

**6.22 METHOXSALEN,
Solution for blood fraction 20 microgram per mL,
10 mL,
Uvadex[®],
Terumo BCT Australia Pty Ltd**

1 Purpose of Application

- 1.1 The Category 3 submission requested a Section 100 (Highly Specialised Drugs Program), Authority Required (STREAMLINED) listing for the treatment of patients with steroid dependent, steroid intolerant or steroid refractory chronic graft versus host disease (herein referred to as treatment refractory cGVHD), as part of treatment with integrated, closed system extracorporeal photopheresis (ECP).
- 1.2 As the medicine (PBAC relevant) component is substantially smaller in overall scope and financial implications compared to the procedure (Medical Services Advisory Committee [MSAC] relevant) component, the clinical and cost effectiveness, and estimated overall financial implications will be considered by MSAC.

2 Background

Registration status

- 2.1 Methoxsalen was TGA registered on 16 September 2019 for extracorporeal administration with the THERAKOS CELLEX Photopheresis System for the following indications:
 - treatment of steroid-refractory and steroid-intolerant chronic graft versus host disease (cGVHD) in adults following allogeneic HSC transplantation.
 - palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.
- 2.2 Integrated, closed system ECP plus methoxsalen is a co-dependent technology consisting of the ECP device component and its drug component, methoxsalen. The application for MBS listing of ECP for the treatment of cGVHD, received in February 2021, will be considered by the MSAC at its July 2021 meeting.

Previous PBAC/MSAC consideration

- 2.3 An integrated co-dependent submission for methoxsalen, as part of the ECP service for the treatment of refractory CTCL, was first considered at the July 2017 PBAC and MSAC meetings. The PBAC deferred its consideration of methoxsalen at that time until both a TGA delegate's overview and an MSAC intention to support the co-dependent

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ECP service via the MBS are available (paragraph 6.1, methoxsalen Public Summary Document (PSD), July 2017).

- 2.4 Subsequently, MSAC also deferred its advice on public funding of ECP pending a revision of the economic model. In July 2017, MSAC noted that while the condition was a rare disease and would have a limited budgetary impact, the evidence base was weak with a high and uncertain incremental cost-effectiveness ratio (ICER). MSAC noted that the PBS listing of vorinostat had substantially changed the treatment pathway for refractory erythrodermic CTCL, and requested that the revised economic model only include comparators with accepted cost-effectiveness (methotrexate and vorinostat). MSAC also considered that there was a need to revisit the proposed MBS fee and align the MBS item descriptor and the proposed PBS restriction (p1, Application No. 1420 PSD, July 2017).
- 2.5 At its April 2020 meeting, following considerations of revisions made by the applicant, MSAC supported public funding of ECP in the treatment of CTCL.
- 2.6 The PBS-listing of methoxsalen for the treatment of refractory CTCL was subsequently considered by the PBAC at its May 2020 meeting. The PBAC recommended the Section 100 (Highly Specialised Drugs Program – Public and Private Hospital) Authority Required (STREAMLINED) listing of methoxsalen, as part of the ECP service for the treatment of refractory CTCL, either as monotherapy or in combination with peginterferon alfa-2a.
- 2.7 Methoxsalen has not been considered by the PBAC for the treatment of patients with treatment refractory cGVHD.

3 Requested listing

3.1 The requested restriction is provided below. Secretariat suggested additions are in italics and deletions are in strikethrough.

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No. of Rpts	Available brands
METHOXSALEN					
methoxsalen 200 microgram/10 mL injection, 12 x 10 mL vials	New	0-4 0.083*	1	5	Uvadex
		Max.qty (packs) multiplier = 1		Repeat increases: nil	
Restriction Summary [new] / Treatment of Concept: [new]					
Category / Program: Section 100 – Highly Specialised Drugs Program - (Public/Private hospitals)					
Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners					
Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new code]					
Episodicity: [blank]					
Severity: Steroid dependent or steroid intolerant or steroid refractory [blank]					
Condition: Chronic graft versus host disease (cGVHD)					
Indication: Steroid dependent or steroid intolerant or steroid refractory Chronic graft versus host disease					
Treatment Phase: Initial treatment [blank]					
Clinical criteria					
Patient must have received prior systemic steroid treatment for this condition and has experienced refractory disease or is dependent or intolerant to steroid treatment.					
The condition must be inadequately managed with systemic corticosteroid treatment at a therapeutic dose					
AND					
Clinical criteria:					
Patient must be receiving the medical service as described in item xxxx of the Medicare Benefits Schedule,					
AND					
Clinical criteria:					
Patient must have demonstrated a response to treatment with this drug if treatment is continuing beyond 6 months of treatment for the first time					
Treatment criteria:					
Patient must be undergoing treatment with this drug for the first time; or					
Patient must be undergoing re-initiation of treatment with this drug; or					
Patient must be undergoing continuing treatment with this drug					
AND					
Treatment criteria:					
Must be treated by a haematologist; or					
Must be treated by an oncologist with allogeneic bone marrow transplantation experience.					
AND					
Treatment criteria:					
Patient must be undergoing treatment with this drug following allogeneic haematopoietic stem cell transplantation.					
AND					
Treatment criteria:					
Patient must be undergoing concurrent treatment with extracorporeal photopheresis as described in item [insert MBS item code corresponding to initial treatment here] (initial PBS treatment) of the Medical Benefits Scheme Schedule; or					
Patient must be undergoing concurrent treatment with extracorporeal photopheresis as described in item [insert MBS item code corresponding to Continuing treatment here] (continuing PBS treatment) of the Medical Benefits Schedule					

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	<p>Prescribing Instructions: 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 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>
	<p>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.</p>
	<p>Caution: This drug is for ex vivo administration and must not to be injected directly into the patient.</p>
<p>Restriction Summary [new] / Treatment of Concept: [new]</p>	
	<p>Category / Program: Section 100 – Highly Specialised Drugs Program (Public/Private hospitals)</p>
	<p>Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners</p>
	<p>Restriction type: <input checked="" type="checkbox"/> Authority Required (STREAMLINED) [new code]</p>
	<p>Episodicity: [blank]</p>
	<p>Severity: Steroid dependent or steroid intolerant or steroid refractory [blank]</p>
	<p>Condition: Chronic graft versus host disease (cGVHD)</p>
	<p>Indication: Steroid dependent or steroid intolerant or steroid refractory Chronic graft versus host disease</p>
	<p>Treatment Phase: Initial Continuing treatment</p>
	<p>Clinical criteria</p>
	<p>Patient must have received PBS-subsidised treatment with this drug for this PBS indication,</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must have demonstrated a response to treatment with this drug if treatment is continuing beyond 6 months of treatment for the first time</p>
	<p>AND</p>
	<p>Clinical criteria:</p>
	<p>Patient must be receiving the medical service as described in item xxxx of the Medicare Benefits Schedule.</p>
	<p>Treatment criteria:</p>
	<p>Must be treated by a haematologist; or</p>
	<p>Must be treated by an oncologist with allogeneic bone marrow transplantation experience.</p>
	<p>Prescribing Instructions: A response, for the purposes of administering this continuing restriction, 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>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.</p>
	<p>Caution: This drug is for ex vivo administration and must not to be injected directly into the patient.</p>

* Note: 0.083 will be rounded up and displayed as 0.1 on www.pbs.gov.au

3.2 The proposed definition of response in the continuing treatment restriction is consistent with that of the proposed MBS item descriptor for continuation of ECP. The pre-PBAC response noted that the 2014 NIH Clinical Response in cGVHD Guideline and associated clinical assessment forms are publicly available on PubMed’s free-full text archive. The pre-PBAC response noted this is the most current version of the Guidelines and that the current international guidelines for haematopoietic stem cell transplantation, Hematopoietic Cell Transplantation Version 2.2020, NCCN Clinical Practice Guidelines in Oncology, incorporates the NIH Clinical Response in cGVHD Guideline and associated clinical assessment forms.

- 3.3 The proposed PBS restriction included a caution around pregnancy and breast feeding. The pre-PBAC response noted these cautions are usually only included in PBS listings for category X drugs and as such, considered it could be removed from the restriction.
- 3.4 The pre-PBAC response proposed including a caution which specifies that methoxsalen is for *ex vivo* administration only and must not be injected directly into the patient, in line with the existing methoxsalen listing.

4 Comparator

- 4.1 The submission nominated current standard of care, which consists of the continued use of steroids from first-line treatment, in combination with mycophenolate mofetil or calcineurin inhibitors with the view of reducing and/or displacing chronic high dose systemic steroidal treatment, as the main comparator. The submission stated this comparator was specified by the PICO Confirmation and ratified by the PASC in January.
- 4.2 PASC advised that the nominated comparators were not appropriate for the relatively small population with ‘steroid-intolerant’ cGVHD as these patients should not be able to continue steroids. PASC advised that 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) (Ratified PICO - Application 1651, December 2020 PASC).

5 Consideration of the evidence

Sponsor hearing

- 5.1 There was no hearing for this item.

Consumer comments

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

Clinical claim

- 5.3 The submission claimed superior comparative effectiveness and non-inferior safety of ECP plus methoxsalen compared to current standard of care alone for the treatment of treatment refractory cGVHD.
- 5.4 The comparative efficacy and economic analysis will be considered by MSAC.

Drug cost/patient: \$9,581.88

- 5.5 The estimated drug cost/patient is \$9,581.88 based on a DPMQ of \$217.77 (weighted by private/public hospital split of 50%/50%), a total of 25 treatments over 12 weeks for initial treatment and an estimated average of 18.5 treatments (wastage included) in continuing treatment. The average duration of continuing treatment was calculated as an average of the median number of treatments reported in the Royal Prince Alfred

Hospital and the Victorian Comprehensive Cancer Centre registry studies. Each ECP treatment requires one 10 mL vial of methoxsalen. The submission proposed the same DPMQ as that of the current listing for the CTCL indication (\$208.94 for Public Hospital and \$226.59 for Private Hospital).

Estimated PBS utilisation and financial implications

- 5.6 Table 1 presents the estimated extent of use, cost of methoxsalen to the PBS/RPBS and the net financial implications to the PBS/RPBS and MBS. The financial impact to Services Australia will be determined by that agency as part of the post PBAC process.
- 5.7 The submission used an epidemiological approach to estimate the expected utilisation and financial impact of listing methoxsalen for the treatment of treatment resistant cGVHD. Data from the Australasian Bone Marrow Transplant Recipient Registry (ABMTRR 2019) was used to calculate the prevalence and incidence of patients who had undergone allogeneic haematopoietic stem cell transplantation (HSCT), as well as the incidence of patients with cGVHD. The proportion of cGVHD patients that develop treatment refractory cGVHD was based on data from a retrospective observational study which assessed the clinical outcomes of 721 allogeneic HSCT patients over a 10-year period (Axt et al., 2019).
- 5.8 The submission estimated a total of 500 to < 5,000 treatment refractory cGVHD patients would be supplied methoxsalen over the first six years of listing (< 500 in Year 1 to < 500 in Year 6).
- 5.9 The cost of methoxsalen to the PBS/RPBS is expected to be \$0 to < \$10 million over six years (\$0 to < \$10 million in Year 1 to \$0 to < \$10 million in Year 6).
- 5.10 The estimated net financial impact to the PBS/RPBS for the listing of methoxsalen for treatment resistant cGVHD is \$0 to < \$10 million over six years (\$0 to < \$10 million in Year 1 to \$0 to < \$10 million in Year 6).
- 5.11 The submission considered that ECP plus methoxsalen may reduce or displace corticosteroids, calcineurin inhibitors and mycophenolate mofetil in the second line treatment of cGVHD; however, this was not accounted for in the financial estimates.

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Table 1: Estimated use and financial implications

	2022	2023	2024	2025	2026	2027
Estimated extent of use						
Number of patients with treatment refractory cGVHD (both incident and prevalent populations)	█ ¹	█ ²	█ ²	█ ²	█ ²	█ ²
Number of patients undertaking initial treatment	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number of patients undertaking continuing treatment ^a	█ ²	█ ²	█ ²	█ ²	█ ²	█ ²
Number of scripts dispensed (initial treatment) ^b	█ ¹	█ ¹	█ ³	█ ³	█ ³	█ ¹
Number of scripts dispensed (continuing treatment) ^c	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹	█ ¹
Drug costs						
Cost of methoxsalen to PBS/RPBS (excl. patient co-payments)	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Cost of methoxsalen to the RPBS (excl. patient co-payments)	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Less patient co-payments	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴	-\$█ ⁴
Estimated net financial implications						
Net cost to the PBS	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Net cost to the RPBS	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴	\$█ ⁴
Net cost to the MBS at 80% rebate	\$█ ⁴	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁴
Net cost to the Government	\$█ ⁴	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵	\$█ ⁵

^a The submission assumed that following initial treatment, 80.2% of patients would have achieved a complete or partial clinical response and receive continuing treatment. This assumption was based on data from the Royal Prince Alfred Hospital and the Victorian Comprehensive Cancer Centre registry studies.

^b Assuming 25 scripts per patient

^c Assuming 18.5 scripts per patient

Source: Excel workbook Attachment E1_financial estimates

Abbreviations: cGVHD: chronic graft versus host disease; MBS: Medicare Benefits Schedule PBS: Pharmaceutical Benefits Scheme; RPBS: Repatriation Pharmaceutical Benefits Scheme.

The redacted values correspond to the following ranges:

¹ 500 to < 5,000

² < 500

³ 5,000 to < 10,000

⁴ \$0 to < \$10 million

⁵ \$10 million to < \$20 million

6 PBAC Outcome

- 6.1 The PBAC deferred its consideration of methoxsalen for the treatment of patients with steroid dependent, steroid intolerant or steroid refractory chronic graft versus host disease (cGVHD), to await the outcome of the Medical Services Advisory Committee (MSAC) consideration on the funding of the co-dependent extracorporeal photopheresis (ECP), before making a final decision on PBS funding.

Outcome:

Deferred

7 Context for Decision

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

8 Sponsor's Comment

The sponsor had no comment.