric patients

Study	N	ORR	CR	Liver	GI	Ocular	Oral	MSK	BO
Berger (2007)	10	40%	30%	50%	0%	NR	33%	100%	0%
Perotti (2010)	23	69.5%	NR	100%	80%	75%	NR	NR	NR
Kanold (2007)	15	73.3%	26%	59%	NR	NR	NR	NR	NR
Gonzalez Vicent (2010)	6	83%	50%	NR	NR	NR	NR	NR	NR
Messina (2003)	44	73%	44%	55%	60%	NR	NR	NR	NR

Source: Table 1-2, p102 of Malik (2014)

BO = bronchiolitis obliterans; CR = complete response; ECP = extracorporeal photopheresis; GI = gastrointestinal; MSK = musculoskeletal; N = number of participants; ORR = overall response rate

Flinn (2020) reported that six of 15 (40%) patients with cGVHD had a complete response, two of 15 (13.3%) had a partial response, and 3 patients had no response (response not known for four patients).

Reductions in immunosuppressant medications

Table 7 summarises the changes in immunosuppressant use among patients in the studies.

In Flowers (2008), significantly more patients reported a $\geq 50\%$ reduction in their daily steroid dose intake and a steroid dose ≤ 10 mg/day following 12 weeks of ECP plus methoxsalen treatment versus patients that received standard care (20.8% versus 6.4%, $p < 0.05$). Moreover, 35.4% of patients in the ECP treatment group reported a $\geq 50\%$ reduction in their daily steroid dose intake and a steroid dose ≤ 10 mg/day after 24 weeks of ECP treatment. These findings are similar to those found in the Greinix (2011) study where 17% and 25% of patients reported a ≥ 50 reduction in their daily steroid dose intake and a steroid dose ≤ 10 mg/day after 12 weeks and 24 weeks of ECP plus methoxsalen treatment, respectively. The other single-arm studies similarly reported reductions in the dose of steroid use, with two studies (VCCC SAS, Dignan 2014) reporting that a number of patients had

ceased steroid therapy completely; notably, four of 11 (36%) of the paediatric patients in the VCCC SAS were reported to cease therapy with steroids.

ECP plus methoxsalen treatment was also associated with reduced intake of commonly used non-steroidal medications for the treatment of cGVHD, including mycophenolate mofetil, cyclosporin and tacrolimus.

Table 7: Reduction in immunosuppressant medication following ECP plus methoxsalen treatment in the included studies

Study	Outcome at 12 weeks	ECP, n/N(%)	SOC, n/N (%)	p-value
Flowers 2008	≥50% reduction in steroids	12/48 (25)	6/47 (13)	NS
	≥50% reduction in steroids AND steroid daily dose <10 mg/day	10/48 (21)	3/47 (6)	<0.04
Study	Reduction in steroids	n/N (%)	Reduction in immunosuppressants	n/N (%)
Flowers 2008	≥50% reduction	24 weeks: NR (40)	NR	
	≥50% reduction AND steroid daily dose <10 mg/day	24 weeks: NR (35)		
Greinix 2011	≥50% reduction	12 weeks 4/24 (17) 24 weeks: 8/24 (33)	NR	
	≥50% reduction AND steroid daily dose <10 mg/day	12 weeks: 4/24 (17) 24 weeks: 6/24 (25)		
RPAH SAS	NR		Reduced ^a , n/N (%)	24/42 (52)
			Completely ceased ^a , n/N (%)	4/42 (10)
VCCC SAS Adults	Reduced	25/33 (76)	NR	
	Reduced by 100%	5/33 (15)		
	Reduced by ≥75%-<100%	9/33 (27)		
	Reduced by ≥50%-<75%	7/33 (21)		
	Reduced by ≥1%-<50%	4/33 (36)		
	Median change from baseline: 17.5 mg (±18.6)			
VCCC SAS Paediatrics	Reduced	11/11 (100)	NR	
	Reduced by 100%	4/11 (36)		
	Reduced by ≥75%-<100%	0/11 (0)		
	Reduced by ≥50%-<75%	6/11 (54)		
	Reduced by ≥1%-<50%	1/11 (9)		
	Median change from baseline: 1 mg (±8.5)			
Dignan 2014	Reduced	17/19 (89)	Reduced	3/6 (50)
	Reduced by 100%	5/19 (26)	Reduced MM by 50%	2/6 (33)
	Reduced by ≥75%-<100%	4/19 (21)	Reduced CsA by 75%	1/6 (17)
	Reduced by ≥50%-<75%	4/19 (21)		
	Reduced by <50%	4/19 (21)		
	Any reduced immunosuppressant medication, n/N (%):20/25 (80) PP; 20/36 (55) ITT			
Foss 2005	Reduced	13/23 (57)	Discontinued (at least one)	11/25 (44)
			Reduced/discontinued MM	12/25 (48)
			Reduced/discontinued TAC	5/25 (20)
Gandelman 2018	Median daily steroid dose intake (SD) [IQR]: Baseline = 0.36 mg/kg [0.21-0.48] Final visit = 0.14 mg/kg [0.10-0.20]		NR	
Okamoto 2018	Median reduction in dose from screening: 24 weeks = 0.115 mg/kg (±0.230) 36 weeks = 0.167 mg/kg (±0.164)		NR	

Source: Table B.29, pp125-127 of the ADAR.

On the basis of the benefits and harms reported in the evidence base, the ADAR proposed that, relative to standard of care, ECP with methoxsalen has non-inferior safety and superior effectiveness.

The Commentary considered that the clinical claims made by the ADAR required consideration.

The Commentary considered that with respect to the claim of non-inferior safety, the only randomised controlled trial (Flowers 2008) comparing ECP with methoxsalen and SOC reported that a statistically significantly greater proportion of those treated with ECP developed anaemia (indicating inferior safety). However, the likely improved safety as a result of the apparent steroid-sparing effect observed with treatment with ECP may not have been adequately captured in the included evidence.

The Commentary considered that with respect to the claim of superior effectiveness, although no statistically significant difference in the median change in TSS after 12 weeks of treatment (the primary outcome of the trial) was observed, statistically significant differences in complete and partial skin and ocular responses were observed, as well a reduction in steroid use ($\geq 50\%$ reduction AND steroid daily dose < 10 mg/day) at 12 weeks. The single-arm studies also reported consistent findings (response in various organ systems and reductions in immunosuppressant use).

12. Economic evaluation

Translation issues

Table 8 summarises the results of the premodelling studies presented in the ADAR.

Table 8: Summary of pre-modelling studies

Pre-modelling study	Description	Results used in economic evaluation
Applicability of clinical evidence to Australian clinical practice	A comparison of patient characteristics and treatments and outcomes in the Australian registry studies with Flowers 2008.	Efficacy of ECP used in the economic model informed from Australian registry studies with the efficacy of SOC based on the relative efficacy of SOC to ECP reported in Flowers (2008).
Natural history of cGVHD	A review of natural history studies of cGVHD for longer-term outcomes (mortality, disease progression and hospitalisations) in the economic model and to assess whether mortality differed for patients who responded to treatment compared with patients who did not.	Rates of mortality reported in the Australian registry studies (stratified by whether or not patients responded to treatment) were used in the model. Hospitalisation data was also used to validate frequency of hospitalisation in the model.
Utility values used in the economic model	Utility values associated with disease progression and treatment were sourced from the literature.	Utility values used in the base case were 0.786 (response) and 0.696 (progressed).

Source: Table C.8, p157 of the ADAR

cGVHD, chronic graft versus host disease; ECP, extracorporeal photopheresis

The ADAR noted that the complete or partial clinical response rate of patients that received ECP plus methoxsalen in the registry (RPAH SAS and VCCC SAS) studies was higher than the complete and partial clinical skin response rate reported by Flowers (2008) (79% and 82% (Table 5) versus 40% (Table 4), respectively). The ADAR attributed this difference to differences in the definition of response from the 2005 NIH guidelines, used in Flowers (2008) and the 2014 NIH guidelines, used in the RPAH SAS and VCCC SAS studies, contending that the clinical assessments made during the RPAH SAS and VCCC SAS studies under the guidance of the 2014 NIH Clinical Guideline may have been more sensitive in detecting partial clinical response following ECP plus methoxsalen treatment than clinical

assessments made in the Flowers (2008) RCT using the 2005 NIH Clinical Guideline. The Commentary noted that the RPAH and VCCC studies did not explicitly define response as per NIH 2014 criteria.

The Commentary highlighted differences in the response rates in the clinical evidence and the economic model. The complete and partial cutaneous response in the ECP arm of Flowers (2008) was 40% compared with 10% in the SOC arm (an increment of 30%). The ADAR assumed that the response rate in the ECP treatment arm is 80.2% (the average of the global complete and partial clinical response rates reported in the RPAH SAS and VCCC SAS – Adult population), and estimated the SOC arm response rate (20.3%) by applying a relative risk of 3.95 based on the complete and partial cutaneous response rates for ECP and SOC at 12 weeks in Flowers (2008), resulting in an increment of 59.9%; i.e. double that observed in the trial. The Commentary suggested that MSAC may wish to consider whether this assumption is adequately justified.

The ADAR estimated that non-responders had a three-times greater per cycle probability of death than in responders. The Commentary noted that this was calculated from RPAH SAS and VCCC SAS data based on an assumption that there was patient follow-up of 4 years. The Commentary noted that, although some of the studies in the natural history review showed statistically significant increases in overall survival associated with response, it did not necessarily support the application of mortality probabilities over assumed time periods from the VCCC SAS and RPAH SAS studies. The Commentary considered that this may be entirely or partially the reason that the model results substantially overestimated mortality in the SOC arm compared to Lee (2018) included in the ADAR’s natural history review.

The economic evaluation is summarised in Table 9.

Table 9: Summary of the economic evaluation

Perspective	Australian health care
Comparator	Standard of Care
Type of economic evaluation	Cost-utility.
Sources of evidence	RPAH and VCCC SAS studies, Flowers 2008
Time horizon	10 years
Outcomes	QALYs
Methods used to generate results	Markov model
Health states	Response (on treatment), response (off treatment), progressed, death
Cycle length	12 weeks
Discount rate	5% for costs and effects
Software packages used	TreeAge 2020 and Excel

Source: Table D.1, p158 of the ADAR

QALY, Quality adjusted life year; RPAH, Royal Prince Albert Hospital; SAS, Special Access Scheme; VCCC, Victorian Comprehensive Cancer Centre

The ADAR presented its economic evaluation in two steps:

- Step 1 is a cost pre responder analysis over a 12 week time horizon.
- Step 2 (base case) is a cost-utility analysis over a 10-year time horizon.

The base case modelled cost-utility analysis has four health states:

- response (on or off treatment),
- progressed,
- death.

Costs in the model included the cost of ECP and SOC treatment as well as health state costs associated with disease monitoring and hospitalisations associated with disease progression.

The Commentary highlighted that the base case of stepped economic evaluation presented in the ADAR inappropriately:

- included the costs (but not effects) of rituximab as a third-line therapy;
- included the costs (but not effects) of IVIg as part of the disease management costs in the ‘progressed’ health state (it is not clear that IVIg is recommended for cGVHD);
- excluded the cost of immunosuppressants in second-line therapy in the ECP arm.

The Commentary considered the inclusion of rituximab as a third-line treatment option contradicted the nominated comparators and clinical management algorithms that do not consider rituximab as part of clinical management. As more patients in the SOC arm continue to third-line therapy in the model, the inclusion of rituximab cost offsets favours ECP.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the intervention and comparator in the model, and using the base case assumptions in the ADAR, are shown in Table 10. The Commentary highlighted that the ADAR did not include model results in terms of life years gained. During the evaluation, all non-death utility health states were set to 1 to estimate the life years accrued in the model. The ECP arm had a mean 5.65 life years versus 4.47 life years in the SOC arm, resulting in an increment of 1.18 life years gained. This was identified by the Commentary as the main driver of QALY gains in the model. However, the Commentary’s sensitivity analyses applying the same per cycle risk of mortality to all patients led to substantial increases in SOC costs, likely due to increased time in progressed health states. The Commentary suggested that MSAC may wish to consider whether the model’s estimation of a survival benefit is reasonable.

Table 10: Results of the stepped analysis

Step	Cost	Incremental cost	Effectiveness	Incremental effectiveness	ICER
<i>Step 1 (cost per response – 12-week time horizon)</i>					
ECP	\$54,178.23	\$48,357	0.80	0.60	\$80,739
SOC	\$5,821.60		0.20		
<i>Step 1B results of step 2 in costs/LYG calculated during the evaluation</i>					
ECP	\$180,020.12	\$24,006	5.65	1.18 LYG	Dominant (-\$20,341)
SOC	\$204,026.09		4.47		
<i>Step 2 (cost per QALY – 10-year time horizon)</i>					
ECP	\$180,020.12	\$24,006	4.31	1.10 QALY	Dominant (-\$21,779)
SOC	\$204,026.09		3.21		

Source: Table D.16, p172 of the ADAR

ECP, extracorporeal photopheresis; ICER, incremental cost-effectiveness ratio; QALY, Quality-adjusted life year; SOC, standard of care.

The Commentary noted that the modelled results were most sensitive (changing from ‘dominant’ to a cost/QALY) to:

- ECP response at 12 weeks (\$24,651/QALY based on a response rate of 40% as reported in Flowers 2008);
- excluding rituximab as third-line therapy (consistent with the ratified PICO Confirmation; \$10,632/QALY); and
- removing intravenous immunoglobulin from progressed state disease management costs (\$20,588/QALY).

Table 11: Key drivers of the economic model

Description	Method/Value	Impact
Removing IVIg from disease management costs of progressed patients	Cost of IVIg is \$5,535 in the base case	High, favours intervention
Excluding rituximab as third-line therapy	Cost of rituximab = \$11,879.67 in the base case	High; favours intervention
ECP week 12 response 40% (as per Flowers 2008)	Response = 80.2% in the base case	High, favours intervention

Source: Table 12, pxxv of the Commentary
ECP, extracorporeal photopheresis; IVIg, intravenous immunoglobulin

On the basis that the inclusion of rituximab as a third-line treatment option is inappropriate and that a 10-year time horizon for the stepped economic evaluation is excessive based on 12 weeks of randomised data, the Commentary suggested that the MSAC may wish to consider a respecified base case. The results of a respecified base case, where the costs of rituximab are removed and the time horizon is reduced to 5 years are presented in Table 12, along with accompanying sensitivity analyses.

Table 12: Alternative base case (5-year duration and rituximab costs removed*) and associated sensitivity analyses

Description	Incremental cost	Incremental QALY	ICER
Alternative base case:	\$25,256	0.52	\$48,754
Response of ECP at week 12 (BC=80.2%) 40%***	\$38,091	0.26	\$147,306
Per cycle probability of death equal for responders and non-responders (0.018)	\$10,398	0.18	\$58,813
Remove IVIg costs from progressed disease management cost**	\$63,429	0.52	\$122,442
Cost of second-line SOC added to ECP (additional \$2,017.52 per cycle)	\$34,192	0.52	\$66,003
Cost of second-line SOC added to ECP and remove IVIg costs	\$72,365	0.52	\$139,692

Source: Analyses conducted during evaluation using Treeage file and clinical inputs attachment

ECP = extracorporeal photopheresis; ICER = incremental cost-effectiveness ratio; QALY = Quality-adjusted life year.

* \$1,558.78 total third line therapy cost after removing rituximab costs and adjusting relative weight of other therapies in “Attachment D1_economic model inputs”

** \$1,612.25 progressed state disease costs after setting IVIg use to 0.

*** The model applies a risk ratio of 3.95 to ECP response at 12 weeks, estimating an SOC response of 10.13% in the alternative base case.

The ICER for the respecified base case is \$48,754/QALY. The Commentary highlighted that this ICER increases substantially with the addition of further reasonable changes to inputs such as treatment effect (40% response in ECP arm = \$147,306/QALY), omission of IVIg costs (\$122,442/QALY) and adding immunosuppressant costs to second-line treatment with ECP (\$66,003/QALY).

The Commentary noted that the response rate (40% for ECP) from Flowers (2008) might not capture potential benefits from reduction in corticosteroids or improvement in extracutaneous

GVHD. The results from Flowers (2008) suggested many patients were able to reduce their corticosteroid dose (>50%) without experiencing a >25% improvement in their TSS. Overall, the Commentary considered that the ADAR’s base case analysis substantially underestimated the ICER. This was largely due to favourable estimates of response, unrealistic long-term modelling of health states, as well as inappropriate costing. The Commentary considered that it was extremely unlikely that ECP would be a cost-saving therapy. However, the Commentary highlighted that ECP could potentially be considered cost-effective with adequate justification for modelling higher response rates than those found in Flowers (2008).

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of ECP treatment for patients with cGVHD who are steroid-refractory, steroid-dependent, or steroid-intolerant. The Commentary noted that, although concern was raised in the PICO Confirmation with respect to use beyond cGVHD patients in patients with aGVHD, PASC confirmed that the population is those with cGVHD and considered that the “chronic” aspect is sufficiently well defined acknowledging the wider consensus amongst treating clinicians in recent times based on the NIH criteria.

The financial implications to the MBS resulting from the proposed listing are summarised in Table 13.

Table 13: Total costs to the MBS associated with ECP treatment in cGVHD

	2022	2023	2024	2025	2026	2027
ECP for cGVHD						
Number of MBS services	5,037	7,354	8,660	8,801	8,119	6,157
Co-payment (80%)	\$ redacted					
<i>Net cost to MBS with corrected co-payment GPG + OMSN^a</i>	\$ redacted					
Methoxsalen 1 vial per ECP session						
Number of scripts	5,037	7,354	8,660	8,801	8,119	6,157
Net cost PBS and RPBS	\$ redacted					
Total net costs						
Total net costs to MBS, PBS and RPBS (ADAR)	\$ redacted					
Total net costs to Government corrected for co-payment, GPG and OMSN^a	\$ redacted					

Source: Table 14, pxxvii of the commentary and calculated by the Department

cGVHD = chronic graft-versus-host disease; ECP = extracorporeal photopheresis; GPG, Greatest Permissible Gap; OMSN, Original Medicare Safety Net

^a Recalculated based on a GPG of \$84.70 and patients exceeding the OMSN (\$477.90) after 6 ECP services.

The Commentary considered that there was potential for the net cost/year to the MBS to be greater than estimated in the ADAR. The ADAR assumed a gradual increase in uptake of

ECP (20%-60%) over the next 6 years. However, the severity of this condition and unmet demand would more likely result in a swifter uptake (depending on specialist staff and device availability). This would increase the net costs for the MBS. The pre-ESC response considered that the uptake rate would likely be limited by the number of closed, integrated ECP machines currently in operation in the two hospitals in Australia.

The ADAR did not consider the [Greatest Permissible Gap](#) which would increase the Medicare benefit to \$1,823.65. Patients would also be eligible for [the Original Medicare Safety Net \(OMSN\)](#) after six ECP services.

The Commentary highlighted that, although estimating the costs to the PBS as a result of methoxsalen being listed for the requested population, the ADAR did not estimate the potential cost savings as a result of the apparent reduction in the use of other immunosuppressants associated with treatment with ECP.

14. Key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Item descriptors restrict the service to adults	ECP is currently used in children in Australia. ESC noted that there is a high clinical need for effective therapies to manage chronic graft-versus-host disease (cGVHD) in children. PASC advised that age should not be specified. Additional data would support use in paediatric populations, including another literature search and inclusion of paediatric data from registry reports.
Unsatisfactory literature search and paucity of high-quality evidence	The literature search was inadequate. Several recent and relevant studies were not included including studies in children. The steroid-sparing effect of ECP was not adequately captured. This resulted in uncertainties throughout the application. MSAC may want to consider requesting the applicant to conduct another literature search.
Uncertain safety and effectiveness	ESC considered that the claim of non-inferior safety and superior effectiveness were uncertain due to small patient numbers, short timeframes, lack of long-term outcomes and high risk of bias in included studies.
Response rate in the economic model	The incremental response rate used in the economic model (60%) was higher than that from the key trial (30%). The pre-ESC response argued the response rate without ECP was based on global response as reported in Australia studies. The incremental cost-effectiveness ratio was sensitive to response rate, increasing from \$48,754 per quality-adjusted life year (QALY) in the revised base case to \$147,306 per QALY.
Issues with the time horizon, structure and inputs of economic model	ESC considered the 10-year time horizon was too long due to the short-term clinical data and considered the 5-year time horizon in the published model may be more appropriate. This is important because the response rates at the end of the initial 12-week cycle of the model were assumed to remain unchanged despite including the use and cost offsets of reduced expensive third-line treatments. ESC considered that this favoured the intervention by overestimating both the survival and quality of life gains. MSAC may therefore consider using the respecified base case with the

	response rates from the key trial, rituximab costs removed and a 5-year time horizon.
Another source of possible underestimation of the ICER	The acceptability of the value of the reduced use of intravenous immunoglobulin (IVIg) as a source of cost offsets is unclear.
Uncertain uptake and financial implications	The financial analysis also did not account for potential financial cost offsets of reduced immunosuppressants which would accrue beyond the MBS.

ESC discussion

ESC noted the purpose of the application to request a new Medicare Benefits Schedule (MBS) listing of an integrated extracorporeal photopheresis (ECP) system, to be used in combination with the drug methoxsalen, to treat patients with chronic graft-versus-host disease (cGVHD) after haematopoietic stem cell transplant who are steroid dependent, intolerant or refractory. This was a codependent submission, with the Pharmaceutical Benefits Advisory Committee (PBAC) consideration to follow MSAC. The technology and drug combination are currently listed on the MBS/Pharmaceutical Benefits Scheme (PBS) for the treatment of end-stage cutaneous T- cell lymphoma.

ESC noted that a treatment session of ECP takes approximately three hours and requires specialised nursing care.

ESC noted the proposed MBS item descriptors for initial and continuing treatment, which restrict the population to adults only, despite advice from PASC that age should not be specified. The proposed technology is currently used in children in Australia, and Australian paediatric clinicians support the use of ECP in children. ESC noted that approximately 20% of allogenic haematopoietic stem cell transplant recipients are aged less than 16 years.⁵ ESC further noted that the requested adult age restriction was based on the Therapeutic Goods Administration– (TGA) approved indication, but PASC had advised the removal of “in adults” from the item descriptor for MSAC consideration. ESC considered that additional data would support use in paediatric populations, including another search of the literature to include paediatric studies that were previously excluded. ESC noted that the ADAR included data from the Victorian Comprehensive Cancer Centre (VCCC) for a small number of children who received ECP until 2018. Paediatric data reported in the systematic review and meta-analysis by Malik (2014)⁶ and the study by Flinn (2020) were extracted for inclusion in the ESC Report. If MSAC was to consider retaining the restriction to adults, ESC advised that the population in the Flowers (2008) trial would support a MBS subsidy limited to patients 13 years and older.

ESC advised that it may be reasonable to limit co-claiming with the specialist MBS item for supervision as this is already included in the proposed fee. ESC confirmed that this would be a Category A procedure, and that both initial and continuing treatment items are required. ESC also agreed with the Department to include “applicable once per treatment cycle” in the item descriptor to align with the existing MBS listing for lymphoma. ESC also noted and supported the Department’s suggested clarifications to the proposed item descriptors.

⁵ Australasian Bone Marrow Transplant Recipient Registry 2019, *Australasian Bone Marrow Transplant Recipient Registry: Annual Data Summary 2018*, ABMTRR, Darlinghurst, NSW, Australia

⁶ Malik MI *et al.* Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis. *Blood Res.* 2014;49(2):100-106.

ESC noted a potential equity issue in that ECP plus methoxsalen is currently only available in two metropolitan centres. The applicant claimed that MBS listing would increase equity, but did not provide supporting information. ESC noted that MBS listing may provide an incentive for highly specialised centres to offer ECP, however it was unclear whether this would be sufficient to widen the provision of ECP.

ESC accepted the comparator (standard of care) and clinical management algorithms in the application, but queried the appropriate standard of care for steroid-intolerant patients.

ESC noted that for people with cGVHD, improvements in mobility from a reduction in skin tightness can be meaningful and provide greater autonomy and dignity. ESC noted that cGVHD can cause significant disability and disfigurement.

ESC noted the Commentary's assessment that the literature search was unsatisfactory. Several apparently relevant studies (including three systematic reviews) were not included, likely because the search and inclusion criteria were overly restrictive. ESC considered all included studies had a high risk of bias, and many had small patient numbers and short timeframes. Studies included one randomised controlled trial (Flowers (2008), a multicentre trial including Australia), Australian registry reports and several prospective observational studies. ESC considered that the included studies were relevant to the proposed listing, but that the literature search was inadequate and results in uncertainties throughout the rest of the application.

ESC noted the claim of non-inferior safety of ECP plus methoxsalen compared with standard of care. The Flowers (2008) study had fewer deaths and similar adverse events to the control arm (except for anaemia being more frequent in the treatment arm), and other studies showed no deaths and a low rate of discontinuation. However, ESC considered that the small patient numbers in the studies and the high risk of bias make this claim uncertain. ESC considered that the evidence presented in the ADAR did not capture the adverse events from long-term high dose corticosteroid use or from other immunosuppressants.

ESC noted the clinical claim of superior effectiveness of ECP plus methoxsalen compared with standard of care. ESC noted that no data were provided for important outcomes such as survival, National Institutes of Health (NIH) score and time-to-event information (e.g. failure-free survival). The key positive results were skin and ocular responses, and reduction in steroid use. The Flowers (2008) study defined its primary endpoint as the median percentage change in total skin score (TTS) after 12 weeks, but found no significant difference between the treatment and control arms. However, in terms of its secondary outcomes, Flowers (2008) reported statistically significant skin response rates and reduction in corticosteroid dose with ECP. ESC considered that interpreting the statistical significance of secondary outcomes was problematic when the primary outcome did not demonstrate superiority. ESC considered that the included studies consistently reported reductions in steroid requirements and increases in quality of life. Overall, ESC considered there was substantial uncertainty regarding the claim for superior effectiveness, given the small patient numbers and high risk of bias in the presented clinical studies.

ESC noted the stepped economic evaluation, which was presented as a cost per responder over 12 weeks, then a cost-utility analysis over 10 years (base case). ESC considered that the 10-year time horizon was too long as it was based on 12 weeks of clinical data and suggested that 5 years may be more appropriate. ESC noted that this would be more consistent with

published models by Crespo (2012)⁷ and de Waure (2015)⁸ that used 5-year and 7-year time horizons, respectively. ESC noted the ADAR did not model the three populations (steroid dependent/refractory/intolerant) separately, and the focus was on steroid-refractory patients. ESC considered that the effect of this on the analysis was uncertain. The model structure did not account for steroid-dependent patients who may already be responding to treatment and thus may not necessarily experience an improvement from ECP treatment.

ESC noted several issues with the model inputs. Response rate is a key input to the model, and the ADAR selected the most favourable input for ECP response at 12 weeks, assuming an 80.2% response rate (average of the global complete and partial clinical response from Australian registry data). However, the Flowers (2008) study showed a response rate of 40% in the ECP arm, and 10% in the standard of care arm based on skin response alone. The ADAR estimated the response rate in the standard of care arm at 20.3% by applying a relative risk of 3.95 based on complete and partial cutaneous response rates for ECP and standard of care at 12 weeks from the Flowers (2008) study. ESC considered that these estimates substantially favoured ECP in the ADAR. The pre-ESC response provided some justification for this, highlighting that 80.2% reflects a global response reflecting criteria used in Australian practice and that the 40% only reflects skin response rather than global response. ESC considered the appropriate response rate may be as low as 40%, reflecting skin response only, and up to 80.2% from Australian registry data.

ESC noted an issue with the model structure, in which the response at the end of the first cycle governs the response for the rest of the model. ESC considered that this was not reasonable. Patients who respond to the current line of therapy may later relapse and patients who do not respond may respond to later-line therapies. ESC considered options for correction could include restructuring the model, or using a 40% response rate (from the Flowers (2008) study) and reducing the time horizon to 5 years to adjust for this indirectly. This indirect adjustment had been done in the Commentary, resulting in an ICER of \$147,306 per QALY gained.

ESC considered that the mortality probabilities were substantially overestimated in the standard of care arm. The model included the costs (but not the health outcomes) of rituximab as a third-line therapy and intravenous immunoglobulin (IVIg) use in the “progressed” health state, and excluded the cost of immunosuppressants in second-line therapy in the ECP arm, which contradicted the clinical management algorithm and the PICO. ESC noted the clinical advice provided in the pre-ESC response that it is “quite common” for patients to develop hypogammaglobulinaemia and therefore require IVIg and qualify for its funded availability through the national blood arrangements. ESC suggested that a basis needed to be found to estimate the extent of reduction in the use of IVIg as a result of using ECP. ESC also noted that MSAC’s judgement of the cost-effectiveness of this use of IVIg would be influenced by the concurrent IVIg review. At its November 2019 meeting, MSAC advised that immunoglobulin (Ig) is not a cost-effective therapy to manage infections in all patients who have acquired hypogammaglobulinaemia secondary to haematological malignancies or post-haemopoietic stem cell transplantation at the current price (p1, [Public Summary Document \[PSD\] Application 1565](#)). ESC considered that the reduction the use of IVIg should be explored in sensitivity analyses of the economic evaluation.

⁷ Crespo C *et al.* Development of a population-based cost-effectiveness model of chronic graft-versus-host disease in Spain. *Clin Ther.* 2012;34(8):1774-1787.

⁸ de Waure C *et al.* Extracorporeal Photopheresis for Second-Line Treatment of Chronic Graft-versus-Host Diseases: Results from a Health Technology Assessment in Italy. *Value Health.* 2015;18(4):457-466.

ESC considered that the ICER in the base case was likely to be substantially underestimated. Model results were most sensitive to changes to ECP response at 12 weeks (changing the ICER from dominant to \$24,651 per QALY gained using the response rates directly from the Flowers study), excluding rituximab as third-line therapy consistent with the PICO Confirmation (ICER of \$10,632 per QALY gained) and removing IVIg from the costs (\$20,588 per QALY gained). The Commentary used a respecified base case, where costs of rituximab were removed and the time horizon was reduced to 5 years, resulting in an ICER of \$48,754. Changing the response rate to ECP to 40% at 12 weeks results in an ICER of \$147,306 per QALY gained; however, the Commentary noted that this may not capture the benefits of reduction of steroids or improvement in extracutaneous GVHD.

ESC noted that the ADAR assumed a gradual increase in uptake of ECP over the next 6 years in its financial analyses, but noted the Commentary's assessment that this was highly uncertain. The Commentary also noted that not all potential cost offsets to all government health budgets had been captured in the financial estimates. ESC noted the revised financial estimates from the Department to account for an 85% benefit for the proposed fee, the Greatest Permissible Gap, and the fact that patients will qualify for the Original Medicare Safety Net after six treatment sessions. ESC considered these revised estimates would be more reflective of the true financial implications of the proposed MBS listing, but noted that the financial cost offsets from the claimed reduction in immunosuppressants and IVIg use were not included.

15. Other significant factors

Nil.

16. Applicant comments on MSAC's Public Summary Document

Mallinckrodt pharmaceuticals and Terumo BCT welcome the positive recommendation that will benefit patients with cGVHD in Australia.

17. Further information on MSAC

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