

5.08 METHOXSALEN, Solution for blood fraction, 20 microgram per mL, 10 mL, Uvadex[®], Terumo BCT Australia Pty Limited

1 Purpose of Application

- 1.1 The submission requested a Section 100 (Highly Specialised Drugs Program) Streamlined Authority Required listing for the treatment of cutaneous T-cell lymphoma (CTCL).
- 1.2 The delivery of the medicine, methoxsalen, is via an integrated, closed system, extracorporeal photophoresis (ECP). 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 of this integrated codependent submission, the assessment of clinical and cost effectiveness and estimated overall financial implications are not presented below.

2 Requested listing

- 2.1 The requested restriction is provided below, including for initial and continuing therapy. Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed for Max. Qty	Price	Proprietary Manufacturer	Name and
METHOXSALEN 20 microgram/mL solution, 10 mL vial, 12	1	nil	\$ [REDACTED] ^a		UVADEX	Terumo BCT Australia Pty Ltd

Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Advanced Erythrodermic stage III-IVa T ₄ M ₀
Condition:	Cutaneous T-cell lymphoma (CTCL)
PBS Indication:	Erythrodermic stage III-IVa T₄ M₀ CTCL
Treatment phase:	Initial treatment

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone (<i>Private Hospitals</i>) <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined (<i>Public Hospitals</i>)
Treatment criteria:	<p>Must be treated in an accredited treatment centre^b by a haematologist,</p> <p>AND</p> <p>Must be treated with an integrated, closed system extracorporeal photopheresis (ECP) device.</p>
Clinical criteria:	<p>Patients must have advanced stage, erythrodermic (stage T4, M0) cutaneous T-cell lymphoma, be refractory to methotrexate one or more other systemic treatments.</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescribing instructions:	A refractory patient is defined as having had disease recurrence while on treatment or experienced intolerance to or toxicity from treatment.
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.
Patient criteria	<p>Not for use in patients with:</p> <p>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>history of heparin-induced thrombocytopenia</p> <p>unsatisfactory cardio-circulatory function</p> <p>Patients with known sensitivity to psoralen compounds</p>
Note	Treatment centres are required to have access to the specialised haematologists for the provision of clinical consultation services for CTCL.

^a Calculated as the DPMQ for a single vial of \$ [REDACTED] x12 to give an indication of the DPMQ pending confirmation of the requested pack size, noting that different mark-ups and a single dispensing fee would apply to a pack of 12 vials.

^b Accreditation would be better linked to the ECP service via the MBS item descriptor.

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Category / Program	Section 100 – Highly Specialised Drugs Program
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	Advanced Erythrodermic stage III-IVa T4 M0
Condition:	Cutaneous T-cell lymphoma (CTCL)
PBS Indication:	Erythrodermic stage III-IVa T4 M0 CTCL
Treatment phase:	Continuing treatment

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Restriction Level / Method:	<input type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input checked="" type="checkbox"/> Authority Required – Telephone (<i>Private Hospitals</i>) <input type="checkbox"/> Authority Required - Emergency <input type="checkbox"/> Authority Required - Electronic <input checked="" type="checkbox"/> Streamlined (<i>Public Hospitals</i>)
Treatment criteria:	<p>Must be treated in an accredited treatment centre^b by a haematologist,</p> <p>AND</p> <p>Must be treated with an integrated, closed system extracorporeal photopheresis (ECP) device.</p>
Clinical criteria:	<p>Patient must have previously received PBS-subsidised treatment with methoxsalen (UVADEX®) this drug for this condition,</p> <p>AND</p> <p>Patient must demonstrate a response to PBS-subsidised treatment with this drug for this condition,</p> <p>AND</p> <p>The treatment must be the sole PBS-subsidised therapy for this condition.</p>
Prescribing instruction:	A response is defined as a greater than or equal to 50% skin score response from baseline for at least 4 weeks, within the first six months of treatment.
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.
Population criteria:	Patient must be aged 18 years or over.
Patient criteria	<p>Not for use in patients with:</p> <p>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>history of heparin-induced thrombocytopenia</p> <p>unsatisfactory cardio-circulatory function</p> <p>Patients with known sensitivity to psoralen compounds</p>
Note	Treatment centres are required to have access to the specialised haematologists for the provision of clinical consultation services for CTCL.

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2.2 The proposed PBS restriction was for a narrower patient group than the indication presented in the draft TGA Product Information (PI). The draft PI indication was for patients with CTCL stage T2-T4 who have not been responsive to other forms of treatment (including skin-directed treatments) compared with erythrodermic stage T4 M0 CTCL (III-IVa) who are refractory to one or more systematic treatments. The proposed TGA indication from the draft PI did not preclude use of ECP in patients with visceral disease (M1).

2.3 The proposed 50% skin score response was not consistent with an “adequate response” as defined in the draft TGA PI. The draft PI stated that “an ‘adequate response’ is considered to be a 25% improvement in the skin score maintained for at least 4 weeks”, based on a skin score determination scale

outlined in the PI. Additionally, the draft PI stated that, “To avoid short-lived, modest waxing and waning of skin lesions being confused with an improvement that is real, any positive changes in skin lesions must be maintained for at least four weeks to be considered clinically significant.” A definition of an “adequate response” in the draft PI that is less stringent than the proposed PBS criterion may lead to leakage in patients with lower response levels in clinical practice. The proposed restriction was also silent on whether the skin score response should be maintained for a minimum duration (e.g. 4 weeks as per the PI).

- 2.4 The Pre-Subcommittee Response (PSCR) requested that the criterion for patients to demonstrate a response based on an assessment of the skin score response from baseline be removed. The PSCR instead proposed the prescribing instructions to be, “A response to initial therapy is based on lack of progression or a patient must demonstrate clinical benefit”. This is inconsistent with the criteria to determine an ‘adequate response’ in the draft TGA PI as outlined in paragraph 2.3 above.
- 2.5 The proposed PBS restriction did not state that methoxsalen cannot be used with other systemic CTCL therapies. The inclusion of clinical criteria stating “The treatment must be the sole PBS-subsidised therapy for this condition” would be appropriate and consistent with the proposed vorinostat listing from March 2017 PBAC meeting.
- 2.6 There was no maximum quantity, number of repeats or recommended treatment regimen proposed in the submission. The evaluation assumed the pack size of 12 vials would be sufficient for approximately six months of initial treatment. However, this quantity would represent more than one year’s treatment in the continuation phase, which may result in wastage and associated financial implications.
- 2.7 The PSCR proposed one pack of 12 vials with no repeats for both the initial and continuing treatment listings. The PSCR suggested that whole vials not used for an individual patient can be used by the hospital to treat a subsequent patient. However, this would not mitigate issues with wastage and financial implications to the PBS.
- 2.8 The proposed PBS restriction should state: for patients aged 18 years and over, to align with the proposed MBS item descriptor.
- 2.9 The proposed PBS listing was broadly consistent with the financial estimates.
- 2.10 The PSCR clarified that the dispensed price for maximum quantity of one pack with 12 vials is \$ [REDACTED].

3 Background

- 3.1 Methoxsalen was submitted to the TGA in October 2016. A recommendation by the TGA delegate for the treatment of CTCL was scheduled for November 2017.
- 3.2 The proposed TGA indication was not stated in the submission. The draft (PI) stated the following proposed indication: UVADEX is used in conjunction with either the THERAKOS® CELLEX® or the UVAR XTS® Photopheresis System in the palliative treatment of the skin manifestations (patch plaque, extensive plaque, erythroderma) of advanced stage (T2 – T4) cutaneous T-cell lymphoma (CTCL), only in patients who have not been responsive to other forms of treatment, (e.g. puva therapy, systemic corticosteroids, caryolysin, interferon alpha).

Sponsor hearing

- 3.3 There was no hearing for this item.

Consumer comments

- 3.4 No consumer comments were received for this item.

4 Population and disease

- 4.1 The submission requested listing ECP with methoxsalen for treatment of patients with erythrodermic (stage T4 [which corresponds to stages III, IIIA, IIIB, IVA1, and IVA2], M0) CTCL, who are refractory to one or more systemic treatments. The requested eligible population would have extensive skin disease (erythema covering $\geq 80\%$ body surface area), variable blood and lymph node involvement but no disease in visceral organs. In the pivotal study, Hughes et al. 2015, approximately 89% of patients treated with ECP had stage T4 skin disease and 97% were without organ disease (M0).
- 4.2 CTCL is a rare disease with an annual incidence of 0.23-0.75 per 100,000 in Australia.
- 4.3 The submission stated that there is a high unmet clinical need for patients with refractory erythrodermic (stage T4 Mo) CTCL.

5 Comparator

- 5.1 The submission nominated a basket of second-line treatments as the main comparator. The basket included three PBS-listed immunomodulation agents: interferon alfa-2b, low dose methotrexate, and alemtuzumab as the treatments most likely to be replaced in practice. However, the submission stated that ECP is not expected to replace any therapy; rather, it would

provide an alternative second-line (or latter) treatment option for patients with refractory erythrodermic (stage T4 M0) CTCL. This was consistent with the submission's economic model and financial estimates (which did not claim any cost offsets for the comparator).

- 5.2 The comparators were based on a survey of 20 Australian clinicians that was undertaken at the request of the PICO Advisory Sub-committee (PASC). The comparators were consistent with the Protocol confirming the PICO. The submission stated that alemtuzumab is not registered for use in CTCL, and that its use in this disease is currently experimental. Interferon alfa-2b is also not TGA-registered for CTCL, however, interferon alfa-2a is TGA-registered for CTCL. Both interferons are PBS-listed for low grade non-Hodgkin lymphomas when treated with an anthracycline. Methotrexate has an unrestricted benefit listing on the PBS. Therefore, methotrexate is the only comparator identified that is currently PBS subsidised for CTCL.
- 5.3 The evaluation considered that alemtuzumab was not an appropriate comparator for second-line CTCL therapy. Data from Hughes et al. 2015, the key Australian observational study presented in the submission, suggested alemtuzumab was more commonly used as a third or fourth line therapy. This appeared consistent with its use under compassionate access schemes, limited evidence for CTCL, significant adverse events, and high cost. The 2017 National Comprehensive Cancer Network (NCCN) guidelines for T-cell lymphomas recommend alemtuzumab for patients with Stage III disease following multiple therapies or for patients with Stage IV disease (patients with SS) after multiple therapies, including combination therapies.
- 5.4 The economic evaluation in the submission applied the following weighted comparator of the top three second-line treatments: interferon alfa (32%), methotrexate (46%), and alemtuzumab (22%).
- 5.5 The evaluation considered that vorinostat (a histone deacetylase inhibitor (HDACi)) may become a relevant comparator if it is listed in the PBS. Vorinostat was recommended at the March 2017 PBAC meeting for relapsed or chemotherapy refractory CTCL. It was noted the clinical place for vorinostat is typically third-line or later.
- 5.6 The PSCR stated that, for patients with advanced-stage CTCL, IFN- α 2 β or methotrexate are considered first-line, with IFN- α 2 β the preferred option unless the patient cannot tolerate IFN- α 2 β therapy; and that clinical feedback suggested treatment choice in the second-line setting is individualised based on disease severity and stage as well as patient location. The PSCR therefore argued that a basket of comparators is appropriate rather than a single therapy.

6 PBAC Outcome

6.1 The PBAC deferred its consideration of methoxsalen until both a TGA delegate's overview and an MSAC intention to support the codependent extracorporeal photopheresis (ECP) service via the MBS are available. The PBAC foreshadowed its support for recommending that methoxsalen be listed and stated that, if MSAC subsequently decides to support the MBS listing of ECP for the treatment of erythrodermic cutaneous T-cell lymphoma, it would support an expedited process for reconsideration to align any PBAC recommendation for listing methoxsalen according to the circumstances supported by MSAC.

Outcome:

Deferred

7 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

8 Sponsor's Comment

The sponsor had no comment.