Australian Government

Department of Health

Application Form

Integrated, closed-system extracorporeal photopheresis with ultraviolet-A irradiation in conjunction with a photoactive drug, methoxsalen, for the treatment of chronic graft-versus-host disease after haematopoietic stem cell transplantation in adults

This application form is to be completed for new and amended requests for public funding (including but not limited to the Medicare Benefits Schedule (MBS)). It describes the detailed information that the Australian Government Department of Health requires to determine whether a proposed medical service is suitable.

Please use this template, along with the associated Application Form Guidelines to prepare your application. Please complete all questions that are applicable to the proposed service, providing relevant information only. Applications not completed in full will not be accepted.

Should you require any further assistance, departmental staff are available through the Health Technology Assessment Team (HTA Team) on the contact numbers and email below to discuss the application form, or any other component of the Medical Services Advisory Committee process.

Email: hta@health.gov.au
Website: www.msac.gov.au

PART 1 – APPLICANT DETAILS

1. Applicant details (primary and alternative contacts)

Corporation / partnership details (where relevant): Mallinckrodt Pharmaceuticals and Terumo BCT Australia Pty Limited
Corporation name: Terumo BCT
ABN: 87130046865
Business trading name: Terumo BCT Australia Pty Limited
Corporation name: Mallinckrodt Pharmaceuticals
ACN: 134086089
Business trading name: Mallinckrodt Pharmaceuticals

Primary contact name: REDACTED

Primary contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

Alternative contact name: REDACTED

Alternative contact numbers
Business: REDACTED
Mobile: REDACTED
Email: REDACTED

2. (a) Are you a lobbyist acting on behalf of an Applicant?

☐ Yes
☒ No

(b) If yes, are you listed on the Register of Lobbyists?

N/A

PART 2 – INFORMATION ABOUT THE PROPOSED MEDICAL SERVICE

3. Application title

The use of integrated, closed-system extracorporeal photopheresis (ECP) with ultraviolet-A (UVA) irradiation in conjunction with a photoactive drug methoxsalen for the treatment of chronic graft-versus-host disease (cGVHD) after haematopoietic stem cell transplantation (HSCT) in adults.

4. Provide a succinct description of the medical condition relevant to the proposed service (no more than 150 words – further information will be requested at Part F of the Application Form)

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 allogenic transplant. Despite prophylactic immunosuppression, there is an increased risk of developing the disease from HSCT. 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. This application focuses on the use of integrated, closed-system ECP in conjunction with methoxsalen for the treatment of cGVHD after HSCT in adults.

This application follows MSAC's (and subsequently PBAC's) recommendation at the April 2020 meeting for a MBS listing of ECP for the treatment of chronic T-cell lymphoma (CTCL).

5. Provide a succinct description of the proposed medical service (no more than 150 words – further information will be requested at Part 6 of the Application Form)

ECP was recently recommended by MSAC in April 2020 for the treatment of CTCL (Application 1420.1). This application proposes the same medical service as described in Application 1420.1 for the treatment of cGVHD in adults.

The details of the key components and clinical steps involved in delivering the intervention refer to the use of THERAKOS CELLEX™ Extracorporeal Photopheresis System; [THERAKOS CELLEX™ ECP].

THERAKOS CELLEX™ 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 (Photopheresis is also performed with open systems, also known as two-step methods, which are characterised by different devices for cell separation and drug photo activation [1, 20]). In these systems the combination of the device for separation and the device for photoactivation has not been approved for use together or specifically approved for Photopheresis [1, 20]. The two-step approach also increases the potential risk of patient reinfusion error, infection and cross-contamination [1, 24]. Open systems are only recommended for use in centres that have approval for handling blood components separately [1].

Figure 1). Integrated, closed ECP systems 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 [1]. All components of the treatment are validated for use together.

6. (a) Is this a request for MBS funding?

☒ Yes
☐ No

(b) If yes, is the medical service(s) proposed to be covered under an existing MBS item number(s) or is a new MBS item(s) being sought altogether?

☐ Amendment to existing MBS item(s)
☒ New MBS item(s)

(c) If an amendment to an existing item(s) is being sought, please list the relevant MBS item number(s) that are to be amended to include the proposed medical service:

N/A

(d) If an amendment to an existing item(s) is being sought, what is the nature of the amendment(s)?

N/A

(e) If a new item(s) is being requested, what is the nature of the change to the MBS being sought?

i. ☐ A new item which also seeks to allow access to the MBS for a specific health practitioner group
ii. ☒ A new item that is proposing a way of clinically delivering a service that is new to the MBS (in terms of new technology and / or population)
iii. ☐ A new item for a specific single consultation item
iv. ☐ A new item for a global consultation item(s)

(f) Is the proposed service seeking public funding other than the MBS?

☒ Yes
☐ No

(g) If yes, please advise:

Should MSAC recommend listing of ECP for cGVHD on the MBS, PBS funding for methoxsalen will be sought.

7. What is the type of service:

☒ Therapeutic medical service
☐ Investigative medical service
☐ Single consultation medical service
☐ Global consultation medical service
☐ Allied health service
☐ Co-dependent technology
☐ Hybrid health technology

8. For investigative services, advise the specific purpose of performing the service *(which could be one or more of the following)*:

i. ☐ To be used as a screening tool in asymptomatic populations
ii. ☐ Assists in establishing a diagnosis in symptomatic patients
iii. ☐ Provides information about prognosis
iv. ☐ Identifies a patient as suitable for therapy by predicting a variation in the effect of the therapy
v. ☐ Monitors a patient over time to assess treatment response and guide subsequent treatment decisions

N/A

9. Does your service rely on another medical product to achieve or to enhance its intended effect?

☒ Pharmaceutical / Biological
☐ Prosthesis or device
☐ No

10. (a) If the proposed service has a pharmaceutical component to it, is it already covered under an existing Pharmaceutical Benefits Scheme (PBS) listing?

☐ Yes
☒ No

(b) If yes, please list the relevant PBS item code(s):

N/A

(c) If no, is an application (submission) in the process of being considered by the Pharmaceutical Benefits Advisory Committee (PBAC)?

☒ Yes (please provide PBAC submission item number below)
☐ No

The PBAC have recently recommended methoxsalen to be used with ECP for CTCL.

(d) If you are seeking both MBS and PBS listing, what is the trade name and generic name of the pharmaceutical?

Trade name: UVADEX®
Generic name: methoxsalen
N/A

11. (a) If the proposed service is dependent on the use of a prosthesis, is it already included on the Prostheses List?

N/A

(b) If yes, please provide the following information (where relevant):

N/A

(c) If no, is an application in the process of being considered by a Clinical Advisory Group or the Prostheses List Advisory Committee (PLAC)?

N/A

(d) Are there any other sponsor(s) and / or manufacturer(s) that have a similar prosthesis or device component in the Australian market place which this application is relevant to?

☐ Yes
☒ No

(e) If yes, please provide the name(s) of the sponsor(s) and / or manufacturer(s):

N/A

12. Please identify any single and / or multi-use consumables delivered as part of the service?

Single use consumable: Each ECP procedure requires a closed-system, single use disposable pre-connected sterile system.

PART 3 – INFORMATION ABOUT REGULATORY REQUIREMENTS

13. (a) If the proposed medical service involves the use of a medical device, in-vitro diagnostic test, pharmaceutical product, radioactive tracer or any other type of therapeutic good, please provide the following details:

Type of therapeutic good: THERAKOS CELLEX™ ECP Medical Device System
Manufacturer's name: Mallinckrodt Pharmaceuticals Ireland Limited
Sponsor's name: Terumo BCT Australia Pty Ltd

(b) Is the medical device classified by the TGA as either a Class III or Active Implantable Medical Device (AIMD) against the TGA regulatory scheme for devices?

☐ Class III
☐ AIMD
☒ N/A

14. (a) Is the therapeutic good to be used in the service exempt from the regulatory requirements of the *Therapeutic Goods Act 1989*?

☐ Yes (If yes, please provide supporting documentation as an attachment to this application form)
☒ No

(b) If no, has it been listed or registered or included in the Australian Register of Therapeutic Goods (ARTG) by the Therapeutic Goods Administration (TGA)?

☒ Yes (if yes, please provide details below)
☐ No

Items on the ARTG that are relevant to this application are shown in

Table 1. The four items listed are:

- The Photopheresis system
- The Photopheresis system lamp assembly
- The Photopheresis system blood set
- UVADEX® (methoxsalen)

Table 1 ECP components listed with the ARTG

ARTG no.	Product description	Product category	Sponsor	Effective date
330061	Photopheresis system blood set	Medical device system	Terumo BCT Australia Pty Ltd	17/02/2020
329261	Photopheresis system lamp assembly	Medical device system	Terumo BCT Australia Pty Ltd	30/01/2020
329260	Photopheresis system	Medical device system	Terumo BCT Australia Pty Ltd	30/01/2020
AUST R 308832	UVADEX® (methoxsalen)	Registered Medicine	Terumo BCT Australia Pty Ltd	16/09/2019

Source: Therapeutic Goods Administration

UVADEX (methoxsalen) is indicated for extracorporeal administration with the THERAKOS CELLEX™ Photopheresis System for the:
-treatment of steroid-refractory and steroid-intolerant chronic graft-versus-host disease (cGVHD) in adults following allogeneic HSCT.
-palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

15. If the therapeutic good has not been listed, registered or included in the ARTG, is the therapeutic good in the process of being considered for inclusion by the TGA?

N/A

16. If the therapeutic good is not in the process of being considered for listing, registration or inclusion by the TGA, is an application to the TGA being prepared?

N/A

PART 4 – SUMMARY OF EVIDENCE

17. **Provide an overview of all key journal articles or research published in the public domain related to the proposed service that is for your application (limiting these to the English language only).** ***Please do not attach full text articles, this is just intended to be a summary.***

	Type of study design*	**Title of journal article or research project (including any trial identifier or study lead if relevant)**	**Short description of research (max 50 words) ****	**Website link to journal article or research (if available)**	**Date of publication*****
1.	RCT	A multicenter prospective phase 2 randomized study of extracorporeal photopheresis for treatment of chronic graft-versus-host disease.[2]	This study (N=100) compared ECP plus standard therapy with standard therapy alone in refractory cGVHD. The skin assessment revealed a significant improvement in favour of ECP (P <0.001). ECP was generally well-tolerated and may have a steroid-sparing effect in the treatment of cGVHD. (NCT00054613).	https://ashpublications.org/blood/article/112/7/2667/24720/A-multicenter-prospective-phase-2-randomized-study	2008
2.	Non-randomised trial	Impact of extracorporeal photopheresis on skin scores and quality of life in patients with steroid-refractory chronic GVHD.[3]	This single-centre prospective study assessed a total of 52 consecutive patients commenced ECP treatment for cGVHD in the UK. 70% of patients achieved a complete or partial response. Improvements in QoL and reductions in immunosuppression doses were also observed.	https://www.nature.com/articles/bmt201421	2014
3.	Single-arm trial	A Prospective Trial of Extracorporeal Photopheresis for Chronic Graft-versus-Host Disease Reveals Significant Disease Response and No Association With Frequency of Regulatory T Cells.[4]	A prospective multicentre clinical trial to assess ECP response rates in 83 patients with cGVHD in the US. ECP treatment induced an overall response rate of 62% by investigator response and significant reduction in steroid dose from baseline.	https://www.bbmt.org/article/S1083-8791(18)30384-7/fulltext	2018
4.	Review	Oral chronic graft-versus-host disease: report from the International Consensus Conference on clinical practice in cGVHD.[5]	The consensus conference summarised the literature on diagnosis and topical treatment options for oral cGVHD and to provide recommendations for clinical practice. Optimal treatment involves interdisciplinary teamwork, and the treatment plan should address the type of oral cGVHD manifestation.	https://link.springer.com/article/10.1007/s00784-010-0450-6	2011

	Type of study design*	Title of journal article or research project (including any trial identifier or study lead if relevant)	Short description of research (max 50 words) **	Website link to journal article or research (if available)	Date of publication***
5.	Systematic review	Extracorporeal photopheresis for chronic graft-versus-host disease: a systematic review and meta-analysis.[6]	The search generated 312 studies, of which 18 met the selection criteria (N=595). ECP was found to be an effective therapy for oral, skin, and liver cGVHD, with modest activity in lung and gastrointestinal cGVHD.	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4090330/	2014
6.	Systematic review	Extracorporeal Photopheresis in Steroid-Refractory Acute or Chronic Graft-versus-Host Disease: Results of a Systematic Review of Prospective Studies.[7]	The search identified 9 studies, including 1 RCT, that met the inclusion criteria (N=323). The studies showed encouraging responses after ECP treatment, particularly in cutaneous, gastrointestinal, hepatic, and oral mucosa.	https://www.sciencedirect.com/science/article/pii/S1083879114003152	2014
7.	RCT	Randomized controlled study of ECP with methoxsalen as first-line treatment of patients with moderate to severe cGVHD.[8]	60 patients were enrolled to investigate ECP use as first-line therapy in cGVHD. The results suggest that ECP with methoxsalen is a well-tolerated first-line treatment of cGVHD in patients who have undergone HSCT. (NCT01380535)	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6650730/	2019
8.	Non-randomised trial	Influence of extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response.[9]	28 patients were treated with ECP, to investigate clinical and laboratory parameters in cGVHD. Encouraging responses were seen for skin scores and systemic immunosuppression was stable or reduced. Overall, baseline parameters predicted a modest response to ECP.	https://ashpublications.org/blood/article/102/4/1217/17103/Influence-of-extracorporeal-photopheresis-on	2003
9.	Non-randomised trial	Prospective study of extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: Analysis of response and survival incorporating prognostic factors.[10]	Enrolled 25 patients with extensive, steroid-refractory cGVHD in a prospective trial evaluating the efficacy of ECP. In summary, the authors reported improvement in skin and/or visceral cGVHD in 71% overall and 61% of high risk patients.	https://www.nature.com/articles/1704984	2005

**Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment, including providing the trial registration number to allow for tracking purposes.*

****If the publication is a follow-up to an initial publication, please advise.*

18. Identify yet to be published research that may have results available in the near future that could be relevant in the consideration of your application by MSAC (limiting these to the English language only). *Please do not attach full text articles, this is just intended to be a summary.*

	Type of study design*	**Title of research (including any trial identifier if relevant)**	**Short description of research (max 50 words)****	**Website link to research (if available)**	**Date*****
1.	Non-randomised trial	Extracorporeal Photopheresis (ECP) at Royal Prince Alfred Hospital for Chronic Graft Versus Host Disease.	44 patients are enrolled in this prospective trial to evaluate the efficacy and safety of ECP treatment in cGVHD patients. The data shows ECP to be safe and well-tolerated. The data supports prior findings from RCTs and prospective, and retrospective, studies.	NA	2018
2.	Non-randomised trial	ECP Activity and Treatment Outcome Summary Report from VCCC.	46 patients are enrolled in this prospective trial to evaluate the efficacy and safety of ECP treatment in Australian cGVHD patients. Overall, response to ECP is shown to be high, with a promising safety profile.	NA	2018

**Categorise study design, for example meta-analysis, randomised trials, non-randomised trial or observational study, study of diagnostic accuracy, etc.*

***Provide high level information including population numbers and whether patients are being recruited or in post-recruitment.*

****Date of when results will be made available (to the best of your knowledge).*

PART 5 – CLINICAL ENDORSEMENT AND CONSUMER INFORMATION

19. **List all appropriate professional bodies / organisations representing the group(s) of health professionals who provide the service (please attach a statement of clinical relevance from each group nominated):**

    Royal Prince Alfred Hospital

    Peter MacCallum Cancer Centre

    Bone Marrow Transplant Society of Australia and New Zealand (BMTSANZ)

    BMT Network NSW

20. **List any professional bodies / organisations that may be impacted by this medical service (i.e. those who provide the comparator service):**

    Same as above

21. **List the consumer organisations relevant to the proposed medical service (please attach a letter of support for each consumer organisation nominated):**

    Leukaemia Foundation

22. **List the relevant sponsor(s) and / or manufacturer(s) who produce similar products relevant to the proposed medical service:**

    N/A

23. **Nominate two experts who could be approached about the proposed medical service and the current clinical management of the service(s):**

    Name of expert 1: REDACTED
    Telephone number(s): REDACTED
    Email address: REDACTED
    Justification of expertise: REDACTED.

    Name of expert 2: REDACTED
    Telephone number(s): REDACTED
    Email address: REDACTED
    Justification of expertise: REDACTED

    Please note that the Department may also consult with other referrers, proceduralists and disease specialists to obtain their insight.

PART 6 – POPULATION (AND PRIOR TESTS), INTERVENTION, COMPARATOR, OUTCOME (PICO)

PART 6a – INFORMATION ABOUT THE PROPOSED POPULATION

24. Define the medical condition, including providing information on the natural history of the condition and a high level summary of associated burden of disease in terms of both morbidity and mortality:

The proposed medical service, integrated, closed-system ECP, is to be used adjunctively with UVA irradiation in conjunction with a photoactive drug methoxsalen, for the treatment of cGVHD after HSCT in adults. GVHD is a common, serious and sometimes fatal immune-mediated disease resulting from a complex interaction between donor and recipient adaptive immunity [11, 12]. Activated donor T cells attack the tissues of the transplant recipient as antigenic differences cause the immune response to recognise host tissues as antigenically foreign. The resulting inflammatory cytokines cause tissue damage, with the most commonly involved organs including the liver, skin, mucosa, and the gastrointestinal tract.

The diagnosis of cGVHD is based on a specific set of clinical features for different organs which are outlines in the National Institutes of Health (NIH) Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease [13].

cGVHD remains one of the major complications after HSCT, and the leading cause of non-relapse mortality in patients surviving more than two years [14]. Despite the advances in transplant practice, the incidence of cGVHD is increasing. Major reasons are increased use of allogenic HSCT in older recipients and improvements made in treatments post allogenic HSCT prolonging survival [15]. In NSW, it is estimated that 69% of allogenic HSCT patients develop cGVHD [16]. cGVHD-related mortality is estimated at between 20% to 40% of affected patients depending on severity [17]. Affected patients require long-term use of immunosuppressive drugs associated with the development of severe side effects and low ongoing quality of life that parallel systemic autoimmune diseases [15, 18]. The greater comorbidity burden is associated with higher rates of non-relapse mortality and inferior overall survival [18]. Options for second-line therapy are numerous but consensus on the most favourable choice of agent(s) has not been reached and patients not responding to steroids are at a high risk of death.

25. Specify any characteristics of patients with the medical condition, or suspected of, who are proposed to be eligible for the proposed medical service, including any details of how a patient would be investigated, managed and referred within the Australian health care system in the lead up to being considered eligible for the service:

The proposed population for cGVHD is based on clinical guidelines, TGA indication and pivotal trial evidence for ECP.

Patients who would be eligible for the proposed medical service is adults with cGVHD following HSCT who are steroid-refractory or steroid-dependent or steroid-intolerant. The 2014 NIH Consensus [13] define cGVHD patients who are steroid-refractory or steroid-dependent as the following:

- Steroid-refractory when manifestations progress despite the use of a regimen containing prednisone at >1 mg/kg/day for at least 1 week or persist without improvement despite continued treatment with prednisone at >.5 mg/kg/day or 1 mg/kg every other day for at least 4 weeks.
- Steroid-dependent when prednisone doses > 0.25 mg/kg/day or > 0.5 mg/kg every other day are needed to prevent recurrence or progression of manifestations as demonstrated by unsuccessful attempts to taper the dose to lower levels on at least two occasions, separated by at least 8 weeks.

In addition, steroid-intolerance is defined as when patients who are unable to tolerate the side effects of adequate doses of systemic steroids [19].

For a patient to receive the proposed medical service, clinicians assess patient response to first-line therapy and define the clinical need for second-line treatment. Patient assessment to first-line therapy depends on the severity of patient condition, where milder cases are reviewed monthly and the more severe presentations on a weekly basis. Clinician follow-up duration also varies depending on the severity of the cases presented. Most respondents use the NIH consensus criteria for diagnosing and scoring the severity of cGVHD, but clinicians also consider patient QoL, the long-term implications of steroid use and if patient response to first-line treatment is unclear, partial, or mixed. These considerations aid respondents to define the clinical need for second-line therapy.

26. Define and summarise the current clinical management pathway *before* patients would be eligible for the proposed medical service (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway up to this point):

International clinical guidelines published in the last 5 years make a consistent recommendation for ECP in steroid-refractory/intolerant/dependent adult cGVHD patients, based on comprehensive reviews of the extensive published data for ECP in this indication [1, 19-25]. Expert panels believe that available evidence supports the second-line use of ECP in GVHD [20].

To better understand the treatment algorithm in Australia, the Sponsor undertook a treatment survey to understand the current cGVHD treatment algorithm and to inform a hypothetical treatment algorithm for cGVHD after MBS listing of ECP. In addition, to understand the nuances in therapy selection between treatment centres, face-to-face clinician interviews were also conducted by the Sponsor to provide the greatest insight into the current cGVHD treatment algorithm and likely impact with the reimbursement of ECP.

The treatment algorithm based on the survey and clinician interviews is summarised in Appendix A – Figure 2. As expected, all clinicians recommended steroids as first-line therapy, administered intravenously or as a tablet (depending on organ involvement) with the most recommended dose being 1 mg/kg on a daily or weekly basis. Steroids are most likely to be considered because international guidelines recognise them as appropriate and effective for first-line treatment [26]. They are also less costly and are more widely available in comparison to other treatment choices. In addition, 71% and 29% of clinicians surveyed also considered calcineurin inhibitors and mycophenalate as treatment options in first-line therapy in combination with steroids.

There was consensus amongst respondents that ECP should be used earlier rather than later for patients with cGVHD. The majority of clinicians (86%) considered that second-line treatment would be most appropriate for ECP. Most clinicians agreed that ECP improves patient symptoms, QoL, survival benefit and reduces the use of other treatments (steroids and other immunosuppressants) associated with severe adverse events (AEs).

Similar to the guidelines, the treatment survey and clinician interviews confirmed that a broad range of other second-line therapies are considered. Importantly, clinicians note that guidelines do not specify what second-line therapy to use, therefore, the treatment algorithm is not standardised and is dependent on physician experience, ease of use, need for monitoring, risk toxicity and pre-existing comorbidities. The most commonly used therapies in the second-line setting were mycophenolate, calcineurin inhibitors, rituximab, ruxolitinib and ibrutinib. The clinicians also indicated that these therapies should be added-on to the existing first-line therapies, with a goal to weaning patients off steroid therapy.

While a preference for ruxolitinib and ibrutinib is noted by clinicians because of prospective trial evidence demonstrating effectiveness, these therapies are prohibitively expensive (not reimbursed on the PBS) and only available through clinical trials or compassionate access from their respective manufacturers. Hence, they would not be a considered comparator option as MSAC have a clear preference for comparator therapies that are widely available and listed on the PBS. Notably, mycophenolate, prednisone, tacrolimus and ciclosporin have unrestricted listings on the PBS. Therefore, considering accessible accessibility, the standard of care second-line reimbursed treatment in Australia is continued steroid use in combination with mycophenolate mofetil or calcineurin inhibitors.

PART 6b – INFORMATION ABOUT THE INTERVENTION

27. Describe the key components and clinical steps involved in delivering the proposed medical service:

The details of the key components and clinical steps involved in delivery the intervention specially refer to the use of THERAKOS CELLEX^{TM} Extracorporeal Photopheresis System; [THERAKOS CELLEX^{TM} ECP].

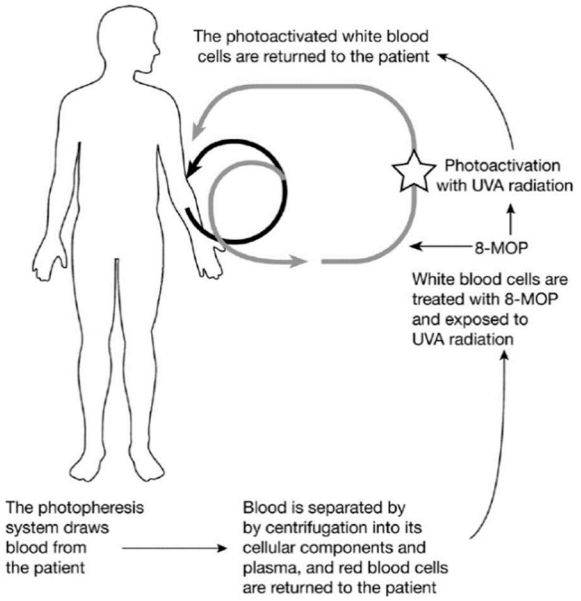
THERAKOS CELLEX^{TM} ECP is a leukapheresis-based, immunomodulatory therapy in which a patient's leukocytes are collected and treated ex vivo with methoxsalen and UVA light and then returned to the patient (Photopheresis is also performed with open systems, also known as two-step methods, which are characterised by different devices for cell separation and drug photo activation [1, 20]). In these systems the combination of the device for separation and the device for photoactivation has not been approved for use together or specifically approved for Photopheresis [1, 20]. The two-step approach also increases the potential risk of patient reinfusion error, infection and cross-contamination [1, 24]. Open systems are only recommended for use in centres that have approval for handling blood components separately [1].

Figure 1). Integrated, closed ECP systems 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 [1]. All components of the treatment are validated for use together.

During the integrated, closed-system ECP procedure, white blood cells are separated from whole blood via apheresis, combined with a photoactive drug, methoxsalen (UVADEX®), and then exposed to UVA light. All blood components, including the treated white blood cells are returned to the patient. There is a high unmet clinical need for GVHD patients to receive ECP as a reimbursed treatment. It is currently used through ad hoc state funding and accessible through two primary users in Australia, despite strong clinician (86%) preference for steroid-refractory/dependent/intolerant cGVHD patient treatment with ECP and very strong (100%) agreement on the significant positive symptom response rates witnessed.

Photopheresis is also performed with open systems, also known as two-step methods, which are characterised by different devices for cell separation and drug photo activation [1, 20]). In these systems the combination of the device for separation and the device for photoactivation has not been approved for use together or specifically approved for Photopheresis [1, 20]. The two-step approach also increases the potential risk of patient reinfusion error, infection and cross-contamination [1, 24]. Open systems are only recommended for use in centres that have approval for handling blood components separately [1].

Figure 1: Overview of ECP. Blood is removed from the patient, and the red blood cells (RBC) and white blood cells (WBC) are separated. RBC are immediately returned to the patient, whereas WBC are treated with methoxsalen (8-MOP) and ultraviolet-A (UVA) radiation to photoactivate the drug; photoactivated WBC are then returned to the patient



28. Does the proposed medical service include a registered trademark component with characteristics that distinguishes it from other similar health components?

The device used to perform the proposed medical service, does include a registered trademark component (THERAKOS CELLEX^{TM}), which is a leukapheresis-based, immunomodulatory therapy available in Australia.

29. If the proposed medical service has a prosthesis or device component to it, does it involve a new approach towards managing a particular sub-group of the population with the specific medical condition?

The proposed medical service has a device component to it and involves the delivery of the application of the photoactive drug methoxsalen that when exposed to ultraviolet light induces apoptosis (programmed cell death) in treated T-lymphocytes. The medical service for cGVHD is the same as for the treatment of CTCL.

30. If applicable, are there any limitations on the provision of the proposed medical service delivered to the patient (i.e. accessibility, dosage, quantity, duration or frequency):

The proposed medical service is to be used adjunctively with UVA irradiation in conjunction with photoactive drug methoxsalen. Methoxsalen dosage is calculated according to the treatment volume (which is displayed on the display panel of the instrument) and the complete photopheresis procedure is up to 3 hours in duration. Three ECP treatments are conducted in the first week followed by two ECP treatments per week for at least 12 weeks, or as clinically indicated.

The proposed medical service is currently only delivered at Royal Prince Alfred Hospital and Victorian Comprehensive Cancer Centre by two primary users through state ad hoc funding. A listing of the proposed medical device on the MBS would help facilitate broader access to ECP.

31. If applicable, identify any healthcare resources or other medical services that would need to be delivered <u>at the same time</u> as the proposed medical service:

The healthcare resources required at the same time as the proposed medical service include specialist consultation fees, ECP service administration and supervision nursing fees, and the cost of consumables. The integrated, closed-system ECP service fee primarily includes professional services associated with three major steps: apheresis, drug administration and photoactivation. The proposed medical device should be delivered by specially trained, experienced nursing staff and supervised by specialised haematologists in accredited medical centres. REDACTED

32. If applicable, advise which health professionals will primarily deliver the proposed service:

The proposed medical service relates to initiation and supervision of ECP by a haematologist.

33. If applicable, advise whether the proposed medical service could be delegated or referred to another professional for delivery:

The proposed medical service could be delegated or referred to nursing staff under the supervision of a consultant haematologist.

34. If applicable, specify any proposed limitations on who might deliver the proposed medical service, or who might provide a referral for it:

As for application 1420.1 for CTCL it is proposed that treatment must be under supervision of a consultant haematologist.

35. If applicable, advise what type of training or qualifications would be required to perform the proposed service, as well as any accreditation requirements to support service delivery:

As detailed for application 1420.1, the training for physicians is done by the Sponsor and includes a comprehensive support programme to ensure the quality use of medicine (QUM) of ECP and methoxsalen. The support programme provided by the Sponsor includes:

- System installation, maintenance and upgrade support, scheduled and preventative maintenance, as well as on-site repair when needed
- On-site initial training for nurses, ECP specialists, physicians and other HCPs
- Periodic on-site training

- Constant on-site procedural support, including bespoke training for CTCL patient populations
- Hotline offering rapid support and troubleshooting services
- Access to an online hub which provides operators of all experience levels with product, training and educational materials

36. (a) Indicate the proposed setting(s) in which the proposed medical service will be delivered (select ALL relevant settings):

☒ Inpatient private hospital (admitted patient)
☒ Inpatient public hospital (admitted patient)
☒ Private outpatient clinic
☒ Public outpatient clinic
☐ Emergency Department
☐ Private consulting rooms - GP
☐ Private consulting rooms – specialist
☐ Private consulting rooms – other health practitioner (nurse or allied health)
☐ Private day surgery clinic (admitted patient)
☐ Private day surgery clinic (non-admitted patient)
☐ Public day surgery clinic (admitted patient)
☐ Public day surgery clinic (non-admitted patient)
☐ Residential aged care facility
☐ Patient's home
☐ Laboratory
☐ Other – please specify below

(b) Where the proposed medical service is provided in more than one setting, please describe the rationale related to each:

The complete photopheresis procedure is up to 3 hours in duration and thus can be delivered in an outpatient setting. Three ECP treatments are conducted in the first week followed by two ECP treatments per week for at least 12 weeks, or as clinically indicated. Patients regarded to be more unwell may need overnight care and therefore inpatient admission may be necessary in both a private and public hospital setting.

37. Is the proposed medical service intended to be entirely rendered in Australia?

☒ Yes
☐ No – please specify below

PART 6c – INFORMATION ABOUT THE COMPARATOR(S)

38. Nominate the appropriate comparator(s) for the proposed medical service, i.e. how is the proposed population currently managed in the absence of the proposed medical service being available in the Australian health care system (including identifying health care resources that are needed to be delivered at the same time as the comparator service):

Based on the treatment survey and clinician interviews described in Section 26, the nominated comparator is continued steroid use in combination with mycophenolate or calcineurin inhibitor. Guidelines do not specify what second-line therapy to use in treating cGVHD, therefore the treatment algorithm is not standardised and is dependent on physician experience, ease of use, need for monitoring, risk toxicity and pre-existing comorbidities. clinician insights suggested a broad range of second-line therapies and as demonstrated with the CTCL MSAC submissions, MSAC have a clear preference for comparator therapies that are listed on the PBS. Notably, mycophenolate mofetil, prednisone, tacrolimus and ciclosporin have unrestricted listings on the PBS. Therefore, considering accessible reimbursed treatments, the stand of care second-line reimbursed treatment in Australia is continued steroid use in combination with mycophenolate or calcineurin inhibitors.

Other alternative therapies considered by clinicians in the second-line setting are rituximab, ruxolitinib, and ibrutinib. clinicians also indicated that these therapies should be added-on to the existing first-line therapies, with a goal to wean patients off steroid therapy. While a preference for ruxolitinib and ibrutinib is noted by clinicians, because of prospective evidence demonstrating effectiveness, these therapies are not reimbursed on the PBS and only available through clinical trials or compassionate access from their respective manufacturers. Hence, they would not be a considered comparator option as MSAC have a clear preference for comparator therapies that are listed on the PBS.

39. Does the medical service (that has been nominated as the comparator) have an existing MBS item number(s)?

☐ Yes (please list all relevant MBS item numbers below)
☒ No

40. Define and summarise the current clinical management pathway/s that patients may follow *after* they receive the medical service that has been nominated as the comparator (supplement this summary with an easy to follow flowchart [as an attachment to the Application Form] depicting the current clinical management pathway that patients may follow from the point of receiving the comparator onwards, including health care resources):

cGVHD patient progression to third-line therapy is considered after assessing patient response to second-line therapy and defining the clinical need for third-line therapy. Patient assessment and establishment for the clinical need of third-line therapy follows the same assessment from first- to second-line therapy Patient progression to third-line therapy is depended on the severity of patient condition and their response to second-line treatment. Clinicians also considered patient QoL and the long-term implications of steroid use. Importantly, guidelines do not specify what third-line therapy to use, therefore the treatment algorithm is not standardised and is dependent on physician experience, ease of use, need for monitoring, risk toxicity and pre-existing comorbidities. Also, by third-line therapy any treatment not previously used in first- or second-line treatment for cGVHD is considered (Appendix A – Figure 2)..

41. (a) Will the proposed medical service be used in addition to, or instead of, the nominated comparator(s)?

☒ In addition to (i.e. it is an add-on service)
☐ Instead of (i.e. it is a replacement or alternative)

(b) If instead of (i.e. alternative service), please outline the extent to which the current service/comparator is expected to be substituted:

N/A

42. Define and summarise how current clinical management pathways (from the point of service delivery onwards) are expected to change as a consequence of introducing the proposed medical service, including variation in health care resources (Refer to Question 39 as baseline):

Integrated, closed-system ECP for the treatment of cGVHD reduces the use of other second- and third-line treatments potentially associated with severe adverse events (AEs), reducing the pill burden that is associated with steroids and other medication treatments (as often patients can end up on a chain of medications) and may also reduce the dependency on high cost procedures (i.e. surgical costs).

PART 6d – INFORMATION ABOUT THE CLINICAL OUTCOME

43. Summarise the clinical claims for the proposed medical service against the appropriate comparator(s), in terms of consequences for health outcomes (comparative benefits and harms):

Based on the evidence available for the proposed medical service, ECP has demonstrated encouraging response, steroid-sparing effect, QoL and overall survival in steroids-refractory/intolerant/dependent cGVHD. ECP is generally well-tolerated with a low incidence rate of adverse events as well as reducing AEs associated with immunosuppressive treatment due to its steroid-and other immunosuppressive-sparing effect.

Therefore, the clinical claim is that ECP has superior efficacy and safety compared with best standard of care.

44. Please advise if the overall clinical claim is for:

☒ Superiority
☐ Non-inferiority

45. Below, list the key health outcomes (major and minor – prioritising major key health outcomes first) that will need to be specifically measured in assessing the clinical claim of the proposed medical service versus the comparator:

Safety Outcomes:
Adverse events, serious adverse events, treatment-related adverse events
Clinical Effectiveness Outcomes:
Objective response, complete and partial response
Total skin score
Steroid dose reduction

PART 7 – INFORMATION ABOUT ESTIMATED UTILISATION

46. Estimate the prevalence and/or incidence of the proposed population:

The incidence of cGVHD in adults is estimated from associated publications from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR). In 2013, 485 allogeneic HSCT in patients aged 16 years and over were performed in Australia [27]. In NSW, it is estimated that 69% of adult patients develop cGVHD following allogeneic HSCT[16]. It is estimated that 40% of patients achieve a complete or partial response to first-line treatment[28, 29]. Therefore, it is estimated that up to 201 (i.e. 485x69%(60%)) could be eligible for ECP treatment per year.

47. Estimate the number of times the proposed medical service(s) would be delivered to a patient per year:

According to the PI, the recommended dosing for cGVHD is three ECP treatments in the first week then two ECP treatments per week for at least 12 weeks, or as clinically indicated.

48. How many years would the proposed medical service(s) be required for the patient?

If there is no evidence of response at 12 weeks, treatment is discontinued. If response is noted, patient can continue two treatments every 4 weeks for another 12 weeks. Treatment beyond 12 - 24 weeks is determined by the treating haematologist.

49. Estimate the projected number of patients who will utilise the proposed medical service(s) for the first full year:

The availability of ECP devices (currently only available at RPAH and VCCC) may restrict the number of patients treated in the first year with ECP.

50. Estimate the anticipated uptake of the proposed medical service over the next three years factoring in any constraints in the health system in meeting the needs of the proposed population (such as supply and demand factors) as well as provide commentary on risk of 'leakage' to populations not targeted by the service:

It is expected that the uptake of ECP would increase in subsequent years as ECP machines become available at more treatment centres following an MBS listing. A more detailed utilisation analysis using the most recent available data from the ABMTRR will be presented in the Assessment Report.

PART 8 – COST INFORMATION

51. Indicate the likely cost of providing the proposed medical service. Where possible, please provide overall cost and breakdown:

REDACTED

52. Specify how long the proposed medical service typically takes to perform:

The complete photopheresis procedure is 2 to 3 hours in duration.

53. If public funding is sought through the MBS, please draft a proposed MBS item descriptor to define the population and medical service usage characteristics that would define eligibility for MBS funding.

Category 3 – Therapeutic procedures
MBS 38xxx INTEGRATED, CLOSED- EXTRACORPOREAL PHOTOPHERESIS SYSTEMS for the ECP treatment of chronic graft-versus-host disease (cGVHD) in adults following allogeneic HSC transplantation, 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. REDACTED

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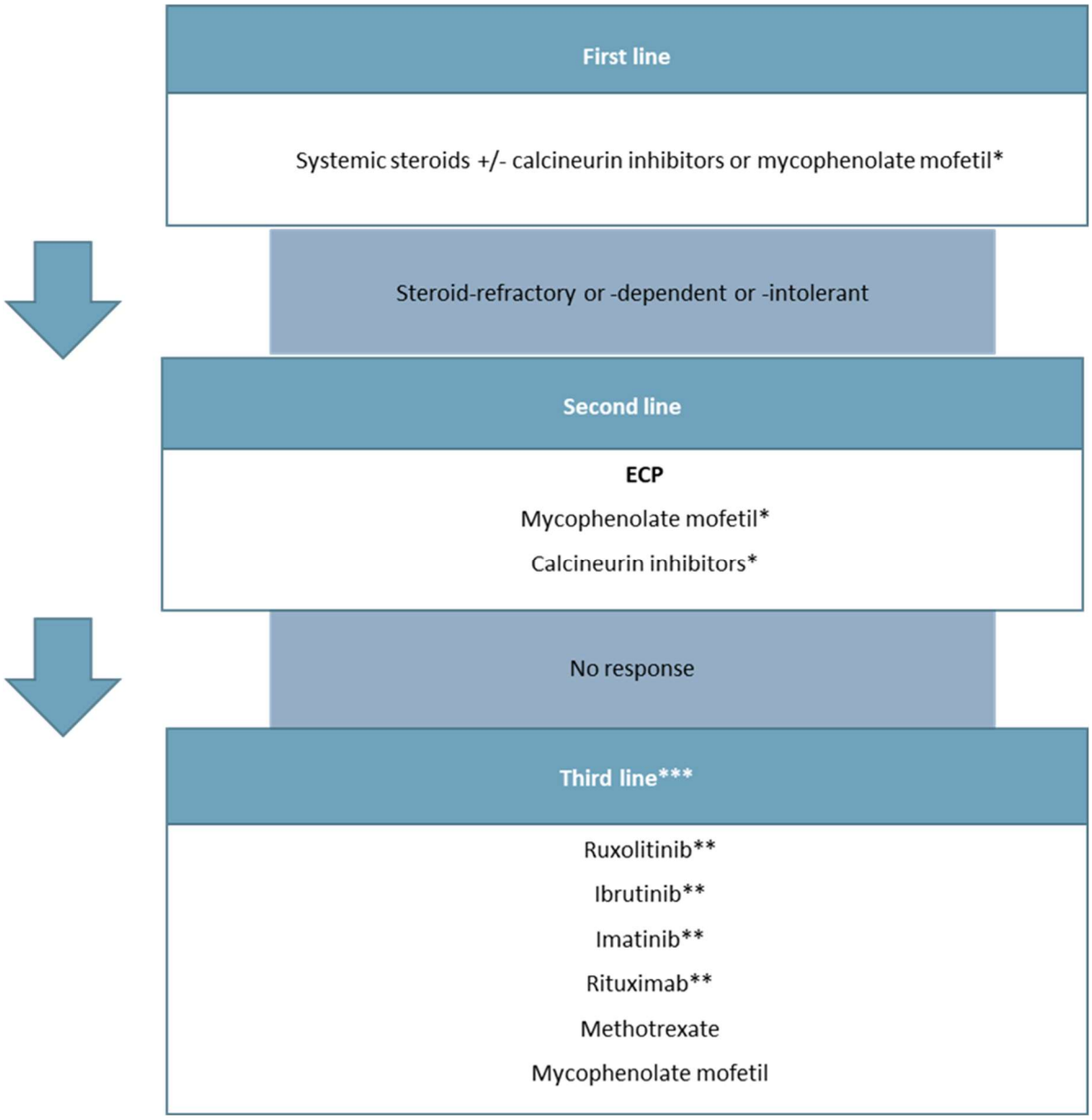
Appendix A

Figure 2: Clinical management algorithm for steroid-refractory/dependent/intolerant cGVHD patients



*mycophenolate mofetil, systemic steroids and calcineurin inhibitors have unrestricted listings on the PBS.
**These therapies are not reimbursed on the PBS and are only available through clinical trials or compassionate access from their respective manufacturers.
***There was a consensus amongst clinicians that by this line of treatment they would consider any therapy they had not already used in first- or second-line treatment for cGVHD.
Abbreviations: ECP, extracorporeal photopheresis; cGVHD, chronic graft versus host disease