▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION – UVADEX® (METHOXSALEN) CONCENTRATED INJECTION

1 NAME OF THE MEDICINE

Methoxsalen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

UVADEX methoxsalen concentrated injection is a sterile, clear, colourless to pale yellow liquid containing 200 microgram of methoxsalen per 10 mL vial, which is equivalent to 20 microgram of methoxsalen per mL. For the full list of excipients, see Section 6.1 List of Excipients.

3 PHARMACEUTICAL FORM

UVADEX is supplied as a sterile concentrated injection for extracorporeal circulation via photopheresis in single-use amber glass vials. UVADEX is used in combination with the THERAKOS® CELLEX® Photopheresis System to extracorporeally treat leukocyte enriched buffy coat.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

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.
- palliative treatment of the skin manifestations of cutaneous T-cell lymphoma (CTCL) that is unresponsive to other forms of treatment.

4.2 DOSE AND METHOD OF ADMINISTRATION

Do not inject directly into patients. Product is for single use in one patient only. Discard any residue.

Photopheresis treatments should always be performed in locations where standard medical emergency equipment is available. Volume replacement fluids and/or volume expanders should be readily available throughout the procedure. Please refer to the THERAKOS CELLEX Operator's Manual for additional warnings and precautions.

In the photopheresis process, the patient is connected to the THERAKOS CELLEX Photopheresis System via a catheter interface. Red blood cells are separated from the white blood cells and plasma in the centrifuge bowl. The red blood cells and excess plasma are returned to the patient while the buffy coat (leukocyte enriched blood) and some plasma are collected into the photoactivation bag located on the side of the instrument.

During each photopheresis treatment with UVADEX, the dosage of UVADEX is calculated according to the treatment volume (which is displayed on the display panel of the instrument) using the formula:

Treatment volume x 0.017 mL of UVADEX for each treatment
For example: Treatment volume = 240 mL x 0.017 = 4.1 mL of UVADEX

The prescribed amount of UVADEX is injected into the photoactivation bag prior to the photoactivation phase. During photoactivation the leukocyte enriched blood is continually circulated through the photoactivation module for the time specified by the device, to a maximum of 90 minutes whilst being exposed to UVA light.

At the end of the photoactivation cycle, the photoactivated cells are then reinfused into the patient; the recommended reinfusion time is 15 to 20 minutes. The complete photopheresis procedure is up to 3 hours in duration.

Chronic Graft versus Host Disease

Three ECP treatments in the first week then two ECP treatments per week for at least 12 weeks, or as clinically indicated.

Cutaneous T-cell Lymphoma

The patient should receive treatment on two successive days each month for six months. Patients who show an increase in skin scores after eight treatment sessions may have their treatment schedule increased to two successive days every two weeks for the next three months.

An adequate response is considered to be a 25% improvement in the skin score maintained for at least 4 weeks.

Skin score determination

The severity of skin lesions should be determined for each of 29 body sections according to the following scale:

0 = normal skin
0.5 = background normal, with scattered erythematous papules
1 = minimal erythema and oedema; no scaling or fissuring
2 = substantial erythema and edema; no scaling or fissuring
3 = submaximal erythema, scaling, and oedema; no fissuring or ectropion
4 = most severe; universal involvement with maximal erythema, oedema and scaling; any fissuring or ectropion

Each severity score should be multiplied by the percentage surface area to obtain a regional score. All regional scores should be added together to obtain an overall lesion score.

Due to the background variation of skin lesions, changes in skin lesions as a result of UVADEX exposure must be maintained for at least four weeks to be considered clinically significant.

The number of photopheresis sessions administered should not exceed 20 in six months.

Dosage in special populations

UVADEX has not been clinically evaluated in patients with renal or hepatic impairment (*see Section 4.4: Special Warnings and Precautions for Use*).

Instructions for use / handling

Do not inject directly into patients.

UVADEX should not be diluted. The calculated dosage of the vial contents should be injected into the THERAKOS CELLEX Photopheresis System immediately after being drawn up into a syringe.

The THERAKOS CELLEX Photopheresis System Operator's Manual should be consulted before using this medicinal product.

UVADEX held in a syringe for more than one hour should be discarded.

4.3 CONTRAINDICATIONS

- History of idiosyncratic or hypersensitivity reaction to methoxsalen, psoralen compounds or any of the excipients of UVADEX
- Co-existing melanoma, basal cell or squamous cell skin carcinoma
- Lactation
- Aphakia

Contraindications to the photopheresis procedure:

- Photosensitive disease
- Inability to tolerate extracorporeal volume loss (e.g. due to severe cardiac disease, severe anaemia, etc.)
- White blood cell count greater than 25,000 mm^3
- Previous splenectomy
- Coagulation disorders

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Only physicians who have special competence in the diagnosis and treatment of cGVHD and CTCL who have special training and experience with the THERAKOS CELLEX Photopheresis System should use UVADEX. Psoralen and ultraviolet radiation therapy should be under constant supervision of such a physician. Because of the possibilities of ocular damage, the patient should be fully informed by the physician of the risks inherent in this therapy. UVADEX should only be used *ex vivo* and administered directly into the photoactivation bag. Visually inspect for haemolysis. In the event of unscheduled damage to the blood during the photopheresis procedure (e.g. >43ºC alarm sounding), the fractionated blood should only be reinfused into the patient if haemolysis has not occurred.

Contraceptive precautions: Both men and women who are being treated with UVADEX should take adequate contraceptive precautions both during and after completion of photopheresis treatment.

Cataractogenicity: Exposure to large doses of UVA causes cataracts in animals, an effect enhanced by the administration of oral methoxsalen. As the concentration of methoxsalen in the human lens is proportional to the serum level, the concentration will be substantially lower following ex vivo methoxsalen treatment (with UVADEX) compared to that seen following oral administration. Nonetheless, if the lens is exposed to UVA during the time

methoxsalen is present in the lens, photochemical action may lead to an irreversible binding of methoxsalen to protein and DNA components of the lens. For this reason the patient's eyes should be protected from UVA light by wearing wrap-around, UVA-opaque sunglasses during the treatment cycle and during the following 24 hours.

Adverse effects on the skin: Following oral administration of psoralen, where serum concentrations may exceed 200 ng/mL, exposure to sunlight or ultraviolet radiation (even through window glass) may result in serious burns and, in the long-term, "premature aging" of the skin. Oral psoralens may increase the risk of skin cancer. Extracorporeal use of UVADEX is associated with much lower systemic exposure than from oral methoxsalen. The phototoxicity of UVADEX has not been characterised; as a precaution patients should avoid exposure to sunlight during the 24 hours following photopheresis treatment.

The evaluation of skin score may be influenced by recent sun exposure (CTCL indication).

Venous and arterial thromboembolism: Thromboembolic events, such as pulmonary embolism and deep vein thrombosis, have been reported with UVADEX administration through photopheresis systems for treatment of patients with graft versus host disease.

Alcohol content: The product contains 4.1% w/v ethanol and each 1 mL of UVADEX contains 40.55 mg of ethanol. With extracorporeal administration, systemic exposure is expected to be low and clinical effect has not been evident; however prescribers should be aware of the potential effect on other medicines and caution is advised in liver disease, alcoholism, epilepsy, brain injury or disease.

Use in hepatic impairment

No specific information is available on the use of photopheresis using UVADEX in patients with hepatic impairment. Since hepatic biotransformation is necessary for urinary excretion, this may lead to prolonged photosensitivity requiring continued precautions against exposure to sunlight beyond 24 hours following photopheresis treatment. The potential benefits of photopheresis treatment should be weighed against any possible risk before embarking on the procedure.

Use in renal impairment

Little information is available on the use of UVADEX in patients with renal impairment. No extra precautions, such as reduction of dose or prolongation of protection from UV light, were taken in the few renal transplant recipients who have undergone photopheresis treatment.

Use in the elderly

There is no evidence of a requirement for reduction in frequency or duration of treatment with UVADEX in elderly patients (*see Section 4.2: Dose and Method of Administration*).

Paediatric use

The safety and efficacy of UVADEX have not been established in children.

Effects on laboratory tests

Small, but statistically significant changes occurred in the following laboratory parameters: albumin, calcium, haematocrit, haemoglobin, potassium and RBC. Routine laboratory monitoring should be performed. Data are not available to determine if any observed effects on laboratory parameters are due to UVADEX or the photopheresis procedure.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Although methoxsalen has been shown to be capable of both induction and inhibition of hepatic enzymes, in humans it appears to act primarily as a potent inhibitor of hepatic microsomal oxidative metabolic processes, including, but not limited to, CYP1A2, 2A6 and 2B1. Thus, it is to be expected that interactions will occur between methoxsalen and other medicinal products whose metabolism involves the hepatic cytochrome P450 system. The clearance of caffeine has been shown to be markedly reduced after methoxsalen treatment. Methoxsalen decreases the metabolic activation of paracetamol in animals and humans, probably as a consequence of methoxsalen-associated inhibition of hepatic cytochrome P450 oxidative transformation of paracetamol.

Methoxsalen is metabolically cleared. Therefore, consumption of other P450 substrates and P450 inhibitors may result in an extended half-life of methoxsalen, and consequently lead to prolonged photosensitivity requiring continued precautions against exposure to sunlight beyond 24 hours following photopheresis treatment.

One report describes a patient with psoriasis and epilepsy in whom phenytoin administration induced increased metabolism of methoxsalen leading to low levels of methoxsalen and failure of PUVA therapy. Substitution of valproate for phenytoin resulted in a three to four fold increase in methoxsalen levels to within the putative therapeutic range.

Methoxsalen is normally moderately bound to albumin but can be displaced by a number of medicinal products such as dicoumarol, promethazine and tolbutamide. As a coumarin derivative, it is conceivable that methoxsalen binds to the warfarin site of albumin, which could be of clinical significance when the two medicinal products are co-administered. However, of the medicinal products studied, only tolbutamide at therapeutic concentrations displaces methoxsalen from its binding site to a clinically relevant extent. Concomitant use of methoxsalen and tolbutamide may therefore lead to enhanced photosensitivity.

Special care should be exercised in treating patients who are receiving concomitant therapy (either topically or systemically) with known photosensitising agents.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Effects on fertility have not been adequately investigated in animal studies. Methoxsalen caused adverse effects on male and female reproductive organs at high oral and intraperitoneal doses (≥20 mg/kg/day, 900x the clinical ECP dose adjusted for body surface area) that induced systemic toxicity in mice and rats with or without UV radiation. In female animals, effects included decreased uterine weight, 17β-oestradiol levels, and follicular damage of the ovary. In male animals, effects included atrophy of seminal vesicles, prostate and testes, and reduced sperm count, seminiferous tubule size and number of spermatogonia and spermatids.

Use in pregnancy – Pregnancy Category D

Methoxsalen may cause fetal harm when given to a pregnant woman. Doses of 80 to 160 mg/kg/day given during organogenesis caused significant fetal toxicity in rats. The lowest of these doses, 80 mg/kg/day, is over 4000 times greater than a single dose of UVADEX on a mg/m^2 basis. Fetal toxicity was associated with significant maternal weight loss, anorexia and increased relative liver weight. Signs of fetal toxicity included increased fetal mortality, increased resorptions, late fetal death, fewer fetuses per litter, and decreased fetal weight. Methoxsalen caused an increase in skeletal malformation and variations at doses of 80 mg/kg/day and above. There are no adequate and well-controlled studies of methoxsalen in pregnant women. If UVADEX is used during pregnancy, or if the patient

becomes pregnant while receiving UVADEX, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

Use in lactation

It is not known whether methoxsalen is excreted in human milk. Because of the pharmacodynamic properties of UVADEX, lactation is a contraindication.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Patients should not drive or operate machinery immediately following photopheresis because of the possibility of transient cardiovascular instability and the recommendation that following photopheresis patients wear sunglasses. Photopheresis treatment using UVADEX is likely to produce minor or moderate undesirable effects.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Graft Versus Host Disease

In the clinical trials, published information and postmarketing surveillance of UVADEX/ECP, adverse events were usually mild and transient and in most cases, related to the underlying pathology.

Table 1 summarises all adverse events that occurred in at least three UVADEX/ECP-treated patients and more frequent than standard of care in a sponsor-initiated study in chronic GVHD.

Table 1: Adverse Events in ≥3 Patients and Occurring More Frequently in the ECP Group (Study GVHD-SK1 Safety Population)

System Organ Class	Preferred Term	GVHD-SK1	
		ECP (N=49) n (%)	Standard of Care (N=50) n (%)
Blood and lymphatic system disorders	Anaemia	13 (26.5)	3 (6.0)
Cardiac disorders	Tachycardia	3 (6.1)	2 (4.0)
Endocrine disorders	Cushingoid	6 (12.2)	1 (2.0)
Eye disorders	Dry eye	6 (12.2)	4 (8.0)
	Photophobia	5 (10.2)	0 (0.0)
	Lacrimation increased	4 (8.2)	0 (0.0)
	Conjunctivitis	3 (6.1)	2 (4.0)
	Eye pain	3 (6.1)	1 (2.0)
	Visual acuity reduced	3 (6.1)	0 (0.0)
Gastrointestinal disorders	Diarrhoea	14 (28.6)	12 (24.0)
	Nausea	10 (20.4)	6 (12.0)
	Toothache	5 (10.2)	0 (0.0)
	Abdominal pain	4 (8.2)	3 (6.0)
	Dysphagia	3 (6.1)	1 (2.0)
General disorders and administration site conditions	Fatigue	8 (16.3)	3 (6.0)
	Pyrexia	7 (14.3)	3 (6.0)
	Chills	3 (6.1)	0 (0.0)
	Mucosal inflammation	3 (6.1)	2 (4.0)
Infections and infestations	Sinusitis	9 (18.4)	3 (6.0)
	Upper respiratory tract	9 (18.4)	2 (4.0)

System Organ Class	Preferred Term	GVHD-SK1	
		ECP (N=49) n (%)	Standard of Care (N=50) n (%)
	infection		
	Nasopharyngitis	3 (6.1)	1 (2.0)
Injury, poisoning, procedural complications	Contusion	3 (6.1)	0 (0.0)
Investigations	Blood pressure diastolic decreased	3 (6.1)	0 (0.0)
	Haemoglobin decreased	3 (6.1)	0 (0.0)
Metabolism and nutrition disorders	Anorexia	5 (10.2)	0 (0.0)
	Hypokalaemia	4 (8.2)	2 (4.0)
	Hyperglycaemia	3 (6.1)	1 (2.0)
	Hypocalcaemia	3 (6.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	Pain in extremity	8 (16.3)	4 (8.0)
Nervous system disorders	Headache	10 (20.4)	6 (12.0)
	Paraesthesia oral	4 (8.2)	0 (0.0)
	Neuropathy peripheral	3 (6.1)	0 (0.0)
	Tremor	3 (6.1)	1 (2.0)
Psychiatric disorders	Depression	5 (10.2)	4 (8.0)
Respiratory, thoracic and mediastinal disorders	Cough	7 (14.3)	5 (10.0)
	Dyspnoea	7 (14.3)	2 (4.0)
	Pharyngolaryngeal pain	4 (8.2)	0 (0.0)
Skin and subcutaneous tissue disorders	Rash	3 (6.1)	0 (0.0)
Vascular disorders	Hypertension	10 (20.4)	6 (12.0)
	Hypotension	3 (6.1)	0 (0.0)

Cutaneous T-Cell Lymphoma

In the clinical study of photopheresis/UVADEX (CTCL 3), adverse events were usually mild and transient and in most cases related to underlying pathology. Nausea and vomiting were reported only once in each of two patients, representing an incidence of 3.9% in the study. Adverse events associated with the photopheresis procedure used in the treatment of CTCL are shown in Table 2.

Table 2: Adverse events associated with the photopheresis procedure from Study CTCL 3

Event	CTCL 3 UVADEX	
	N° of Patients (%) N = 51	Total N° by Treatments N° of Treatments = 1032
Vascular access complication	9 (17.6)	10 (<0.1)
Vasovagal spasm	3 (5.9)	3
Hickman catheter infection	1 (2.0)	2 (<0.1)
Hickman catheter infection/thrombosis	1 (2.0)	1
Headache	1 (2.0)	2
Hypercoagulability	1 (2.0)	1
Haemolysis	1 (2.0)	1
Nausea	1 (2.0)	1

The frequencies of the adverse events reported below (very common >10%, common >1–10%, uncommon 0.1–1%, rare 0.01–0.1% and very rare <0.01%) are based on clinical trial data.

Cardiac disorders: Common: hypotension

Gastrointestinal disorders: Common: nausea, vomiting

Infections: Common: Infections

Procedural complications: Common: Transient fever, vascular access complication

Post-marketing Experience

The following adverse reactions have been identified during post-marketing use of UVADEX: rash, anaphylactic reaction, allergic reaction, nausea, pyrexia, dysgeusia, anaemia, exacerbation of congestive heart failure, sepsis, endocarditis, vomiting, and photosensitivity reactions.

Thromboembolism and severe allergic reactions have been reported in association with the use of THERAKOS CELLEX.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

There is no human experience of overdose with UVADEX; animal data suggests a large margin of safety. In the event of methoxsalen overdose, the patient should be kept in a darkened room for at least 24 hours.

If overdose is suspected or an incorrect dose of UVADEX is delivered into the photoactivation bag, immediately terminate treatment.

There is one case of overdosage with oral methoxsalen recorded in the medical literature. A 25-year-old woman ingested a dose equivalent to about 85 mg/kg body weight (i.e. approximately 140 times the therapeutic dose of oral methoxsalen). The major symptoms of intoxication were nausea, vomiting and dizziness. The patient was kept in a darkened room and her cardiovascular function was monitored. She recovered without sequelae and was released from hospital 36 hours after admission.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

Methoxsalen is a naturally occurring photoactive substance found in the seeds of the Ammi majus (Umbelliferae) plant. It belongs to a group of compounds known as psoralens or furocoumarins.

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

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 DNA molecule within the nucleus.

On activation by exposure to 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 recognizes and specifically suppresses photo-treated effector T-cell populations.

Clinical trials

Chronic GVHD:

The clinical data in support of the efficacy and safety of UVADEX and the THERAKOS CELLEX Photopheresis System for treatment of chronic GVHD consists of sponsor-initiated clinical trials and published clinical studies in adult populations. Given the rare incidence of cGVHD following allogeneic haematopoietic stem cell transplantation (HSCT), patient numbers in prospective studies are low; however many large retrospective analyses from local and international apheresis centres provide evidence of clinical benefit and safety of the therapy.

Sponsor-initiated clinical study:

GVHD-SK1:

In this sponsor-initiated study, 99 patients with corticosteroid-refractory, corticosteroid-dependent, or corticosteroid-intolerant cGVHD were treated with THERAKOS ECP using UVADEX in conjunction with standard therapy (ECP group) (n=49) or standard therapy alone (ST group) (n=50) for 24 weeks. Forty-four patients completed the study (36 ECP and 8 ST). The primary objective was the comparison of the percent change from baseline in the total skin score (TSS) at week 12.

Patients who received ECP plus ST showed a greater improvement in TSS than the ST group at 12 and 24 weeks, however this difference did not reach statistical significance. During the study, 3 ECP patients and 1 ST patient achieved complete resolution (CR) of skin

cGVHD. Partial response (PR) of skin cGVHD, as assessed by the investigator, was achieved at 12 weeks by 17 (39.5%) ECP patients and 4 (10.3%) ST patients and at 24 weeks by 16 (46%) ECP patients and 1 (8%) ST patient. These differences in CR and PR did not reach statistical significance.

Published clinical studies:

Dignan 2014:

This single centre prospective study enrolled 38 patients; 27 were evaluable for response after 6 months of THERAKOS ECP using UVADEX. Treatment was administered on 2 consecutive days every 2 weeks until a partial clinical response was achieved and then treatment was reduced to a monthly schedule. Patients had steroid-refractory or steroid-dependent cGVHD or were intolerant of corticosteroids. Response was assessed after 6 months of treatment using reduction in immunosuppression and NIH scoring criteria i.e. complete overall response was defined as complete resolution of all symptoms and signs of cGVHD; a partial overall clinical response was defined as a 50–99% improvement in one organ when compared with baseline and no evidence of cGVHD progression in other organs.

An intention-to-treat analysis showed that 19/38 (50%) of patients had a complete or partial improvement in symptoms and signs of cGVHD. Nineteen out of 27 (70%) patients who completed 6 months of ECP showed an overall complete or partial response. Two patients had a complete improvement and seventeen had a partial improvement. Three patients had progressive disease, two had a minimal response and three had a mixed response. Twenty-two out of 27 (80%) patients who completed 6 months of ECP had a reduction in immunosuppression dose.

Limitations of this study included failure to complete 6 months treatment in 29% of patients, reflecting the high morbidity and mortality rate in patients with steroid-refractory cGVHD. This study confirms that ECP can lead to objective clinical responses in cGVHD.

Gandelman 2018:

In this prospective, multi-center clinical trial, 83 patients with cGVHD were treated with THERAKOS ECP using UVADEX twice a week for 4 weeks, then twice a week every 2 weeks for 8 weeks, then tapered at the discretion of the physician. NIH 2005 Consensus Criteria were recorded at baseline and patient response recorded at 2, 4, and 6 months of treatment. Study endpoints were response defined by the 2005 NIH response criteria and investigator-assessed response, with overall response defined by response at last visit. Most patients had classic cGVHD (n=62, 82%). The most commonly involved organ was skin, affecting 89% of patients. All patients enrolled had either moderate (n=37, 48%) or severe (n=40, 52%) cGVHD defined by NIH criteria.

Forty-eight patients (62.3%) completed the full 6 months of the study. Of the 29 patients (37.7%) who discontinued treatment early, 6 discontinued because of progression of cGVHD; 2 patients died of GVHD-related causes; and 2 patients discontinued because of improvement of cGVHD.

By investigator assessment, THERAKOS ECP treatment induced an overall response rate of 62.3% (95% CI, 51.5% to 73.1%). Specifically, CR: 14%; PR: 48%; SD: 19%; PD: 14% and 4% did not follow-up.

By assessment with NIH criteria, THERAKOS ECP treatment induced an overall response rate of 43.5% (95% CI, 31.8% to 55.2%) to ECP at last study visit. Specifically, CR: 6%; PR: 38%; SD: 15%; PD: 38% and 4% did not follow-up. Eight patients did not have enough data to assess NIH response and were excluded from the analysis.

In addition, ECP treatment was associated with a significant decrease in median prednisone dose (0.36 to 0.14 mg/kg, p<0.001) as well as investigator-assessed global severity score (6.0 [4.0-7.0] decreasing to 3.0 [2.0-6.0] at last visit, p<0.001. The percent total body surface with erythematous rash decreased from baseline to last visit (6.8 [0.9-15.4] decreasing to 1.7 [0.0-7.2] at last visit, p=0.01).

Within the context of this open label, uncontrolled study, ECP was able to deliver response using NIH response criteria in a highly pre-treated cohort with moderate and severe cGVHD independent of most previous risk factors for adverse outcomes of cGVHD.

Cutaneous T-Cell Lymphoma

Sponsor-initiated clinical study:

CTCL 3 was a prospective, uncontrolled study conducted in 51 patients with advanced stage CTCL. UVADEX was administered using the THERAKOS UVAR Photopheresis System.

Patients enrolled in CTCL 3 were adults with a diagnosis of CTCL based on the presence of skin lesions consistent with CTCL or lymph node biopsy consistent with CTCL. In this trial 59%, of patients had erythroderma and 12% had extensive plaque disease. The distribution of particular subsets of CTCL e.g. mycosis fungoides (MF), Sezary syndrome (SS) in the trial population was not defined.

Patients were excluded from CTCL-3 if they had:

- Skin tumours without erythroderma
- Skin tumours 5mm in diameter or larger
- Clinically evident CTCL involvement of liver, spleen, bone marrow or other viscera.
- WBC >25,000/mL

Hence the trial included patients with T2 and T4 disease, but not T3 disease. It excluded patients with Stage IV disease on the basis of systemic involvement.

The primary endpoint was the proportion of patients achieving a 25% reduction in 'skin score.' The Skin Score was calculated as a function of percentage of skin area affected and a rating between 0 and 4 of severity of disease (*see Section 4.2: Dosage and Method of Administration*), giving a possible score between 0-400.

The efficacy outcomes for this trial were:

Classification	**Response n (%)**	**Binomial 95% CI**
Responders	17 (33)	21 to 48
Non-responders	34 (67)	

CI – Confidence interval

33% of enrolled patients achieved 25% or greater reduction in their baseline skin scores within 180 days of initiation of treatment. The baseline skin score for this group was 277/400, indicating extensive skin involvement.

There is no evidence that UVADEX influences the progression of non-skin manifestations of CTCL.

Published clinical studies:

Published, uncontrolled prospective and retrospective studies conducted with THERAKOS Photopheresis Systems, CELLEX and UVAR XTS, have confirmed the efficacy and safety of UVADEX in advanced stage CTCL.

Overall response rates of approximately 60% with complete response rates of 14– 26% have been reported in recent studies using UVADEX (Alfred, 2017). Overall survival of approximately 5 years with an estimated 5 year probability of survival of >55% has been reported by Raphael (2001) and McGirt (2012).

Australian Patient Data under the Special Access Scheme:

A case series of 65 patients with SS or erythrodermic MF treated at the Victorian Comprehensive Cancer Centre (VCCC) using the THERAKOS photophoresis systems between 1997 and 2018 has been published (Gao, 2019). Median follow-up for surviving patients is 48 months (range 1-225 months).

The majority of patients commenced ECP at treatment lines 1 – 3 (n = 57). Patients received treatment one day per week for 6 weeks, one day every 2 weeks for 12 weeks, then one treatment monthly thereafter. This differs from the dosage regimen stated in Section 4.2 Dose and Method of Administration, that recommends 2 successive treatment days every month for six months. While the total number of ECP treatments given over a 6 month period was similar in this analysis, the VCCC used a more rapid induction, single treatment regimen.

The median time on ECP for the entire cohort of 65 patients was 17 months (range 0.5 – 159 months). The median time on treatment of 42.5 months for the 20 patients who commenced ECP as monotherapy at lines 1 – 3 was significantly longer than those who commenced ECP in combination with other systemic agents at lines 1 - 3 (13 months, p = 0.0002). The median Time to Next Treatment (TTNT) of the ECP-containing regimens was 19 months.

5.2 PHARMACOKINETIC PROPERTIES

The pharmacokinetics of intravenously administered methoxsalen have been studied in three groups of healthy volunteers who received 5, 10 or 15 mg methoxsalen infused over 60 minutes. The pharmacokinetics of methoxsalen were best described by a three-compartment, mammillary model in which the volumes and clearances were proportional to weight. The mean pharmacokinetic parameters are shown in Table 3 below.

Table 3 Summary of Pharmacokinetic Parameters for IV Methoxsalen

	Cmax ($ng\ mL^{-1}$)	**AUC ($ng\ mL^{-1}\ min$)**	**Clearance ($L\ kg^{-1}\ min^{-1}$)**	**MRT (min)**	**Vss ($L\ kg^{-1}$)**
5 mg dose (n=6)					
Mean	60.2	4756	0.012	50.4	0.52
s.d.	10.4	978	0.0035	35.1	0.022
10 mg dose (n=6)					
Mean	138.7	11626	0.011	56.8	0.61
s.d.	33.3	3366	0.0018	16.5	0.09
15 mg dose (n=6)					
Mean	195.8	16340	0.014	58.5	0.81
s.d.	89.2	8474	0.0034	23.9	0.34

In a clinical study conducted with UVADEX, methoxsalen concentrations in plasma 30 minutes after reinfusion of the photoactivated cells were less than 10 ng/mL in 82% of the 754 samples measured. The mean plasma methoxsalen level was approximately 25 ng/mL.

Distribution: Results of autoradiographic studies show that in rats psoralens distribute into most organs, with the highest concentrations of active substance in the liver and kidneys. Binding to human albumin is high (80–90%). In humans following IV infusion of methoxsalen over 60 minutes, the range of volume of distribution at steady state was 0.52 to 0.81 L/kg.

Metabolism: In humans, methoxsalen undergoes nearly complete biotransformation with little or no unchanged active substance being found in the urine or faeces. Both conjugated and unconjugated metabolites have been identified. Few data are available regarding the activity of the metabolites. Following IV infusion of methoxsalen over 60 minutes, systemic clearance ranged from 11 to 14 mL/min per kg.

Excretion: In humans, virtually no unchanged methoxsalen is recovered in the urine or faeces following oral administration. In radiolabelled studies, at 48 hours post-dosing, urinary excretion of radioactivity averaged 74%. Biliary excretion of methoxsalen and its metabolites, as reflected by faecal recovery, was relatively minor at 14%.

5.3 PRECLINICAL SAFETY DATA

Preclinical effects were observed only at exposures significantly in excess of the maximum human exposure indicating little relevance to clinical use except as described in other sections (*see Section 4.4: Special Warnings and Precautions for Use*).

No potential manifestations of toxicity were identified as a result of a four week simulation toxicity study in dogs subjected to extracorporeal photopheresis, at 1–2 J/cm^2, on a total of eight occasions when UVADEX was added to the buffy coat at concentrations of 100 and 500 ng/mL.

The potential for phototoxicity has been extensively studied in animal models. Manifestations of phototoxic responses have been identified in the skin and eye after oral dosing and the liver after intraperitoneal dosing. Studies in humans have shown that phototoxic responses are unlikely to occur unless systemic exposures of at least 30 ng/mL are achieved. As plasma methoxsalen concentrations following re-infusion of leukocyte enriched plasma after completion of extracorporeal photopheresis are consistently below the level of detection (10 ng/mL), the findings from the animal studies are of limited relevance in the context of the use of UVADEX.

Genotoxicity

Non-photoactivated methoxsalen has been shown to induce gene mutations in bacteria, and chromosomal aberrations and sister chromatid exchanges in cultured mammalian cells. In the presence of photoactivation, methoxsalen was mutagenic, and induced unscheduled DNA synthesis *in vivo* and *in vitro* and cross-links and mono-adduct formation *in vitro*.

Carcinogenicity

Some experimental studies have indicated that methoxsalen may increase susceptibility to skin carcinogenesis as a result of exposure to UV light. Studies in rats at oral doses of 37.5 and 75 mg/kg/day, 5 days per week for 103 weeks increased incidence of adenomas and adenocarcinomas of the tubular epithelium of the kidneys, carcinoma or squamous cell carcinoma of the Zymbal gland, alveolar or bronchiolar adenomas, and fibromas in subcutaneous tissue. Methoxsalen by topical and intraperitoneal administration is a photo-carcinogen in mice.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

UVADEX contains the following excipients: ethanol; propylene glycol; glacial acetic acid; sodium acetate trihydrate; sodium chloride; sodium hydroxide; water for injections. The drug product formulation contains 4.1% w/v ethanol and each 1 mL of UVADEX contains 40.55 mg of ethanol.

6.2 INCOMPATIBILITIES

Only the photopheresis procedural kits supplied for use with the THERAKOS CELLEX Photopheresis System should be used to administer this medicinal product. In-vitro studies indicate that typical sorption of UVADEX by plastics in the instrument's photopheresis photoactivation circuit during a photopheresis treatment is approximately 30%; however, sorption is significantly reduced once the product is diluted with plasma/buffy coat in clinical practice, resulting in no clinical impact.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

UVADEX methoxsalen 200 microgram/10 mL concentrated injection for extracorporeal circulation via photopheresis contains 200 microgram of methoxsalen (or 20 microgram per 1 mL) and is available in single-use, amber glass Type 1 vials in a pack size of 12 x 10 mL vials.

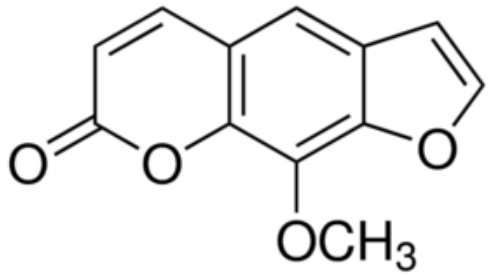
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

The chemical name of methoxsalen is 9-methoxy-7*H*-furo[3,2-g][1]-benzopyran-7-one; it has the following structure:



Molecular formula: $C_{12}H_8O_4$

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agents

ATC Code: LO3AX

CAS number

298-81-7

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

16 September 2019

10 DATE OF REVISION

19 November 2020

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.8 Adverse effects (Undesirable Effects)	Post-marketing Experience: added 'photosensitivity reactions'
References	Updated for published citations

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