



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Methoxsalen

Proprietary Product Name: Uvadex

Sponsor: Terumo BCT Australia Pty Ltd

November 2019

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- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

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Common abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
AE	Adverse event(s)
ARTG	Australian Register of Therapeutic Goods
CI	Confidence interval
CMI	Consumer Medicines Information
CR	Complete response
CSA	Cyclosporin A
CTCL	Cutaneous T cell lymphoma
cGvHD	Chronic graft versus host disease
CYP450	Cytochrome P450
DNA	Deoxyribonucleic acid
EBMT	European Group for Blood and Marrow Transplantation
ECP	Extracorporeal photopheresis
ELN	European Leukaemia Network
EMA	European Medicines Agency (EU)
EU	European Union
FDA	Food and Drug Administration (USA)
GIT	Gastrointestinal tract
GvHD	Graft versus host disease
HSC	Haematopoietic stem cell
HSCT	Haematopoietic stem cell transplant(ation)
J	Joule
LDH	Lactate dehydrogenase
LOCF	Last observation carried forward
mITT	Modified intention-to-treat

Abbreviation	Meaning
mL	Millilitre
MMF	Mycophenolate mofetil
NC	No change
PD	Pharmacodynamic(s)
PG	Progressive graft versus host disease
PI	Product Information
PK	Pharmacokinetic(s)
PR	Partial response
RCT	Randomised controlled trial
RMP	Risk management plan
SAE	Serious adverse event(s)
SAS	Special Access Scheme
TGA	Therapeutic Goods Administration
TNF	Tumour necrosis factor
TSA	Targeted Symptoms Assessment
TSS	Total Skin Score
UVA	Ultraviolet A
VTE	Venous thromboembolism

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New chemical entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	13 September 2019
<i>Date of entry onto ARTG:</i>	16 September 2019
<i>ARTG number:</i>	308832
<i>, Black Triangle Scheme</i>	Yes This product will remain in the scheme for 5 years, starting on the date the product is first supplied in Australia
<i>Active ingredient:</i>	Methoxsalen
<i>Product name:</i>	Uvadex
<i>Sponsor's name and address:</i>	Terumo BCT Australia PO Box 1424 Lane Cove NSW 1595
<i>Dose form:</i>	Concentrated injection
<i>Strength:</i>	200 µg/10 mL
<i>Container:</i>	Vial
<i>Pack size:</i>	12
<i>Approved therapeutic use:</i>	<i>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 HSC transplantation.</i>
<i>Route of administration:</i>	Extracorporeal circulation via photopheresis
<i>Dosage:</i>	Three extracorporeal photopheresis (ECP) treatments in the first week then two ECP treatments per week for at least 12 weeks, or as clinically indicated. For further information refer to the Product Information (PI).

Product background

This AusPAR describes the application by Terumo BCT Australia (the sponsor) to register methoxsalen as Uvadex for the following proposed indication:

Uvadex (methoxsalen) is indicated for extracorporeal administration with the Therakos Cellex Photopheresis System for the treatment of steroid-refractory graft versus host disease (GVHD) following allogeneic HSC transplantation.

Allogeneic haematopoietic stem cell transplantation (HSCT) is an established treatment for several haematological disorders. Graft versus host disease (GvHD) is a common complication of allogeneic HSCT, in which donor T lymphocytes included in the graft recognise the recipient's tissues as being foreign. GvHD presents in two clinical forms; acute GvHD or chronic GvHD. Acute GvHD generally presents within the first 3 months following transplantation with symptoms and signs involving the skin, gastrointestinal tract (GIT) and liver body systems. Approximately 30 to 50% of subjects undergoing allogeneic HSCT experience acute GvHD. Chronic GvHD usually presents 3 to 12 months after transplantation. Signs and symptoms can include those associated with acute GvHD but the disease process may involve any other organ system. Approximately 30 to 70% of subjects undergoing allogeneic HSCT experience chronic GvHD.

Corticosteroids are the standard first-line treatment of acute and chronic GvHD, however treatment of steroid-refractory or steroid-resistant disease poses a challenge. In acute GvHD steroid resistance or refractoriness has been defined as:

- Progression of acute GvHD within 3 to 5 days of therapy onset with ≥ 2 mg/kg/day of prednisone; or
- Failure to improve within 5 to 7 days of treatment initiation; or
- Incomplete response after more than 28 days of immunosuppressive treatment including steroids.

There are no established second-line treatments for acute GvHD. Multiple therapies have been studied. Agents currently used after failure of steroids include extracorporeal photopheresis (ECP), anti-tumour necrosis factor (TNF) agents such as infliximab and etanercept, sirolimus, mycophenolate and interleukin-2 receptor antagonists (for example, basiliximab and denileukin diftitox).

In chronic GvHD, steroid resistance or refractoriness has been defined as:

- Chronic GvHD progression while on prednisone at ≥ 1 mg/kg/day for 1 to 2 weeks; or
- Incomplete response after more than 28 days of immunosuppressive treatment including steroids.

In August 2017 the US Food and Drug Administration (FDA) approved ibrutinib for the treatment of adult patients with chronic GvHD after the failure of one or more treatments. Apart from ibrutinib there are no other established second line therapies for chronic GvHD.

Methoxsalen is a naturally occurring photoactive substance found in the seeds of the *Ammi majus* plant of the Apiaceae family. Although ECP with methoxsalen has been used clinically for many years, knowledge regarding the full mechanism underlying ECP has not been fully elucidated. It is generally accepted that the molecular processes which lead to apoptotic cell death involve the intercalating of methoxsalen into the double-stranded deoxyribonucleic acid (DNA) molecule within the nucleus. On activation by exposure to ultraviolet A (UVA) light, methoxsalen binds to the pyrimidine bases of the nucleic acid (thymine, cytosine and uracil) and forms covalent cross-links between the two DNA strands. The formation of these photoadducts results in the proliferative arrest and death of lymphocytes. In addition, studies have demonstrated that photopheresis may result in

the induction of an autoregulatory host response which recognises and specifically suppresses photo-treated effector T-cell populations.

Regulatory status

Uvadex was granted Orphan Drug designation by the TGA on 19 June 2018. The indication for which the designation was granted was for the:

Treatment of Graft versus Host Disease (GvHD) following allogeneic Hematopoietic Stem Cell (HSC) transplantation.

Uvadex is considered a new chemical entity for regulatory purposes in Australia. At the time of lodgement of the current submission with the TGA (August 2018), no registration applications for the proposed indication of GvHD had been submitted in foreign jurisdictions.

The product has been approved in multiple foreign markets for the treatment of cutaneous T cell lymphoma (CTCL), including the United States (February 1999), Canada (May 2013), Sweden (February 2010) and the United Kingdom (April 2000). Approvals in European countries were via the Mutual Recognition Procedure (MRP) and not a centralised approval through the European Medicines Agency (EMA).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Registration timeline

Table 1 captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 1: Timeline for Submission PM-2018-03515-1-2

Description	Date
Submission dossier accepted and first round evaluation commenced	28 September 2018
First round evaluation completed	1 March 2019
Sponsor provides responses on questions raised in first round evaluation	6 May 2019
Second round evaluation completed	20 June 2019
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	2 July 2019
Sponsor's pre-Advisory Committee response	15 July 2019
Advisory Committee meeting	1-2 August 2019

Description	Date
Registration decision (Outcome)	13 September 2019
Completion of administrative activities and registration on ARTG	16 September 2019
Number of working days from submission dossier acceptance to registration decision*	184

*Statutory timeframe for standard applications is 255 working days

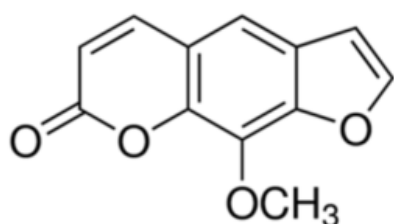
III. Submission overview and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

The chemical name of methoxsalen is 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one and it has the structure shown in Figure 1.

Figure 1: Chemical structure of methoxsalen



In the ECP procedure, white blood cells (buffy coat) are separated from blood via leukopheresis. These are treated with the methoxsalen solution, exposed to UVA radiation for a maximum of 90 minutes, and the resulting solution which contains buffy coat and the drug product is then re-infused into the patient. The Therakos Cellex and the Uvar Xts Photopheresis Systems are designated as Class 2b medical devices which have previously been evaluated and approved for use by the TGA. Only the Cellex device is currently listed on the ARTG.

Methoxsalen is extracted from the seeds of the *Ammi majus* (Apiaceae) plant. Whilst the starting material complies with the requirements of the United States Pharmacopeia (USP) monograph for methoxsalen, a drug substance of greater purity was considered necessary for the proposed parenteral drug product for infusion. A two-step recrystallisation process results in the drug substance, methoxsalen.

Three potential organic impurities have been identified in purified methoxsalen for which appropriate limits are included in the drug substance specification.

The drug product formulation was developed using co-solvents ethanol and propylene glycol to increase the solubility of methoxsalen in the aqueous based solution for infusion. Bioavailability and/or bioequivalence studies are not required for this product.

Approval is recommended on pharmaceutical chemistry and quality control aspects.

Nonclinical

The mechanism of action for methoxsalen in ECP is thought to be through immune modulation. When activated by UVA radiation, methoxsalen intercalates into DNA in cells and induces cell cycle arrest and apoptosis. ECP-induced lymphocyte apoptosis stimulates the differentiation of monocytes into mature dendritic cells which can then become active antigen-presenting cells capable of controlling immunity and triggering immune responses.

Nonclinical studies demonstrate antigen-specific immune tolerance after ECP treatment of lymphocytes with methoxsalen and UVA radiation. The proposed clinical indication is supported by nonclinical data.

Toxicological advice was requested regarding the proposed limits for five potential identified packaging-related impurities in the methoxsalen (Uvadex Concentrated Injection (20 µg/mL). The *in silico* prediction of genotoxicity showed a negative result for all the impurities tested. The proposed limits were considered toxicologically acceptable.

There are no nonclinical objections to the registration of Uvadex for the treatment of acute and chronic GvHD following allogeneic human stem cell transplantation.

Clinical

Pharmacology

Pharmacokinetics

No new clinical pharmacology data were submitted. In subjects with CTCL undergoing ECP with Uvadex, plasma methoxsalen concentrations observed 30 minutes after the procedure were notably lower than those typically observed following oral administration of the drug. On 82.0% of occasions, methoxsalen concentration was below the limit of quantification of the assay. Uvadex for ECP will avoid problems produced by high inter-individual variability in pharmacokinetic (PK) parameters associated with oral administration of methoxsalen.

Oral administration of methoxsalen has been shown to inhibit cytochrome P450 (CYP450) mediated metabolism of other drugs. Given the lower systemic concentrations obtained with extracorporeal administration, clinically significant interactions should be less likely to occur with Uvadex than with oral methoxsalen.

Pharmacodynamics

A series of nonclinical, *in vitro* pharmacodynamic (PD) studies were included.

The second generation Uvar Xts and third generation Cellex photopheresis systems produced similar effects in terms of inhibition of lymphocyte proliferation and reduction in lymphocyte viability.

Dose finding for clinical studies

The optimum combination to induce greater than background levels of apoptosis within 24 hours of treatment appeared to be 2.0 joule (J) of UVA per cm² and 50 to 100 ng of methoxsalen per mL. The amount of Uvadex added to the photoactivation bag was chosen after it had been shown that this dose resulted in bag levels of methoxsalen greater than 50 ng/mL (typically averaging 200 ng/mL). *In vitro* data has shown that bag

concentrations of methoxsalen are > 50 ng/mL both before and after photoactivation for the Uvar (first generation photopheresis system), Uvar Xts and Cellex systems.

[Information redacted]

The submission relies, to a significant extent, on published clinical trial data to establish efficacy. The lack of consistency in ECP treatment schedules across the published studies is therefore a concern.

Efficacy

Sponsor initiated clinical studies were:

- Study GvHD-SK1: a randomised, open label parallel group trial in subjects with steroid-refractory chronic GvHD;
- Study GvHD-SK1 Extension and Study TKS-01: two open label, single-arm trials in subjects with steroid-refractory chronic GvHD;
- Study 10-005: a randomised, open label parallel group trial in subjects with newly-diagnosed chronic GvHD;
- Study Acute-GvHD-1: a randomised, open-label parallel group trial in subjects with newly-diagnosed acute GvHD.

Study GvHD-SK1

Study GvHD-SK1 was a Phase II, randomised, multicentre, single-blind trial with two parallel groups (ECP plus standard therapy versus standard therapy alone), in subjects with corticosteroid-refractory, corticosteroid-dependent or corticosteroid-intolerant chronic GvHD. The submitted study report described efficacy data only for those subjects (n = 100) who enrolled after protocol Amendment 2. The study commenced in February 2001 and was completed in April 2005. The study report was dated 16 March 2009.

The overall objective of the study was to compare the safety and efficacy of ECP in conjunction with standard therapy to that of standard therapy alone in the treatment of GvHD in subjects with corticosteroid-refractory, corticosteroid-dependent, or corticosteroid-intolerant chronic GvHD.

The primary objective was to assess improvement in skin chronic GvHD in subjects receiving ECP and standard therapy compared to that in subjects receiving standard therapy alone. Secondary objectives were to assess the corticosteroid-sparing effect of ECP; to assess changes in quality of life and other organ systems involved in chronic GvHD, as well as subject response patterns including duration of response; and to evaluate the safety of ECP in chronic GvHD.

Subjects with histologically confirmed chronic GvHD and documented skin disease classical for chronic GvHD and corticosteroid refractoriness, corticosteroid dependence or corticosteroid intolerance were included.

The Therakos Uvar Xts photopheresis system and Therakos Uvadex (methoxsalen) Concentrated Injection were used in this study to administer ECP, in the mode of administration recommended by the approved labelling. ECP treatments were given 3 times in the first 7 days, then 2 times per week from Weeks 2 to 12, then 2 times per week every 4 weeks until Week 24. Treatments were to be administered on consecutive days when feasible.

The Uvadex dosage was calculated using the following formula:

Treatment volume* (in mL) multiplied by 0.017 = amount of Uvadex (in mL)
required for administration into the recirculation bag.

*Treatment volume is displayed on the Cellex device

Standard therapy was corticosteroid, cyclosporin A (CSA) or tacrolimus, with or without mycophenolate mofetil (MMF). Subjects did not need to be on corticosteroids, CSA, tacrolimus, or MMF, if they experienced unacceptable toxicity or intolerance before study. Each centre was to select either CSA or tacrolimus and to use it for subjects enrolled at the centre. Each centre was to choose, before enrolling any subjects, whether subjects in both treatment groups would receive MMF or not.

Subjects in the standard therapy group who withdrew from study after Week 12 because of inadequate response to treatment were eligible to receive ECP treatment in an extension study (Study GvHD-SK1 Extension).

The primary assessment of efficacy was performed at 12 weeks, and subjects who had an inadequate response to treatment at this time were discontinued from the study. An inadequate response was defined as a change from baseline in skin scores of 15% or less or decrease in corticosteroid use by 25% or less. In addition, subjects who had progression of their skin chronic GvHD at any time were discontinued from the study. Disease progression was defined as a 25% worsening in skin score.

The primary efficacy variable for the trial was the Total Skin Score (TSS) as assessed by a blinded assessor. The TSS is a scoring system for assessing the extent and severity of skin involvement with chronic GvHD. The score can potentially range from 0 to 50.

A total of 100 subjects were enrolled in the study after protocol Amendment 2. Fifty subjects were randomised to each arm. One subject randomised to the ECP arm did not receive treatment due to lack of venous access. Four subjects (1 in the ECP arm and 3 in the control arm) did not have a post-baseline TSS assessment and were therefore excluded from the modified intention-to-treat (mITT) population. Discontinuations due to inadequate response or progressive disease were notably more common in the control arm.

A total of 29 subjects (18 in the ECP arm and 11 in the control arm) had protocol violations that were sufficient to warrant exclusion from the per-protocol population. Dose of immunosuppressants changed > 25% from Baseline and use of prohibited medications were most frequent protocol violations leading to exclusion.

In the mITT population median age was approximately 41 years (range 13 to 67). 58.9% of subjects were male and 90.5% were Caucasian.

Median change in TSS at 12 weeks (primary endpoint) was -14.5% in the ECP arm and -10.4% in the control arm. Regardless of the method used for imputation of missing data, the difference between treatment arms was not statistically significant.

Five prospectively defined sensitivity analyses of the primary endpoint were conducted according to rules for imputation of missing data. There were no statistically significant differences between treatment groups for median percentage change in TSS in any of these five analyses.

A per protocol analysis for percentage change in TSS at Week 12 also failed to demonstrate a statistically significant difference between treatments.

Median percentage change from Baseline in TSS at Week 24: using the multiple imputation method for missing data, there was no significant difference between treatment arms (median percentage change -33.1% versus -14.0%; $p = 0.4458$). Using the last observation carried forward (LOCF) method of imputation for missing data, the difference between treatments was significant (median percentage change -31.4% versus -12.7%; $p = 0.0286$).

The proportion of subjects who achieved a substantial improvement in TSS ($\geq 25\%$) was shown. Statistical analyses of the data were not valid.

The proportion of subjects achieving a > 50% reduction in steroid dose was shown. Using the multiple imputation method for missing data, statistical analyses of the data were not valid. However, using the LOCF method of imputation for missing data, the difference between treatments was marginally significant at Week 24.

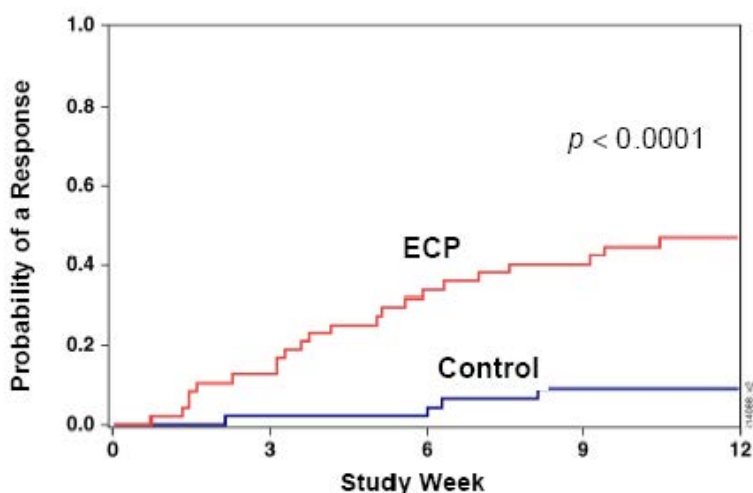
The proportion of subjects who achieved both a $\geq 25\%$ improvement in TSS and a $\geq 50\%$ reduction in steroid dose was summarised. Using the multiple imputation method for missing data, statistical analyses of the data were not valid. Using the LOCF method of imputation for missing data, the difference between treatments was marginally significant at Weeks 12 and 24.

Average daily dose of corticosteroid was similar in the two treatment arms at Baseline, and decreased in both arms over time.

Changes in other organs were assessed based on an overall assessment of the subject's condition by the treating physician and any available supportive diagnostic test results. The data suggest there was a favourable effect of ECP treatment on joint manifestations at Week 12. Otherwise, there were no significant differences between treatment arms.

Three subjects in the ECP group and 1 subject in the standard therapy group achieved complete resolution of skin chronic GvHD at some time during the study. Partial resolution of skin chronic GvHD was defined as improvement in skin GvHD and/or skin involvement on at least 50% of body surface area, as assessed by the investigator. Figure 2 displays the cumulative incidence of a complete or partial cutaneous response from baseline to week 12 ($p < 0.0001$). Sixteen (46%) subjects in the ECP group and 1 (8%) subject in the standard therapy group achieved partial resolution of skin chronic GvHD at Week 24.

Figure 2: Study GvHD-SK1; Cumulative incidence of complete or partial resolution of skin disease to Week 12



Targeted Symptoms Assessment (TSA) score results were summarised. Percentage reductions in symptom scores were numerically greater in the ECP arm at Weeks 12 and 24.

The study report also presented the results for several exploratory endpoints.

Study GvHD-SK-1 Extension

Study GvHD-SK-1 Extension was an open-label single-arm extension study, which enrolled subjects who had participated in the control arm of Study GvHD-SK1. The study was conducted at 15 of the original 23 study centres involved in Study GvHD-SK1. The study commenced in September 2003 and was completed in May 2006. The study report was dated 11 March 2009.

The overall objective was to provide subjects who were previously randomised into the standard therapy group of Study GvHD-SK1 access to ECP treatment upon skin disease progression or if their skin disease failed to respond adequately after three months.

All subjects were treated with ECP. The ECP treatment regimen was identical to that used in Study GvHD-SK1. Subjects were to continue the standard therapy they received in that study (corticosteroids, CSA or tacrolimus, with or without MMF).

The primary efficacy endpoint was percentage change in TSS at Week 12, as defined in Study GvHD-SK1, described above.

A total of 29 subjects were enrolled and treated. Of these, 25 subjects completed the study, and 4 subjects discontinued prematurely (1 death due to suicide, 2 due to adverse events and 1 due to withdrawal of consent).

Four subjects were excluded from the per-protocol population. All four were excluded because their dose of immunosuppressant medication changed from Baseline by more than 25% during the randomised portion of Study GvHD-SK1.

Baseline demographic data showed a median age of 43.0 years (range 20 to 67). There were 15 males and 14 females. All were Caucasian.

Twenty subjects were evaluable for efficacy at Week 12.

Median percentage change from Baseline in TSS (primary efficacy outcome) was -8.0% (compared with -14.5% in the ECP arm of the controlled study).

No results were presented in the study report for the other secondary efficacy endpoints.

According to the published version of the study, results for other secondary endpoints included:

- Complete and partial cutaneous responses (by investigator assessment) were observed in 26% and 31% of patients at Weeks 12 and 24 respectively; and
- 17% and 33% of patients achieved a $\geq 50\%$ reduction in corticosteroid dose at Weeks 12 and 24 respectively.

Study TKS-01

Study TKS-01 was an open label, single arm study. The trial was conducted at 3 institutions in Japan. It commenced in August 2014 and was completed in June 2016. The study report was dated 13 October 2016.

The objective of the study was to evaluate the efficacy and safety of ECP therapy using the Cellex device in patients with chronic GvHD.

Included patients were diagnosed with chronic GvHD according to GvHD guidelines after transplantation of hematopoietic stem cells derived from a related or unrelated donor. Included patients who were judged to be steroid-resistant, dependent or intolerant according to the following:

- Exacerbation even with the administration of 1 mg/kg/day of prednisolone for 2 weeks; or
- No improvement even after the continued administration of 0.5 mg/kg/day or more of prednisolone for 4 to 8 weeks; or
- The dose of prednisolone could not be decreased to less than 0.5 mg/kg/day due to flare-up of symptoms; or
- Long-term decrease in dose of prednisolone to 0.25 mg/kg/day or lower was not possible; or
- The patient was intolerant to steroids due to side effects.

All subjects were treated with ECP. The ECP treatment regimen was identical to that used in Study GvHD-SK1.

The introduction of other drugs used to treat chronic GvHD were prohibited during the trial. For subjects who were on such drugs at Baseline, the dose could not be increased except to maintain therapeutic drug concentrations.

The primary efficacy endpoint was a composite endpoint which combined an assessment of 'response' with an assessment of change in steroid dose. This endpoint was measured at Week 24. Responses were evaluated as complete response (CR), partial response (PR), no change (NC) or progressive GvHD (PG). Treatment was assessed as being 'effective' or having 'no effect' based on response assessment and change in steroid dose.

Fifteen subjects were enrolled and treated. 12 subjects completed 24 weeks of treatment. Three subjects discontinued prematurely; 2 due to an adverse event (AE) and 1 due to worsening of chronic GvHD.

Median age was 46.0 years (range 18 to 66). There were 10 males and 5 females. Race was not stated but presumably all were Japanese. The indication for transplant was leukaemia in 9 subjects, lymphoma in 3 subjects and myelodysplastic syndrome in 3 subjects.

Eight of the 15 subjects achieved a partial response. The response rate was 53.3% (95% confidence interval (CI): 26.6 to 78.7). Treatment was deemed 'effective' in the same 8 patients.

In the per-protocol analysis the response rate was 8 of 12 subjects (66.7%; 95%CI: 34.9 to 90.1).

Results for response over time were summarised. Twelve of the 15 subjects (80%; 95%CI: 51.9 to 95.7) achieved a partial response at some time point during the study.

Average daily steroid dose decreased over the first 16 weeks of the study. At Week 24, 9 subjects had a reduction in steroid dose. Two subjects had reductions in other medications used to treat GvHD (1 mycophenolate and 1 tacrolimus). There were no notable improvements in quality of life over time.

Study 10-005

Study 10-005 was a randomised, open-label parallel group trial in subjects with newly-diagnosed chronic GvHD. It was not a requirement for subjects to have steroid refractory chronic GvHD.

The sponsor also presented summaries of clinical data obtained from the two centres in Australia where ECP is currently performed. Uvadex has been supplied to these centres under the Special Access Scheme (SAS) for unregistered drugs.¹ The submission also included published meta-analyses of clinical trial data on the efficacy of ECP in chronic GvHD.

Study Acute GvHD-1

Study Acute GvHD-1 was a randomised, controlled open label study with two parallel groups (ECP plus standard therapy versus standard therapy alone). It was conducted between 2006 and 2007. The study was planned to be multinational, multicentre trial.

The trial enrolled adult subjects with new onset acute GvHD (Grade II to III). In order to be eligible subjects must have been randomised within 72 hours of initial diagnosis. The first

¹ Most therapeutic goods are required to undergo an evaluation for quality, safety and efficacy and be included in the Australian Register of Therapeutic Goods (ARTG) before they can be supplied in Australia. In recognition that there are circumstances where patients need access to therapeutic goods that are not included in the ARTG, the Therapeutic Goods Administration (TGA) manages the Special Access Scheme (SAS) and Authorised Prescriber Scheme (AP).

dose of corticosteroid treatment must have been administered within 24 hours of initial diagnosis.

The primary efficacy variable in this study was complete resolution of acute GvHD, defined as < Grade I acute GvHD, according to the modified Glucksberg criteria.² The primary endpoint was treatment success defined as complete resolution of acute GvHD at Weeks 4 and 8.

The study was terminated by the sponsor due to slow recruitment. Only 19 subjects had been enrolled. Complete resolution of acute GvHD at Weeks 4 and 8 was achieved by 33.3% of subjects in both treatment arms.

Study TKS-2014-001

Study TKS-2014-001 was to enrol paediatric subjects (age 1 to 21) with steroid-refractory acute GvHD. A protocol for the study was included in the submission. This study is an ongoing, single arm, open label, multicentre trial. An interim analysis was included in the sponsor's response to TGA's request for further information, with 11 subjects who had completed 12 weeks of treatment of 48 planned subjects.

Published retrospective studies of the efficacy of ECP in acute GvHD were included. Complete response rates varied from 10 to 87%. The SAS data provided from the Victorian Comprehensive Cancer Centre indicated that 3 subjects with acute GvHD had been treated.

Safety

In the sponsor initiated studies, a total of 131 subjects were treated with Uvadex/ECP. In addition, 400 subjects were treated in the published prospective studies, over 1,000 subjects were described in retrospective reviews and 90 were treated under Australian SAS. Uvadex/ECP has been approved in foreign markets since 1999 for the treatment of CTCL and the sponsor estimates that over 69,000 subjects have treated since then. In Studies GvHD-SK1 and GvHD-SK1 Extension median duration of treatment was 163 and 164 days, respectively.

In Study GvHD-SK1 in the first 12 weeks the incidence of AE was comparable in the two treatment groups; 89.8% in the ECP arm and 92.0% in the control arm. AE that were notably more common in the ECP arm were:

- Anaemia (24.5% versus 6.0%);
- Fatigue (14.3% versus 4.0%);
- Hypertension (16.3% versus 8.0%);
- Dyspnoea (14.3% versus 2.0%);
- Sinusitis (12.2% versus 2.0%); and
- Upper respiratory tract infection (10.2% versus 4.0%).

The pattern of AEs in the ECP arm was similar over Weeks 12 to 24 to that observed over the initial 12 weeks.

The most common events assessed as treatment-related were anaemia (31.3%), headache (15.6%), fatigue, dizziness, hypotension, tachycardia and photophobia (all 9.4%).

More subjects in the control arm discontinued the study (17 versus 7 by Week 12 and 42 versus 13 by Week 24), predominantly due to disease progression or inadequate response.

² Das-Gupta, E., et al., *Extracorporeal photopheresis for treatment of adults and children with acute GVHD: UK consensus statement and review of published literature*. Bone Marrow Transplant, 2014; 49: 1251-1258.

In Study 10-005 the incidence of AE was comparable in the two treatment groups; 96.6% in the ECP arm and 90.3% in the control arm. AE that were notably more common in the ECP arm were:

- Hypertension (31.0% versus 12.9%);
- Cough (20.7% versus 3.2%);
- Dyspnoea (17.2% versus 6.5%);
- Fatigue (17.2% versus 3.2%);
- Dizziness (13.8% versus 6.5%); and
- Dry mouth (10.3% versus 0%).

The incidence of AE assessed as being related to any of the study treatments was 72.4% in the ECP arm and 64.5% in the control arm. The study report stated that there were no unexpected ECP-related AE in the study.

In Study GvHD-SK1 Extension, all 29 subjects experienced at least one AE. The most common AE were anaemia (24.1%), cough (20.7%), fatigue, pyrexia, pain in the extremity, diarrhoea, nausea and increased weight (all 17.2%). The incidence of AE considered by the investigator to be related to ECP treatment was 75.9%. Decreased weight occurred in 3 subjects (10.3%)

In Study TKS-01, all 15 subjects experienced at least one AE. The most common AE were drug-induced liver injury (33.3%), pneumonia (26.7%), abnormal hepatic function, nasopharyngitis, blood lactate dehydrogenase (LDH) increased, anaemia and thrombocytopaenia (all 20.0%). Thirteen of 15 subjects (86.7%) experienced at least one treatment-related AE. The most common were thrombocytopaenia (20.0%), anaemia, oedema and blood LDH increased (all 13.3%).

In Study Acute GvHD-1, all nine subjects treated in the ECP arm (100%) experienced at least one AE, compared with 8 out of 9 (88.9%) in the control arm. AE that were more common in the ECP arm were hypertension (44.0% versus 0%) and pyrexia (33.0% versus 0.0%). Five of the 9 subjects (55.6%) in the ECP arm experienced an ECP related AE, none of which was reported in more than one subject.

Deaths and other serious adverse events

In Study GvHD-SK1, there were two deaths in the ECP arm (4.1%) and six in the control arm (12.0%). Neither of the deaths in the ECP arm were assessed as being related to ECP.

In Study GvHD-SK1, the incidence of all serious AE (including the deaths) during treatment was 44.9% in the ECP arm and 28.0% in the control arm. The imbalance in incidence may have been related to the longer duration of treatment in the ECP arm. The serious adverse events (SAE) were listed. Serious infections were more common in the ECP arm (26.5% versus 20.0%). There were no notable imbalances in the incidence of individual AE terms.

In Study 10-005, there were four deaths in the ECP arm (13.8%) and none (0.0%) in the control arm. None of the deaths were assessed as being related to ECP. Three of the deaths were assessed as being related to concomitant treatment (steroids and/or calcineurin inhibitors).

The incidence of SAE was 27.6% in the ECP arm and 29.0% in the control arm. The incidence of treatment-related SAEs was 20.7% in the ECP arm and 22.6% in the control arm.

In Study GvHD-SK1 Extension, 2 subjects died. Neither was assessed as being related to ECP.

SAE were reported for 41.4% of subjects during the treatment period. No single AE term was reported for more than 1 subject.

In Study TKS-01, there were no fatal AE during the study.

SAEs were reported in 6 out of 15 subjects (40.0%). One SAE was assessed as being possibly related to treatment (heart failure).

In Study Acute GvHD-1, in the ECP arm, 4 out of 9 subjects (44.4%) had fatal AE compared with 1 out of 9 (11.1%) in the control arm. None of these deaths were assessed as related to ECP or study treatment. Seven out of 9 subjects (77.8%) in each treatment arm developed SAE. One of these events was assessed as being related to treatment (status epilepticus in a subject in the ECP arm).

Discontinuations due to AE

In Study GvHD-SK1, AEs leading to study withdrawal occurred in 16.3% of subjects in the ECP arm and 10.0% of subjects in the control arm. Catheter-related complication was reported in more than 2 subjects in the ECP arm.

In Study 10-005, AEs leading to study withdrawal occurred in 20.7% of subjects in the ECP arm and 19.4% of subjects in the control arm. In the ECP arm no specific AE term was reported in more than 1 subject.

Published studies and Special Access Scheme use

The published studies reported limited safety data.

AE reported with Australian SAS use included infections/sepsis and catheter-related issues (infection, thrombosis) with one case of thrombosis leading to superior vena cava stenosis.

The current submission included two new post-marketing reports. As of February 2018, the sponsor estimates that 69,402 subjects had been treated with Uvadex. One new safety issue had arisen during the time period covered by the new reports. In an analysis of the sponsor's post-marketing adverse event database for embolic and thrombotic events with Uvadex, 22 case reports were identified and the sponsor provided a brief description of each. The US prescribing information has a precautionary statement regarding the potential for venous thromboembolism (VTE).

Conclusions on safety

Based on the sponsor-initiated studies in this submission, the clinical evaluator concludes the following toxicities appear to be associated with Uvadex/ECP:

- Anaemia: the incidence of anaemia reported as an AE was increased in the ECP arm of Study GvHD-SK1 (24.5% versus 6.0%), as was the incidence of clinically significant reductions in haemoglobin (26.5% versus 4.0%). There were no reported SAE of anaemia.

The mechanism of the anaemia was not discussed in any of the sponsor reports, however mechanical haemolysis has been reported with ECP.

- Thrombocytopenia was reported with an increased incidence in the ECP arm of Study GvHD-SK1 (4.1% versus 2.0%) and Study Acute GvHD-1 (33.1% versus 11.1%).
- Hypertension was reported as an AE more commonly in the ECP arm of Study GvHD-SK1 (16.3% versus 8.0%), Study 10-005 (31.0% versus 12.9%) and Study Acute GvHD-1 (44.0% versus 0%). Alterations in blood pressure may be related to fluid shifts associated with the ECP procedure.
- Fatigue was reported as an AE more commonly in the ECP arm of Study GvHD-SK1 (14.3% versus 4.0%) and Study 10-005 (17.2% versus 3.2%).

- Respiratory AEs: cough and/or dyspnoea were reported more commonly in the ECP arm in Study GvHD-SK1, 10-005 and Study Acute GvHD-1.
- Catheter-related complications: complications related to indwelling catheters required for ECP (infections, thrombosis, and so on) were commonly reported in the submitted studies.
- VTE: based on post-marketing reports submitted to the FDA there appears to be a potential increased risk of VTE with Uvadex/ECP. Although this risk has not been definitively established, it would be prudent to include a precautionary statement in Australian PI, especially as most cases appear to have occurred in GvHD subjects.
- Other toxicities known to be associated with Uvadex (according to the sponsor) include rash, allergic reaction, pyrexia, chills, hypotension and vasovagal episodes, nausea and taste perversion.

Given the serious nature of GvHD, the safety profile of Uvadex/ECP is considered acceptable by the clinical evaluator. There are insufficient data to establish safety in children.

Clinical evaluator's benefit risk assessment

ECP with Uvadex for steroid refractory chronic GvHD was associated with benefits:

- Improvements from Baseline in the disease manifestations of chronic GvHD; and
- Reductions in dose of concomitantly administered corticosteroids.

Uncertainties of these benefits identified included:

- The only randomised controlled trial in subjects with steroid-refractory chronic GvHD failed to demonstrate a clear efficacy benefit for Uvadex/ECP plus standard therapy over standard therapy alone.
- The single-arm studies had numerous limitations including:
 - Variety of definitions for disease response;
 - Variability in response rates achieved;
 - Lack of information on duration of response;
 - Lack of information on controls implemented for the use of other chronic GvHD treatments;
 - Variability in the ECP schedules used; and
 - Variability in ECP treatment duration.
- Efficacy has not been established in children.

ECP with Uvadex for steroid refractory acute GvHD was associated with the following benefits:

- Improvements from baseline in the disease manifestations of acute GvHD; and
- Reductions in dose of concomitantly administered corticosteroids.

Uncertainties of these benefits were identified:

- There were no randomised controlled trials and therefore no data to establish an efficacy benefit for Uvadex/ECP plus standard therapy over standard therapy alone.
- Evidence to support efficacy came from a small number of published prospective single-arm studies. These studies had numerous limitations including:
 - A variety of definitions for disease response;

- Variability in response rates achieved;
 - Lack of information on duration of response;
 - Lack of information on controls implemented for the use of other acute GvHD treatments;
 - Variability in the ECP schedules used; and
 - Variability in ECP treatment duration.
- Efficacy has not been established in children.

ECP with Uvadex was associated with risks including:

- An increased incidence of the following risks:
 - Anaemia;
 - Thrombocytopaenia;
 - Hypertension;
 - Fatigue;
 - Cough and dyspnoea; and
 - Catheter-related adverse events.
- Post-marketing data suggests that Uvadex/ECP may be associated with an increased risk of VTE.
- Other events known to be associated with Uvadex/ECP include rash, allergic reaction, pyrexia, chills, hypotension and vasovagal episodes, nausea and taste perversion.

Strengths of the assessment of risks identified were:

- In two randomised studies in the submission, ECP was associated with a small increase or no increase in the incidence of SAE or discontinuations due to AE.
- Uvadex/ECP has been in use in foreign markets since 1999. Apart from the possible increased risk of VTE, no major safety concerns have been identified in that time

Uncertainties of the assessment of risks were identified:

- Only small numbers of subjects were studied in the submitted clinical trials.
- Safety has not been established in children.

Benefit-risk balance in chronic GvHD

Steroid-refractory chronic GvHD is a rare disease with Orphan Drug designation. In Australia there are currently no therapies approved for steroid-refractory chronic GvHD. The clinical evaluator considered that the evidence to support efficacy of Uvadex/ECP in chronic GvHD was limited. The only randomised controlled study failed to provide persuasive evidence of efficacy. Multiple prospective, single-arm studies demonstrated evidence of improvement in disease manifestations compared to baseline. However, these studies had several limitations which complicate their interpretation. The safety data in the submission indicate that Uvadex/ECP has an acceptable safety profile, although there are insufficient data to establish safety in children. The clinical evaluator stated that a favourable balance between benefits and risks cannot be concluded due to concerns regarding the adequacy of the submitted efficacy data.

Benefit-risk balance in acute GvHD

Steroid-refractory acute GvHD is also a rare disease with Orphan Drug designation, for which there is no established treatment.

The clinical evaluator considered that data to support the efficacy of Uvadex/ECP in the treatment of steroid-refractory acute GvHD were inadequate, both in adults and children. Despite the favourable safety profile for Uvadex/ECP, a favourable balance between benefits and risks cannot be concluded.

Second round clinical evaluation

International clinical guidelines

The sponsor stated in their response to the TGA's request for further information that it was unclear whether 'International clinical guidelines published recently by GvHD expert panels that confirm the use of ECP as second-line treatment in steroid-refractory GvHD' were fully assessed by the clinical evaluator.

In the second round clinical evaluation report, the clinical evaluator describes current consensus clinical practice guidelines for chronic GvHD have been published on behalf of the following peak bodies:

- The European Group for Blood and Marrow Transplantation (EBMT) and the European Leukaemia Network (ELN) in 2014;³
- The British Society for Blood and Marrow Transplantation in 2012.⁴

The European guideline states the following:

'There is no standard second-line treatment for chronic GvHD, [...] patients should be treated in trials as far as possible.'

The British guideline states:

'Ideally patients with steroid-refractory chronic GvHD should be entered into clinical trials.'

The clinical evaluator noted that such guidelines recommend a variety of therapies that can be tried for the second-line treatment of chronic GvHD. ECP is one of these therapies. Other potential therapies recommended in the guidelines include rituximab, calcineurin inhibitors (for example, cyclosporin), mycophenolate, mammalian target of rapamycin (mTOR) inhibitors (for example, sirolimus), pentostatin and imatinib. The guidelines emphasise the paucity of evidence available to support these treatment recommendations. ECP is not recommended as the preferred treatment, even though Study GvHD-SK1 has been to date the only randomised controlled trial conducted in the second-line setting.

The clinical evaluator described current consensus clinical practice guidelines for acute GvHD that have been published on behalf of the following peak bodies:

- EBMT/ELN in 2014;³
- The American Society of Blood and Marrow Transplantation in 2012;⁵
- The British Society for Blood and Marrow Transplantation in 2012.⁶

³ Ruutu, T. et al. (2014), Prophylaxis and treatment of GVHD: EBMT-ELN working group recommendations for a standardized practice. *Bone Marrow Transplant.* 2014; 49: 168-173.

⁴ Dignan, F.L. et al. (2012), Diagnosis and management of chronic graft-versus-host disease. *Br J Haematol.* 2012; 158: 46-61.

⁵ Martin, P.J. et al. (2012), First- and second-line systemic treatment of acute graft-versus-host disease: recommendations of the American Society of Blood and Marrow Transplantation. *Biol Blood Marrow Transplant.* 2012; 18: 1150-1163.

The European guideline states the following:

‘There is no standard second-line treatment for acute GvHD, [...] patients should be treated in trials as far as possible.’

The American guideline states the following:

‘Enrollment in well-designed clinical trials should be encouraged, because no standard, effective second-line therapy for steroid refractory acute GvHD has been identified and because no treatment has been definitively shown to be superior to any others.’

Again, guidelines such as these recommend a variety of therapies that can be tried for the second-line treatment of acute GvHD and ECP is one of these therapies. ECP is not recommended as the preferred option.

Use in children

The sponsor disagreed with the evaluator’s recommendation that Uvadex should not be approved for use in children. The clinical evaluator reviewed the sponsor’s response. The clinical evaluator noted that only two of the studies were published prospective studies. The clinical evaluator commented that two papers (one abstract;⁷ and one brief letter to the Editor;⁸) did not have sufficient detail to be evaluated.

Interim results were included on an ongoing Study TKS-2014-001. The clinical evaluator noted that the data are preliminary with only 11 of 48 planned subjects having completed 12 weeks of treatment. [Information redacted] The clinical evaluator considered it would be prudent to await final results of the study.

Second round benefit-risk balance

After consideration of the sponsor’s response, for the reasons outlined by the clinical evaluator, it could not be concluded that Uvadex has a favourable balance of benefits and risks.

Risk management plan

There were two outstanding recommendations from the first round risk management plan (RMP) evaluation.⁹

1. The RMP should be resubmitted with the version number corrected.
2. The sponsor has included a table in the Australian RMP to summarise the safety concerns and the proposed (routine and additional) pharmacovigilance and risk minimisation activities. This is generally acceptable however this table includes the important potential risk of genotoxicity, separate to carcinogenicity, which is not included as a stand-alone safety concern throughout the rest of the document. The sponsor is requested to confirm if this is to be included in the summary of safety concerns as an important potential risk (and if so amend the relevant sections of the entire RMP as appropriate) or an error.

⁶ Dignan, F.L. et al. (2012), Diagnosis and management of acute graft-versus-host disease. *Br J Haematol.* 2012; 158: 30-45.

⁷ Nelson, A.S. et al. (2016), Extracorporeal Photopheresis (ECP) for Treatment of Refractory Acute Graft-Versus-Host Disease in Children (GVHD) after Allogeneic Hematopoietic Stem Cell Transplantation (HSCT), *Biology of Blood and Marrow Transplantation*, 2016; 22: S255-S256.

⁸ Sauret, A. et al. (2016), Shortened apheresis-based extra-corporeal photochemotherapy for acute refractory GVHD in children: a prospective study, *Bone Marrow Transplantation*, 2016; 51: 866-868.

⁹ These were addressed by the sponsor in subsequent and final versions of the RMP.

As Uvadex is a new chemical entity it should be included in the Black Triangle Scheme as a condition of registration.

The inclusion of a precaution on the risk of carcinogenicity should be considered in the 'Special Warnings and Precautions for Use' section of the PI.

The summary of safety concerns and the proposed (routine and additional) pharmacovigilance and risk minimisation activities following the second round RMP evaluation are shown in Table 2.¹⁰

Table 2: Summary of safety concerns

Summary of safety concerns		Pharmacovigilance		Risk Minimisation	
		Routine	Additional	Routine	Additional
Important identified risks	Aphakia	Ü	-	Ü	-
	Photosensitive diseases (porphyria, systemic lupus erythematosus or albinism)	Ü	-	Ü	-
Important potential risks	Ocular damage (including cataractogenicity)	Ü	-	Ü	-
	Carcinogenicity	Ü	-	Ü	-
Missing information	Use during pregnancy and lactation	-	-	Ü	-
	Use in patients with renal or hepatic impairment	-	-	Ü	-
	Paediatric use	-	-	Ü	-

Risk-benefit analysis

Delegate's considerations

Discussion

There were serious deficiencies in each of the sponsor initiated clinical studies.

In Study GvHD-SK1 the primary endpoint of TSS at 12 weeks, the study failed to demonstrate a significant benefit for the addition of ECP treatment to standard therapy. The duration of therapy may have been too short to demonstrate benefit. Baseline TSS scores were at the lower end of the possible range of 0 to 50 (median scores of 9.4 and 9.2 in the two treatment groups). A number of the positive findings were of marginal statistical

¹⁰ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

significance, or were based on an un-blinded assessment of a subjective endpoint. Also, no corrections were made for multiple statistical comparisons.

In Study GvHD-SK1 Extension, percentage changes from Baseline in TSS in this study were somewhat smaller than those observed in the ECP arm of the randomised controlled study. In addition, there were no prohibited medications in this study and there were no analyses presented on actual use of other therapies for chronic GvHD that may have been prescribed during the trial.

In Study TKS-01 the primary endpoint for the study was not well described and it is therefore difficult to interpret the clinical significance.

Study 10-005 investigated the efficacy of ECP in the first-line treatment of chronic GvHD and hence subjects were not steroid-refractory.

Study Acute GvHD-1 was conducted in subjects with new onset acute GvHD and hence subjects were not steroid-refractory.

In chronic GvHD multiple prospective, single-arm studies demonstrated evidence of improvement in disease manifestations compared to baseline. However, these studies had several limitations which complicate their interpretation, particularly variety of definitions for disease response, variability in response rates achieved, lack of information on duration of response and lack of information on other chronic GvHD treatments.

In steroid refractory acute GvHD, there were no sponsor initiated studies and no randomised controlled clinical studies. Two prospective single arm studies were considered to provide useful efficacy data.^{11,12} These two studies used different definitions of response and obtained very different response rates. The clinical evaluator considered that the evidence is inadequate to support approval of Uvadex for the treatment of steroid-refractory acute GvHD.

Given the serious nature of GvHD, the safety profile of Uvadex/ECP is considered acceptable by the clinical evaluator. There are insufficient data to establish safety in children.

There are no established second-line treatments for chronic GvHD or acute GvHD, apart from ibrutinib for chronic GvHD which was approved by the FDA in 2017.

The sponsor has revised the proposed indication to restrict Uvadex to use in adults and included the precaution statement 'The safety and efficacy of Uvadex have not been established in children'.

The sponsor identified a UK Photopheresis Society: ECP Consensus Statement Update;¹³ which allocated a level of evidence for ECP in GvHD.¹⁴

Chronic GvHD

- Cutaneous/mucous membrane; Quality of evidence II-ii;
- Hepatic; Quality of evidence II-iii;

¹¹ Greinix, H.T. et al. (2006), The effect of intensified extracorporeal photochemotherapy on long-term survival in patients with severe acute graft-versus-host disease. *Haematologica*. 2006; 91:405-408.

¹² Ussowicz, M. et al. Steroid-sparing effect of extracorporeal photopheresis in the therapy of graft-versus-host disease after allogeneic hematopoietic stem cell transplantation. *Transplant Proc*. 2013; 45:3375-3380.

¹³ Alfred, A. et al. The role of extracorporeal photopheresis in the management of cutaneous T-cell lymphoma, graft-versus-host disease and organ transplant rejection: a consensus statement update from the UK Photopheresis Society. *BJH*, 2017; 177: 287-310.

¹⁴ Levels of evidence (as per Alfred, A. et al 2017, above):

II-ii Evidence obtained from well-designed cohort or case-control analytical studies, preferably from more than one centre or research group.

II-iii Evidence obtained from multiple time series with or without the intervention.

- GI/pulmonary; Quality of evidence II-ii.

Acute GvHD

- Cutaneous; Quality of evidence II-ii;
- Hepatic; Quality of evidence II-ii;
- GI/pulmonary; Quality of evidence II-ii.

This reference was reviewed and it was concluded that there is no consensus of expert opinion that the available evidence for the efficacy of ECP is sufficient to establish it as a standard second-line treatment for GvHD.

The sponsor maintains that studies which used the Cobe device, rather than the Therakos device, are relevant to include in meta-analyses of the ECP process in treatment of GvHD.

Summary of issues

GvHD is a rare condition and Orphan Drug designation has been approved for Uvadex. Methoxsalen has been marketed overseas for treatment of CTCL from 1999. There has been SAS use of ECP with Uvadex for treatment of GvHD in relatively small numbers of patients at two centres in Australia, at one since 2002 and at the other since 2010.

The submission has not provided a comprehensive dossier for a new chemical entity. The submitted clinical dossier consisted of submitted studies and literature references. The published literature reflects large variations in diagnostic criteria and concomitant therapy. The hybrid dossier, consisting, of published literature, sponsor initiated studies, and analysis of Australian SAS database, was accepted in a pre-submission meeting with TGA. The literature search strategy was approved by TGA.

In chronic GvHD the single randomised parallel group clinical study in adults did not provide convincing evidence of efficacy. The randomised controlled trial (RCT) did not use contemporary disease response criteria. The primary objective in the RCT related to skin chronic GvHD. Multiple prospective, single-arm studies demonstrated evidence of improvement in disease manifestations compared to baseline. However, these studies had several limitations which complicate their interpretation, particularly variety of definitions for disease response, variability in response rates achieved, lack of information on duration of response and lack of information on other chronic GvHD treatments.

In steroid refractory acute GvHD, there were no sponsor-initiated studies and no randomised controlled clinical studies. Two prospective single arm studies were considered to provide useful efficacy data.^{11,12} These two studies used different definitions of response and obtained very different response rates. The clinical evaluation report considered that the evidence is inadequate to support approval of Uvadex for the treatment of steroid-refractory acute GvHD.

Given the serious nature of GvHD, the safety profile of Uvadex/ECP is considered acceptable in the clinical evaluation report. There are insufficient data to establish safety in children.

There are no established second-line treatments for chronic GvHD or acute GvHD, apart from ibrutinib for chronic GvHD which was approved by the US FDA in 2017.

In the sponsor's response to the second round clinical evaluation the proposed indications have been restricted to adults and the precaution statement included for Paediatric use, 'The safety and efficacy of Uvadex have not been established in children'.

The sponsor's response to the second round clinical evaluation identified a UK Photopheresis Society: ECP Consensus Statement Update (see above).¹³

This reference was reviewed in the second round clinical evaluation which concluded there is no consensus of expert opinion that the available evidence for the efficacy of ECP is sufficient to establish it as a standard second-line treatment for GvHD.

The sponsor's response to the second round clinical maintains that studies which used the Cobe device, rather than the Therakos device, are relevant to include in meta-analyses of the ECP process in treatment of GvHD.

The Delegate concurs with the clinical evaluator's benefit-risk assessment. It cannot be concluded that Uvadex has a favourable balance of benefits and risks. Efficacy of Uvadex/ECP has not been adequately demonstrated in chronic GvHD and in acute GvHD.

Proposed action

The Delegate was not in a position to say, at this time, that the application for Uvadex, for extracorporeal administration with the Therakos Cellex Photopheresis System for the treatment of steroid-refractory and steroid-intolerant GvHD following allogeneic HSC transplantation, should be approved for registration.

Request for ACM advice

The Advisory Committee on Medicines (ACM) is requested to provide advice on the following specific issues:

1. Has the efficacy of ECP with Uvadex been adequately demonstrated in treatment of chronic GvHD?
2. Has the efficacy of ECP with Uvadex been adequately demonstrated in treatment of acute GvHD?
3. The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Advisory committee considerations¹⁵

The Advisory Committee on Medicines (ACM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following.

The ACM advised the following in response to the Delegate's specific request for advice:

1. *Has the efficacy of ECP with Uvadex been adequately demonstrated in treatment of chronic GvHD?*

The ACM advised that the efficacy of ECP with Uvadex has not been adequately demonstrated in the treatment of chronic GvHD. However, the ACM noted that opportunities for large RCTs are unlikely to occur, the safety profile is considered acceptable and that ECP with Uvadex has been available for several years under the

¹⁵ The ACM provides independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010. ACM encompass pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

SAS. Based on these factors and the seriousness of the condition, the ACM advised that ECP with Uvadex should be approved for the treatment of chronic GvHD.

2. *Has the efficacy of ECP with Uvadex been adequately demonstrated in treatment of acute GvHD?*

The ACM advised that the efficacy of ECP with Uvadex has not been adequately demonstrated in acute GvHD. Data to support safe adult/paediatric use in acute GvHD is more limited in than in chronic GvHD, as such the ACM does not support approval of ECP with Uvadex for acute GvHD.

3. *The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.*

The ACM advised that the alert by the FDA (5 February 2018) and TGA (27 February 2018) regarding VTE and severe allergic reactions associated with the use of Therakos Cellex should be included in the PI and CMI.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Uvadex (methoxsalen) 200 µg/10 mL solution for extracorporeal circulation via photopheresis, indicated for:

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 HSC transplantation.

Specific conditions of registration applying to these goods

- Uvadex (methoxsalen) is to be included in the Black Triangle Scheme. The Product Information (PI) and Consumer Medicines Information (CMI) for Uvadex must include the black triangle symbol and mandatory accompanying text for five years, which starts from the date that the sponsor notifies the TGA of supply of the product.
- The methoxsalen Australian-Risk Management Plan (Aus-RMP) (version 3.0, dated 15 April 2019, data lock point 25 February 2018), included with submission PM-2018-03515-1-2, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

An obligatory component of risk management plans is routine pharmacovigilance. Routine pharmacovigilance includes the submission of periodic safety update reports (PSURs).

As agreed between the TGA and the supplier who is the recipient of the approval, annual PSURs with the data lock point of 25th February are to be provided until the period covered by such reports is not less than three years from the date of this approval letter.

The reports are to at least meet the requirements for PSURs as described in the European Medicines Agency's Guideline on good pharmacovigilance practices (GVP) Module VII-periodic safety update report (Rev 1), Part VII.B Structures and processes. Note that submission of a PSUR does not constitute an application to vary the registration. Each report must have been prepared and submitted to the TGA within ninety calendar days of the data lock point for that report.

- For all injectable products the Product Information must be included with the product as a package insert.

Attachment 1. Product Information

The PI for Uvadex approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Therapeutic Goods Administration

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