SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Uvadex 20 micrograms/ml Solution for blood fraction modification

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml solution contains 20 micrograms methoxsalen.
One vial of 10 ml contains 200 micrograms methoxsalen.

Excipient(s) with known effect
The product contains 5% (v/v) of ethanol and each dose contains up to 217 mg of alcohol. It also contains less than 1 mmol sodium (23 mg) per dose administered (maximum volume 5.6 ml).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for blood fraction modification.

Clear, colourless to pale yellow solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

UVADEX is used in conjunction with the THERAKOS CELLEX Photopheresis System in the palliative treatment of the skin manifestations (patch plaque, extensive plaque, erythroderma) of advanced stage (T2 - T4) cutaneous T-cell lymphoma (CTCL), only in patients who have not been responsive to other forms of treatment, (e.g. puvatherapy, systemic cortocosteroids, caryolysin, interferon alpha).

4.2 Posology and method of administration

Posology

Adults

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

Paediatric population
The safety and efficacy of UVADEX in children has not been clinically evaluated for this indication.

Hepatic or renal impairment
UVADEX has not been clinically evaluated in patients with renal or hepatic impairment. (see 4.4.)

Method of administration

Extracorporeal use.

Do not inject directly into patients.

In the photopheresis process, the patient is connected to the THERAKOS CELLEX instrument 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. The buffy coat collection cycle is repeated three or six times, depending on the size of centrifuge bowl used in the instrument.

The prescribed amount of UVADEX is injected into the recirculation bag prior to the photoactivation phase. During photoactivation the leukocyte-enriched blood is continually circulated through the photoactivation chamber (photoceptor) for a maximum of 90 minutes whilst being exposed to UVA light (1-2 J/cm^2) from a single bank of UVA lamps.

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

The patient should receive treatment on two successive days each month for six months. Patients who fail to show an adequate response to treatment 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 (see below) maintained for at least 4 weeks.

Skin score determination:

The severity of skin lesions should be determined for each of 29 body sections (similar to these used in the estimation of burn damage) from 0 to 4, according to the following scale:

0 = normal skin
0.5 = background normal, with scattered erythematous papules
1 = minimal erythema and edema; no scaling or fissuring

2 = substantial erythema and edema; no scaling or fissuring
3 = submaximal erythema, scaling, and edema; no fissuring or ectropion
4 = most severe; universal involvement with maximal erythema, edema 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.

A 25% improvement is a clinically significant change that is typically associated with the extent of overall disease burden (degree of blood and lymph node involvement with malignant T-lymphocytes), an improvement in the skin manifestations of the disease being accompanied by a parallel improvement in systemic disease. To avoid short-lived, modest waxing and waning of skin lesions being confused with an improvement that is real, any positive changes in skin lesions must be maintained for at least four weeks to be considered clinically significant.

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

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
History of idiosyncratic or hypersensitivity reaction to methoxsalen, psoralen compounds or any of the excipients.

Use by sexually active men and women of childbearing potential unless adequate contraception is used during treatment (see section 4.6).

During pregnancy and lactation

Aphakia

Contraindications to the photopheresis procedure:

Photosensitive disease (eg porphyria,systemic lupus erythematosus, or albinism).

Inability to tolerate extracorporeal volume loss (eg due to severe cardiac disease, severe anaemia etc).

White blood cells count greater than 25,000 per 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 cutaneous T-cell lymphoma and 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 administered directly into the photoactivation

bag. If there is any possibility of unscheduled damage to the blood during the procedure (e.g. > 43ºC alarm sounding), the blood should only be reinfused into the patient if hemolysis 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 therapy.

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

Oral doses of psoralen compounds (e.g. methoxsalen) followed by exposure to UVA irradiation are used in PUVA therapy. Serum concentrations of psoralen may exceed 200 ng/ml in PUVA therapy and exposure to sunlight or ultraviolet radiation (even through window panes) may result in serious burns and, in the long-term, "premature aging" of the skin.

Extracorporeal use of UVADEX is associated with considerably lower systemic exposure to methoxsalen. However, the amount of phototoxicity from low levels of methoxsalen has not been investigated systematically. Therefore, as a precaution, patients should avoid exposure to sunlight during the 24-hours following photopheresis treatment.

PUVA therapy has been associated with dose dependent development of squamous cell carcinoma, basal cell carcinoma and possibly malignant melanoma. There is no evidence that there is an increased risk of these skin cancers with the extracorporeal use of UVADEX, nevertheless, patients with co-existing basal cell carcinoma, squamous cell carcinoma or malignant melanoma should be monitored for any changes of their skin cancer.

Renal impairment

Although several renal transplant recipients with poor renal function have been treated with photopheresis using UVADEX, little additional information is available on the use of UVADEX in renally-impaired patients. 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 and the procedures were well tolerated and effective.

Hepatic diseases

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, it is possible that hepatic impairment may result in an extended half life of methoxsalen. This may lead to prolonged photosensitivity and thus require 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.

Paediatric population
UVADEX has not been clinically evaluated in children.

Alcohol content
This medicinal product contains small amounts of 5% (v/v) of ethanol and each dose (maximum volume 5.6 ml) contains up to 217 mg of alcohol (ethanol), which is equivalent to 3.1 mg/kg per 5.6 ml dose. The amount in one 5.6 ml dose of this medicine is equivalent to less than 6 ml beer or 3 ml wine.
With extracorporeal administration systemic exposure is expected to be low and a clinical effect has not been evident, however Prescriber's should be aware of the potential effects of other medicines and caution is advised in liver disease, alcoholism, epilepsy, brain injury or disease.

Sodium content
UVADEX contains less than 1 mmol sodium (23 mg) per dose administered (maximum volume 5.6 ml).

4.5 Interaction with other medicinal products and other forms of interaction

Although methoxsalen has been shown to be capable of both induction and inhibition of hepatic enzymes, in man 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 and antipyrine have been shown to be markedly reduced after methoxsalen treatment. Therefore, consumption of other P450 substrates may result in an extended half life of methoxsalen, and consequently lead to prolonged photosensitivity and thus requiring continued precautions against exposure to sunlight beyond 24 hours following photopheresis treatment.

Studies have shown that methoxsalen also 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.

One report describes a psoriatic and epileptic patient 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.

In the blood methoxsalen is normally highly 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. Such agents include fluoroquinolones, furosemide, nalidixic acid, phenothiazines, retinoids, sulfonamides, sulfonylureas, tetracyclines, and thiazides.

4.6 Fertility, pregnancy and lactation

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

Pregnancy
Although there is no human experience of the use of UVADEX during pregnancy, animal data suggest that methoxsalen may cause foetal harm when administered to a pregnant woman. Therefore, UVADEX is contraindicated in women who are or may become pregnant (see section 4.3)

Breast-feeding
It is not known whether methoxsalen is excreted in human milk. Thus and because of the pharmacodynamic properties of UVADEX, lactation is a contraindication.

Fertility
Fertility studies to assess the reproductive toxicity of UVADEX have not been conducted.

4.7 Effects on ability to drive and use machines

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 and patients should not drive or operate machinery immediately following photopheresis.

4.8 Undesirable effects

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 (commonly associated with methoxsalen when administered orally) 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 were as follows:

Event	CTCL 3 UVADEX		CTCL 1 & 2 Oral Methoxsalen	
	Nº of Patients (%) N=51	Total Nº by Treatments Nº of Treatments = 1032	Nº of Patients (%) N=96	Total Nº by Treatments Nº of Treatments = 4319
Hypotension	0	0	7 (7.3)	7 (< 0.2)
Transient fever 6-8 hrs after reinfusion of photoactivated cells	0	0	8 (8.3)	17 (< 0.4)
Vascular access complication	9 (17.6)	10 (< 0.1)	0	0
Infection	1 (2.0)	1 (< 0.1)	5 (5.2)	5 (< 0.2)

Adverse events associated with the photopheresis procedure from clinical experience (clinical trials) with UVADEX in other indications are presented below.

Event	Other Clinical Trial Experience with UVADEX	
	By Patients	By Number of Treatments
Hypotension	< 2/100	<8/10,000
Transient fever 6-8 hrs after reinfusion of photoactivated cells	< 1/100	<2 /10,000
Vascular access complication	< 5/100*	<4/1000**
Infection/ Catheter related infection/sepsis	< 4/100	<2/1000

* Two thirds of patients had progressive systemic sclerosis

** Two thirds of events occurred in progressive systemic sclerosis patients

Small, but statistically significant, changes occurred in several biochemical and haematological parameters during treatment of CTCL with UVADEX. These are not considered to be of clinical relevance and are summarised below.

Statistically Significant Laboratory Value Changes
Mean ± SD

Parameter	N	Baseline	Final	Delta
Albumin (g/l)	51	13.8 ± 16.8	12.8 ± 15.6	-1.0
Calcium (mg/dl)	51	7.8 ± 3.2	7.5 ± 3.1	-0.3
Haematocrit (%)	51	41.1 ± 4.3	38.0 ± 4.7	-3.1
Haemoglobin (g/dl)	51	13.8 ± 1.4	12.7 ± 1.6	-1.1
Potassium (mEq/l)	48	4.4 ± 0.5	4.1 ± 0.4	-0.3
RBC ($x10^{12}$/l)	51	4.6 ± 0.5	4.4 ± 0.6	-0.2

Tabulated list of adverse reactions

The following list of adverse reactions is based on experience from clinical trials and on post marketing experience and are displayed by system organ class and frequency in table below: very common (1/10); common (1/100 to < 1/10); uncommon (1/1,000 to< 1/100); rare (1/10,000 to < 1/1,000); and not known (cannot be estimated from the available data).

System organ class	Adverse reaction(s)	Frequency
Infections and infestations	Infections	Common
Immune system disorders	Allergic reaction	Not known
Nervous system disorders	Dysgeusia	Common
Cardiac disorders	Hypotension	Common
Gastrointestinal disorders	Nausea and vomiting	Common
Skin and subcutaneous tissue disorders	Photosensitivity reaction	Uncommon
Injury, poisoning and procedural complications	Transient fever & Vascular access complication	Common

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute animal experience suggests a large margin of safety and dangerous overdose is extremely unlikely to occur.

Whilst there is no human experience of overdose with UVADEX, 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 (ie 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.

In the event of methoxsalen overdose, the patient should be kept in a darkened room for at least 24 hours.

The THERAKOS CELLEX instrument has been engineered to deliver the optimum level of UVA energy to the leukocyte enriched blood fraction when the UVA exposure time is set to 1.5 hours at the end of collection. In the event of UVA energy overexposure of the leukocyte enriched blood fraction beyond 30 additional minutes the photoactivated cells should not be returned to the patient.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agents, ATC code: LO3AX

Mechanism of action
Methoxsalen is a photosensitising agent which preferentially accumulates in epidermal cells.

Although photochemotherapy has been used clinically for many years, the mechanism by which the therapy is effective remains to be fully elucidated. Although the precise mode of action has not been established, 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. The nucleic acid-furocoumarin complexes formed in this intercalation process involve weak bonding forces such as Van der Waal's, hydrogen bonding and hydrophilic forces. Their formation is easily reversed and, in the absence of photoactivation, they are without pharmacological consequence. However, 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 reaction occurs in a few microseconds and when the radiation is turned off, the active substance returns immediately to its inert form.

Pharmacodynamic effects
The formation of photoadducts results in the proliferative arrest of lymphocytes and, over a period of about 72 hours, they die. This acute effect on the T-cell is probably a minor effect with regard to therapeutic efficacy. There is an increasingly large body of evidence suggesting that photopheresis may act as an immunomodulator leading to the augmentation of systemic antitumour responses.

Clinical efficacy and safety
Efficacy of UVADEX has been shown in one single arm, uncontrolled, open label, multicentre study with 51 patients. Patients who had tumours of 5 mm in diameter or larger and patients who had clinically evident CTCL involvement of liver, spleen, bone marrow or other viscera have been excluded in this study. Within the initial six months of treatment, 17/51 (33%) were reported with an adequate clinical response. Details of the definition of an adequate clinical response are provided in section 4.2.

5.2 Pharmacokinetic properties

Absorption
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, mammilary model in which the volumes and clearances were proportional to weight. The mean pharmacokinetic parameters are shown in the table below.

Summary of Pharmacokinetic Parameters for Intravenously Administered Methoxsalen

	C_{max} (ng ml^{-1})	**AUC (ng ml^{-1} min)**	**Clearance (l kg^{-1} min^{-1})**	**MRT (min)**	**V_{ss} (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 the 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 but binding appears to be short-lived and reversible. Other studies in the rat have shown the highest concentrations of active substance in the liver and kidneys and a fat/muscle ratio of 3:1. Binding to human albumin is high (80-90%).

Biotransformation
In man, 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. Such few data as are available regarding the activity of the metabolites suggest that they do not possess the pharmacological activity of the parent compound.

Elimination
In man, 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).

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/cm², on a total of eight occasions when UVADEX was added to the buffy coat at concentrations of 100 and 500 ng/ml.

Reproductive toxicity studies in the rat have indicated that methoxsalen adversely affects foetal growth, viability and morphological development at doses that caused significant maternal toxicity.

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.

Some experimental studies have indicated that methoxsalen may increase susceptibility to skin carcinogenesis as a result of exposure to UV light. Non-photoactivated methoxsalen has been shown to induce gene mutations in bacteria, and chromosomal aberrations and sister chromatid exchanges in cultured mammalian cells and is reported to have induced an excess

of renal, subcutaneous and lung tumours in male rats after oral administration at doses of 37.5 and 75 mg/kg/day (5 x weekly) for up to two years.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 95%
Propylene Glycol
Glacial Acetic Acid
Sodium Acetate Trihydrate
Sodium Chloride
Sodium Hydroxide
Water for Injections

6.2 Incompatibilities

UVADEX can sorb onto PVC and other plastics; only the THERAKOS CELLEX photopheresis procedural kit supplied for use with the instrument should be used to administer this medicinal product. Typical sorption of UVADEX by plastics in the instrument's photopheresis photoactivation circuit during a photopheresis treatment is approx 30%. Once UVADEX is drawn into a plastic syringe it should be immediately injected into the photoactivation bag.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Do not store above 25°C

6.5 Nature and contents of container

10 ml of solution in amber glass vials (Type 1) with laminated stoppers (butyl rubber laminated with fluorocarbon polymer film), sealed with aluminium flip-off caps. Pack size: 12x 10 ml.

6.6 Special precautions for disposal

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

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

UVADEX exposed to a plastic syringe for more than one hour should be discarded.

7. MARKETING AUTHORISATION HOLDER

THERAKOS (UK) Limited, 3 Lotus Park, The Causeway, Staines-upon-Thames, Surrey TW18 3AG, United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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