

THERAKOS® Photopheresis – Ambassador video transcript – Lou

<u>VIDEO</u>	<u>AUDIO</u>
<div data-bbox="203 317 794 646"><p>You're about to hear from a patient about his experience with skin symptoms of Cutaneous T-Cell Lymphoma (CTCL) and treatment with THERAKOS® Photopheresis.</p><p>This patient has been compensated by Mallinckrodt for his time in sharing his story, however the views and opinions expressed by him are his own and do not necessarily reflect those of Mallinckrodt.</p><p>Please remember that this is just his experience and that every patient's experience is unique.</p><p>This information does not take the place of talking with your healthcare professional.</p><p>It is recommended that you discuss the therapy and your conditions with your doctor.</p></div> <p>FSG:</p> <p>You're about to hear from a patient about his experience with skin symptoms of Cutaneous T-Cell Lymphoma (CTCL) and treatment with THERAKOS® Photopheresis.</p> <p>This patient has been compensated by Mallinckrodt for his time in sharing his story, however the views and opinions expressed by him are his own and do not necessarily reflect those of Mallinckrodt.</p> <p>Please remember that this is just his experience and that every patient's experience is unique.</p> <p>This information does not take the place of talking with your healthcare professional.</p> <p>It is recommended that you discuss the therapy and your conditions with your doctor.</p>	<p>ANNOUNCER VO:</p> <p>You're about to hear from a patient about his experience with skin symptoms of Cutaneous T-Cell Lymphoma and treatment with THERAKOS® Photopheresis.</p> <p>This patient has been compensated by Mallinckrodt for his time in sharing his story, however the views and opinions expressed by him are his own and do not necessarily reflect those of Mallinckrodt.</p> <p>Please remember that this is just his experience and that every patient's experience is unique.</p> <p>This information does not take the place of talking with your healthcare professional.</p> <p>It is recommended that you discuss the therapy and your conditions with your doctor.</p>

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<div data-bbox="203 254 807 590"><p>The following information is about UVADEX® (methoxsalen [meth-ox-sah-len]) Sterile Solution and its use in photopheresis.</p><p>In the United States, UVADEX® (methoxsalen) Sterile Solution is used with the THERAKOS® UVAR XTS® or THERAKOS CELLEX® Photopheresis Systems for the treatment of skin problems associated with CTCL in patients who have not responded to other types of treatment given by their doctor.</p></div> <p>The following information is about UVADEX® (methoxsalen [meth-ox-sah-len]) Sterile Solution and its use in photopheresis.</p> <p>In the United States, UVADEX® (methoxsalen) Sterile Solution is used with the THERAKOS® UVAR XTS® or THERAKOS CELLEX® Photopheresis Systems for the treatment of skin problems associated with CTCL in patients who have not responded to other types of treatment given by their doctor.</p>	<p>The following information is about UVADEX® (methoxsalen [meth-ox-sah-len]) Sterile Solution and its use in photopheresis.</p> <p>In the United States, UVADEX® (methoxsalen) Sterile Solution is used with the THERAKOS® UVAR XTS® or THERAKOS CELLEX® Photopheresis Systems for the treatment of skin problems associated with CTCL in patients who have not responded to other types of treatment given by their doctor.</p>
<div data-bbox="203 1098 807 1434"><p>SELECT IMPORTANT SAFETY INFORMATION</p><p>UVADEX (methoxsalen) Sterile Solution should only be used by doctors who have special skills in the diagnosis and treatment of CTCL and who have received special training and have experience in the THERAKOS UVAR XTS or THERAKOS CELLEX Photopheresis Systems.</p></div> <p>SELECT IMPORTANT SAFETY INFORMATION</p> <p>(Text surrounded by black box)</p> <p>UVADEX (methoxsalen) Sterile Solution should only be used by doctors who have special skills in the diagnosis and treatment of CTCL and who have received special training and have experience in the THERAKOS UVAR XTS or THERAKOS CELLEX Photopheresis Systems.</p>	<p>SELECT IMPORTANT SAFETY INFORMATION</p> <p>UVADEX (methoxsalen) Sterile Solution should only be used by doctors who have special skills in the diagnosis and treatment of CTCL and who have received special training and have experience in the THERAKOS UVAR XTS or THERAKOS CELLEX Photopheresis Systems.</p>

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<div data-bbox="203 254 805 590"><p>Please carefully review and consider all the Important Safety Information at the end of this video.</p><p>Please click below for the Full Prescribing Information, including the BOXED WARNING, for UVADEX.</p><p>For more information on the THERAKOS Photopheresis Systems, please speak to your doctor.</p></div> <p data-bbox="203 617 743 716">Please carefully review and consider all the Important Safety Information at the end of this video.</p> <p data-bbox="203 747 784 846">Please click below for the Full Prescribing Information, including the BOXED WARNING, for UVADEX.</p> <p data-bbox="203 877 743 976">For more information on the THERAKOS Photopheresis Systems, please speak to your doctor.</p>	<p data-bbox="826 617 1367 716">Please carefully review and consider all the Important Safety Information at the end of this video.</p> <p data-bbox="826 747 1367 846">Please click below for the Full Prescribing Information, including the BOXED WARNING, for UVADEX.</p> <p data-bbox="826 877 1367 976">For more information on the THERAKOS Photopheresis Systems, please speak to your doctor.</p>
<div data-bbox="203 1087 805 1423"><p>How did you feel about starting treatment with photopheresis?</p></div> <p data-bbox="203 1451 269 1482">FSG:</p> <p data-bbox="203 1514 743 1581">How did you feel about starting treatment with photopheresis?</p>	

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LOU INTERVIEW:



Lower Third Graphic: Lou / Living with Skin Symptoms of Cutaneous T-Cell Lymphoma (CTCL)



LOU:

I started out with phototherapy. And then I went to topical chemo, and then pills, and then to radiation. And then, when those weren't managing my skin symptoms as we had hoped, my doctor suggested photopheresis.

I was hopeful this one would work for me because you get to lay down in the bed, watch TV, talk to your doctors, and you even get to sleep.

How has the healthcare team at your photopheresis center been helpful to you?

FSG:

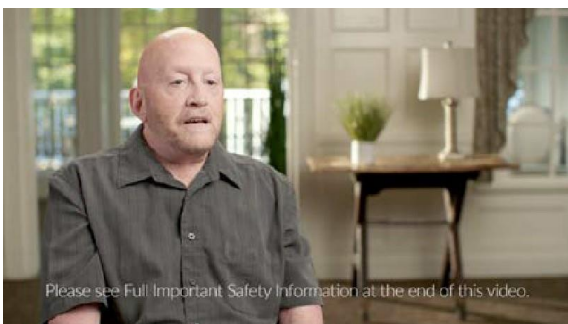
How has the healthcare team at your photopheresis center been helpful to you?

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LOU:

My healthcare team—I'm being biased—are the best. My doctors, my nurses run the show. They're courteous. They're helpful. They'll listen to you if you have any questions, any issues. They help you through everything.



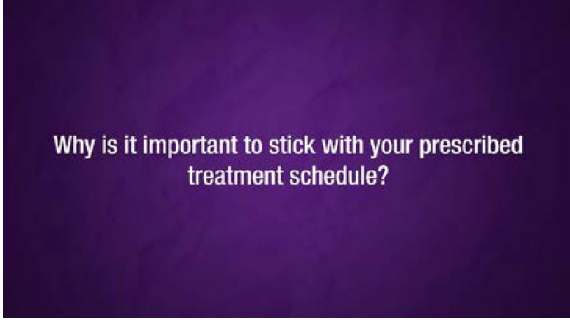



Lower Third Graphic: Please see Full Important Safety Information at the end of this video.



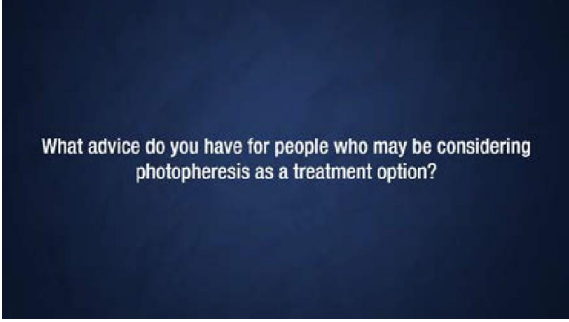

My nurses check to see if I have possible side effects like low blood pressure after my procedure, redness of the skin at the injection site, and possible fever eight hours after the procedure.

They don't let me leave until I put on my special sunglasses that I have to wear 24 hours after the procedure because photopheresis may increase my sensitivity to the sun.

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 <p>FSG:</p> <p>Why is it important to stick with your prescribed treatment schedule?</p>	
  	<p>LOU:</p> <p>After starting treatment with photopheresis, my friends and family saw a change. My skin was, my skin was less red. I wasn't totally convinced it was helping me until I went on vacation and I missed a photopheresis treatment, and then symptoms of my CTCL began to flare up. I began itching, my skin became hot, and rashes started forming.</p> <p>That's when I realized that photopheresis was really having an effect for me. Of course, this is my experience and everybody else is different.</p>

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 <p>What advice do you have for people who may be considering photopheresis as a treatment option?</p> <p>FSG:</p> <p>What advice do you have for people who may be considering photopheresis as a treatment option?</p>	
	<p>LOU:</p> <p>My advice for people seeking out photopheresis as a treatment is talk to your doctors. Have them explain it to you before you go and have your treatment. It's not as intimidating as it seems.</p> <p>Plus, your nurses and your doctors help you get through any and every thing that you need, and they make you feel at ease.</p>

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<div data-bbox="207 254 794 579"><p>The following information is about the use of UVADEX® (methoxsalen) Sterile Solution with the THERAKOS® UVAR XTS® or THERAKOS CELLEX® Photopheresis Systems for the treatment of skin conditions associated with Cutaneous T-Cell Lymphoma (CTCL). This information does not take the place of talking with your healthcare professional. It is recommended that you discuss the therapy and your conditions with your doctor.</p></div> <p>FSG:</p> <p>The following information is about the use of UVADEX® (methoxsalen) Sterile Solution with the THERAKOS® UVAR XTS® or THERAKOS CELLEX® Photopheresis Systems for the treatment of skin conditions associated with Cutaneous T-Cell Lymphoma (CTCL). This information does not take the place of talking with your healthcare professional. It is recommended that you discuss the therapy and your conditions with your doctor.</p>	<p>ANNOUNCER VO:</p> <p>The following information is about the use of UVADEX® (methoxsalen) Sterile Solution with the THERAKOS® UVAR XTS® or THERAKOS CELLEX® Photopheresis Systems for the treatment of skin conditions associated with Cutaneous T-Cell Lymphoma (CTCL). This information does not take the place of talking with your healthcare professional. It is recommended that you discuss the therapy and your conditions with your doctor.</p>
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<div data-bbox="207 1041 794 1367" data-label="Image"> </div> <p>DO NOT USE UVADEX IF:</p> <ul style="list-style-type: none"> • You are allergic to methoxsalen, any product similar or related to it, such as psoralen, or any of the other ingredients in UVADEX. • You have a history of a light-sensitive condition or disease. • You have had an eye lens removed; use of UVADEX in this condition can increase the risk of retinal damage. 	<p>DO NOT USE UVADEX IF:</p> <ul style="list-style-type: none"> • You are allergic to methoxsalen, any product similar or related to it, such as psoralen, or any of the other ingredients in UVADEX. • You have a history of a light-sensitive condition or disease. • You have had an eye lens removed; use of UVADEX in this condition can increase the risk of retinal damage.

WARNINGS

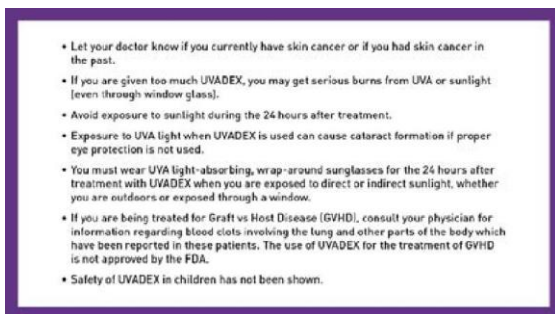
- You may be at greater risk of sun sensitivity with UVADEX. Tell your doctor if you are taking other medications that cause sensitivity to sunlight, such as anthralin, coal tar or coal tar derivatives, griseofulvin, phenothiazines, nalidixic acid, halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides, and certain organic staining dyes, such as methylene blue, toluidine blue, rose bengal, and methyl orange.
- If you are pregnant or plan to become pregnant, tell your doctor. Methoxsalen can harm your unborn baby. Tell your doctor right away if you become pregnant during your UVADEX treatment. If you are breastfeeding or plan to breastfeed, tell your doctor. It is not known if methoxsalen passes into your breastmilk.
- After UVADEX is given, exposure to sunlight and/or ultraviolet radiation may result in premature aging of your skin.

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| <ul style="list-style-type: none"> • Let your doctor know if you currently have skin cancer or if you had skin cancer in the past. • If you are given too much UVADEX, you may get serious burns from UVA or sunlight (even through window glass). • Avoid exposure to sunlight during the 24 hours after treatment. • Exposure to UVA light when UVADEX is used can cause cataract formation if proper eye protection is not used. • You must wear UVA light-absorbing, wrap-around sunglasses for the 24 hours after treatment with UVADEX when you are exposed to direct or indirect sunlight, whether you are outdoors or exposed through a window. • If you are being treated for Graft vs Host Disease (GVHD), consult your physician for information regarding blood clots involving the lung and other parts of the body which have been reported in these patients. The use of UVADEX for the treatment of GVHD is not approved by the FDA. • Safety of UVADEX in children has not been shown. | <ul style="list-style-type: none"> • Let your doctor know if you currently have skin cancer or if you had skin cancer in the past. • If you are given too much UVADEX, you may get serious burns from UVA or sunlight (even through window glass). • Avoid exposure to sunlight during the 24 hours after treatment. • Exposure to UVA light when UVADEX is used can cause cataract formation if proper eye protection is not used. • You must wear UVA light-absorbing, wrap-around sunglasses for the 24 hours after treatment with UVADEX when you are exposed to direct or indirect sunlight, whether you are outdoors or exposed through a window. • If you are being treated for Graft vs Host Disease (GVHD), consult your physician for information regarding blood clots involving the lung and other parts of the body which have been reported in these patients. The use of UVADEX for the treatment of GVHD is not approved by the FDA. • Safety of UVADEX in children has not been shown. |
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<div data-bbox="227 804 766 1106" data-label="Image"> </div> <div data-bbox="196 1144 708 1211" data-label="Section-Header"> <h2>For the THERAKOS UVAR XTS/CELLEX Photopheresis Systems procedure:</h2> </div> <div data-bbox="196 1249 696 1312" data-label="Section-Header"> <h3>What is the THERAKOS Photopheresis Systems procedure?</h3> </div> <div data-bbox="196 1339 800 1862" data-label="Text"> <p>The THERAKOS UVAR XTS/CELLEX Photopheresis Systems procedure is a medical procedure in which blood from a patient is collected into a specialized machine that separates the white blood cells from the other blood components. The other blood components are returned to the patient and white blood cells are then treated with UVADEX, which makes them sensitive to ultraviolet light. The treated white blood cells are exposed to UVA irradiation inside the machine, and then returned to the patient. This medical procedure is used to treat skin problems associated with CTCL in patients who have not been responsive to other forms of treatment given by their doctor.</p> </div>	<div data-bbox="818 1119 1331 1186" data-label="Section-Header"> <h2>For the THERAKOS UVAR XTS/CELLEX Photopheresis Systems procedure:</h2> </div> <div data-bbox="818 1224 1320 1285" data-label="Section-Header"> <h3>What is the THERAKOS Photopheresis Systems procedure?</h3> </div> <div data-bbox="818 1314 1385 1873" data-label="Text"> <p>The THERAKOS UVAR XTS/CELLEX Photopheresis Systems procedure is a medical procedure in which blood from a patient is collected into a specialized machine that separates the white blood cells from the other blood components. The other blood components are returned to the patient and white blood cells are then treated with UVADEX, which makes them sensitive to ultraviolet light. The treated white blood cells are exposed to UVA irradiation inside the machine, and then returned to the patient. This medical procedure is used to treat skin problems associated with CTCL in patients who have not been responsive to other forms of treatment given by their doctor.</p> </div>

<div data-bbox="224 226 776 535"><p>DO NOT UNDERGO THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE IF:</p><ul style="list-style-type: none">• You have a condition that makes you unable to tolerate loss of blood volume.• You are allergic or hypersensitive to 8-methoxypsoralen, methoxsalen, or psoralen compounds.• Your doctor has diagnosed you with a blood-clotting or bleeding problem that can lead to either a blood clot or excessive bleeding.• You have had your spleen removed.</div> <div data-bbox="203 569 782 625"><p>DO NOT UNDERGO THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE IF:</p></div> <div data-bbox="203 661 776 1104"><ul style="list-style-type: none">• You have a condition that makes you unable to tolerate loss of blood volume.• You are allergic or hypersensitive to 8-methoxypsoralen, methoxsalen, or psoralen compounds.• Your doctor has diagnosed you with a blood-clotting or bleeding problem that can lead to either a blood clot or excessive bleeding.• You have had your spleen removed.</div>	<div data-bbox="824 562 1367 651"><p>DO NOT UNDERGO THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE IF:</p></div> <div data-bbox="824 686 1377 1163"><ul style="list-style-type: none">• You have a condition that makes you unable to tolerate loss of blood volume.• You are allergic or hypersensitive to 8-methoxypsoralen, methoxsalen, or psoralen compounds.• Your doctor has diagnosed you with a blood-clotting or bleeding problem that can lead to either a blood clot or excessive bleeding.• You have had your spleen removed.</div>
<div data-bbox="224 1213 792 1528"><p>WARNINGS FOR THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE</p><ul style="list-style-type: none">• Treatments with THERAKOS Photopheresis Systems should always be performed where standard medical emergency equipment is available.• THERAKOS Photopheresis Systems procedures should not be performed on the same day as procedures that can cause fluid changes, such as renal dialysis.</div> <div data-bbox="203 1562 743 1619"><p>WARNINGS FOR THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE</p></div> <div data-bbox="203 1654 773 1789"><ul style="list-style-type: none">• Treatments with THERAKOS Photopheresis Systems should always be performed where standard medical emergency equipment is available.</div>	<div data-bbox="824 1549 1367 1606"><p>WARNINGS FOR THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE</p></div> <div data-bbox="824 1642 1364 1778"><ul style="list-style-type: none">• Treatments with THERAKOS Photopheresis Systems should always be performed where standard medical emergency equipment is available.</div>

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<div data-bbox="219 453 790 770" data-label="Image"> </div> <p>SIDE EFFECTS OF THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE</p> <ul style="list-style-type: none"> • Low blood pressure can occur with the THERAKOS Photopheresis Systems procedure. • You may get an infection and/or feel pain at the site of injection. • Fevers of 100–102°F (37.7–38.9°C) have been seen in some patients within 6 to 8 hours after treatment. Redness of the skin may also occur with the fever. • A decrease in red blood cells can occur if the THERAKOS Photopheresis Systems procedure is given too frequently. Low levels of red blood cells may cause you to feel tired. <p>SIDE EFFECTS OF THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE</p> <ul style="list-style-type: none"> • Low blood pressure can occur with the THERAKOS Photopheresis Systems procedure. • You may get an infection and/or feel pain at the site of injection. • Fevers of 100–102°F (37.7–38.9°C) have been seen in some patients within 6 to 8 hours after treatment. Redness of the skin may also occur with the fever. • A decrease in red blood cells can occur if the THERAKOS Photopheresis Systems procedure is given too frequently. Low levels of red blood cells may cause you to feel tired. 	<p>SIDE EFFECTS OF THE THERAKOS PHOTOPHERESIS SYSTEMS PROCEDURE</p> <ul style="list-style-type: none"> • Low blood pressure can occur with the THERAKOS Photopheresis Systems procedure. • You may get an infection and/or feel pain at the site of injection. • Fevers of 100–102°F (37.7–38.9°C) have been seen in some patients within 6 to 8 hours after treatment. Redness of the skin may also occur with the fever. • A decrease in red blood cells can occur if the THERAKOS Photopheresis Systems procedure is given too frequently. Low levels of red blood cells may cause you to feel tired.

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UVADEX®

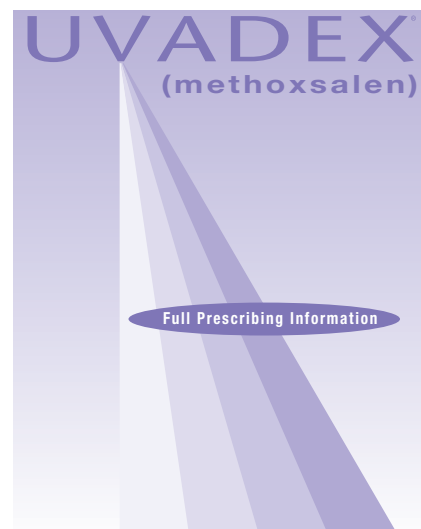
(Methoxsalen)

STERILE SOLUTION, 20 mcg/mL

Rx ONLY.

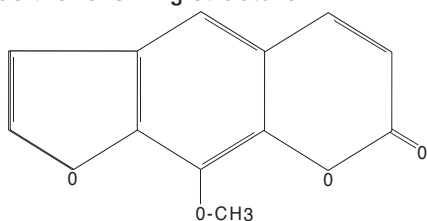
CAUTION: READ THE THERAKOS® UVAR XTS® or THERAKOS® CELLEX®
PHOTOPHERESIS SYSTEM OPERATOR'S MANUAL PRIOR TO
PRESCRIBING OR DISPENSING THIS MEDICATION.

UVADEX® (methoxsalen) Sterile Solution should be used only by physicians who have special competence in the diagnosis and treatment of cutaneous T-cell lymphoma and who have special training and experience in the THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System. Please consult the appropriate Operator's Manual before using this product.



DESCRIPTION

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



Each mL of UVADEX® (methoxsalen, 8-methoxypsoralen) Sterile Solution contains methoxsalen 20 mcg, propylene glycol 50 mg, sodium chloride 8 mg, sodium acetate 1.75 mg, ethanol 40.550 mg, glacial acetic acid 1.260 mg, and Water for Injection q.s. to 1.0 mL. Glacial acetic acid and sodium hydroxide are used to adjust the pH of the solution if necessary. UVADEX® is a clear, colorless to pale yellow liquid.

UVADEX® is used in combination with the THERAKOS® UVAR XTS® and THERAKOS® CELLEX® Photopheresis Systems to extracorporeally treat leukocyte enriched buffy coat.

CLINICAL PHARMACOLOGY

Mechanism of action: The exact mechanism of action of methoxsalen is not known. The best-known biochemical reaction of methoxsalen is with DNA. Methoxsalen, upon photoactivation, conjugates and forms covalent bonds with DNA which leads to the formation of both monofunctional (addition to a single strand of DNA) and bifunctional adducts (crosslinking of psoralen to both strands of DNA). Reactions with proteins have also been described. The formation of photoadducts results in inhibition of DNA synthesis, cell division and epidermal turnover.

For the palliative treatment of Cutaneous T-Cell Lymphoma, Photopheresis consists of removing a portion of the patient's blood and separating the red blood cells from the white cell layer (buffy coat) by centrifugation. The red cells are returned to the patient and the UVADEX® Sterile Solution is then injected into the instrument and mixed with the buffy coat. The instrument then irradiates this drug-cell mixture with ultraviolet light (UVA light, 320–400 nm) and returns the treated cells to the patient. See the appropriate Operator's Manual for details of this process. Although extracorporeal phototherapy exposes less than 10% of the total body burden of malignant cells to methoxsalen plus light, some patients achieve a complete response. Animal studies suggest that the photopheresis may activate an immune-mediated response against the malignant T-cells.

Use of the UVAR and UVAR XTS® Systems after oral administration of methoxsalen were previously approved for the treatment of Cutaneous T-Cell Lymphoma. Interpatient variability in peak plasma concentration after an oral dose of methoxsalen ranges from 6 to 15 fold. UVADEX® is injected directly into the separated buffy coat in the instrument in an attempt to diminish this interpatient variability and to improve the exposure of the cells to the drug.

Methoxsalen is reversibly bound to serum albumin and is also preferentially taken up by epidermal cells. Methoxsalen is rapidly metabolized in humans, with approximately 95% of the drug excreted as metabolites in the urine within 24 hours.

Systemic administration of methoxsalen followed by UVA exposure leads to cell injury. The most obvious manifestation of this injury after skin exposure is delayed erythema, which may not begin for several hours and peaks at 48–72 hours. The inflammation is followed over several days to weeks, by repair which is manifested by increased melanization of the epidermis and thickening of the stratum corneum.

The total dose of methoxsalen delivered in UVADEX® is substantially lower (approximately 200 times) than that used with oral administration. More than 80% of blood samples collected 30 minutes after reinfusion of the photoactivated buffy coat had methoxsalen levels below detection limits of the assay (<10 ng/ml), and the mean plasma methoxsalen concentration was approximately 25 ng/ml.

CLINICAL STUDIES

Three single-arm studies were performed to evaluate the effectiveness of photopheresis in the treatment of the skin manifestations of Cutaneous T-Cell Lymphoma (CTCL). In the first study (CTCL 1), 39 patients were treated with the oral formulation of methoxsalen in conjunction with the UVAR Photopheresis System. The second study (CTCL 2) was a 5-year post approval follow-up of 57 CTCL patients that was conducted to evaluate long-term safety. This study also used the oral dosage formulation of methoxsalen. In the third study (CTCL 3), 51 patients were treated with the UVADEX® formulation of methoxsalen in conjunction with the UVAR Photopheresis System. In study CTCL 3, 86% of the patients were Caucasian, the median age was 62 years, and the average number of prior therapies was 4.3.

In study CTCL 1, prednisone up to 10 mg/day was permitted in addition to topical steroids. In CTCL 2, there was no concomitant medication restriction. In CTCL 3, topical steroids were permitted only for the treatment of fissures on the soles of the feet and the palms of hands. All other steroids, topical or systemic, were prohibited.

In all three studies, patients were initially treated on two consecutive days every four to five weeks. If the patient did not respond after four cycles, treatment was accelerated to two consecutive days every other week. If the patient did not respond after four cycles at the accelerated schedule, the patient was treated on two consecutive days every week. If the patient still did not respond after four cycles of weekly treatments, the schedule was increased to three consecutive days every week for three cycles. In study CTCL 3, 15 of the 17 responses were seen within six months of treatment. Only two patients responded to treatment after six months. Clinical experience does not extend beyond this treatment frequency and there is no evidence to show that treatment with UVADEX® beyond six months or using a different schedule provided additional benefit.

Overall skin scores were used in the clinical studies of photopheresis to assess the patient's response to treatment. The patient's baseline skin score was used for comparison with subsequent scores. A 25% reduction in skin score maintained for four consecutive weeks was considered a successful response to photopheresis therapy. Table 1 indicates the percent of successful

responses within six months of beginning therapy for all patients who received at least one course of photopheresis. Only patients with patch plaque, extensive plaque and erythrodermic disease were enrolled in these studies. No patients with disease in the tumor phase were treated. There are no data available regarding the efficacy of UVADEX® in patients with disease in the tumor phase.

Table 1:
Percentage of Successful Responses
Within Six Months of Beginning Therapy

Study	Response % Within Six Months
CTCL 3 (UVADEX®)	17/51 (33)
CTCL 2 (oral methoxsalen)	16/57 (28)
CTCL 1 (oral methoxsalen)	21/39 (54)

Although the response rate with UVADEX® in CTCL 3 was similar to with oral methoxsalen in CTCL 2, the possibility that UVADEX® is inferior in efficacy to oral methoxsalen cannot be excluded due to the design and size of the clinical trials. The higher response rate with oral methoxsalen in CTCL 1 may be partly due to patients receiving more treatments (mean of 64 in CTCL 1, 31 in CTCL 2, and 20 in CTCL 3), and to the administration of systemic steroids in CTCL 1.

Retrospective analyses of three clinical benefit parameters from the Body Area Severity Scores in CTCL 3 suggested a correlation between skin score response and improvement in edema, scaling and resolution of fissures.

INDICATIONS AND USAGE

UVADEX® (methoxsalen) Sterile Solution is indicated for extracorporeal administration with the THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System in the palliative treatment of the skin manifestations of Cutaneous T-Cell Lymphoma (CTCL) that is unresponsive to other forms of treatment.

CONTRAINDICATIONS

PHOTOSENSITIVITY: UVADEX® (methoxsalen) Sterile Solution is contraindicated in patients exhibiting idiosyncratic or hypersensitivity reactions to methoxsalen, other psoralen compounds or any of the excipients. Patients possessing a specific history of a light sensitive disease state should not initiate methoxsalen therapy. Diseases associated with photosensitivity include lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum and albinism.

UVADEX® Sterile Solution is contraindicated in patients with aphakia, because of the significantly increased risk of retinal damage due to the absence of lenses.

Patients should not receive UVADEX® if they have any contraindications to the photopheresis procedure.

WARNINGS

Concomitant Therapy: Patients who are receiving concomitant therapy (either topically or systemically) with known photosensitizing agents such as anthralin, coal tar or coal tar derivatives, griseofulvin, phenothiazines, nalidixic acid, halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides, and certain organic staining dyes such as methylene blue, toluidine blue, rose bengal and methyl orange may be at greater risk for photosensitivity reactions with UVADEX®.

Carcinogenicity, Mutagenesis, Impairment of Fertility: Oral administration of methoxsalen followed by cutaneous UVA exposure (PUVA therapy) is carcinogenic. In a prospective study of 1380 patients given PUVA therapy for psoriasis, 237 patients developed 1422 cutaneous squamous cell cancers. This observed incidence of cutaneous carcinoma is 17.6 times that expected for the general population. Previous cutaneous exposure to tar and UVB treatment, ionizing radiation or arsenic increased the risk of developing skin carcinomas after PUVA therapy. Because the dose of methoxsalen with UVADEX® therapy is about 200 times less than with PUVA and the skin is not exposed to high cumulative doses of UVA light, the risk of developing skin cancer following UVADEX® therapy may be lower.

Methoxsalen was carcinogenic in male rats that were given the drug by oral gavage five days per week for 103 weeks at doses of 37.5 and 75 mg/kg. The 37.5 mg/kg dose is about 1900 times greater than a single human methoxsalen dose during extracorporeal photopheresis treatment on a body surface area basis. The neoplastic lesions in rats included adenomas and adenocarcinomas of the tubular epithelium of the kidneys, carcinoma or squamous cell carcinoma of the Zymbal gland and alveolar or bronchiolar adenomas. Topical or intraperitoneal methoxsalen is a potent photo-carcinogen in albino mice and hairless mice.

With S9 activation, methoxsalen is mutagenic in the Ames test. In the absence of S9 activation and UV light, methoxsalen is clastogenic in vitro (sister chromatid exchange and chromosome aberrations in Chinese hamster ovary cells). Methoxsalen also causes DNA damage, interstrand cross-links and errors in DNA repair.

Pregnancy: 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/m² 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.

PRECAUTIONS

General: ACTINIC DEGENERATION:

After methoxsalen administration, exposure to sunlight and/or ultraviolet radiation may result in "premature aging" of the skin.

BASAL CELL CARCINOMAS:

Since oral psoralens may increase the risk of skin cancers, monitor closely those patients who exhibit multiple basal cell carcinomas or who have a history of basal cell carcinomas.

SERIOUS SKIN BURNS:

Serious burns from either UVA or sunlight (even through window glass) can result if the recommended dosage of methoxsalen is exceeded or precautions are not followed. Advise patients to avoid all exposure to sunlight during the 24 hours following photopheresis treatment.

CATARACT FORMATION:

Exposure to large doses of UVA light causes cataracts in animals. Oral methoxsalen exacerbates this toxicity. The concentration of methoxsalen in the human lens is proportional to the concentration in serum. Serum methoxsalen concentrations are substantially lower after extracorporeal UVADEX® treatment than after oral methoxsalen treatment. Nevertheless, if the lens is exposed to UVA light while methoxsalen is present, photoactivation of the drug may cause adducts to bind to biomolecules within the lens. If the lens is shielded from UVA light, the methoxsalen will diffuse out of the lens in about 24 hours.

Patients who use proper eye protection after PUVA therapy (oral methoxsalen) appear to have no increased risk of developing cataracts. The incidence of cataracts in these patients five years after their first treatment is about the same as that in the general population.

Instruct patients emphatically to wear UVA absorbing, wrap-around sunglasses for twenty-four (24) hours after UVADEX® treatment. They should wear these glasses any time they are exposed to direct or indirect sunlight, whether they are outdoors or exposed through a window.

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, a disease for which UVADEX is not approved.

Information for Patients:

Patients should be told emphatically to wear UVA-absorbing, wrap-around sunglasses and cover exposed skin or use a sunblock (SP 15 or higher) for the twenty-four (24) hour period following treatment with methoxsalen, whether exposed to direct or indirect sunlight in the open or through a window glass.

Drug Interactions:

See **Warnings** Section.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:

See **Warnings** Section.

Pregnancy:

Pregnancy Category D. See **Warnings** Section.

Nursing Mothers:

It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when methoxsalen is administered to a nursing woman.

Pediatric Use:

Safety in children has not been established. Potential hazards of long-term therapy include the possibilities of carcinogenicity and cataractogenicity as described in the Warnings Section as well as the probability of actinic degeneration which is also described in the Warnings Section.

Patients with Renal or Hepatic Impairment

UVADEX® has not been evaluated in patients with renal or hepatic impairment

Renal impairment: Although 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 patients with varying degree of renal impairment. No reduction of dose or prolongation of UV light protection were reported in the renal transplant recipients who have undergone photopheresis treatment.

Hepatic impairment: No specific information is available on the use of photopheresis with UVADEX® in patients with hepatic impairment. In view of the very low systemic exposure to methoxsalen, it is unlikely that patients with severe hepatic impairment will be at greater risk than patients with normal hepatic function. However, the potential benefits of photopheresis treatment should be weighed against any possible risk before embarking on the procedure.

ADVERSE REACTIONS

Side effects of photopheresis (UVADEX® used with the THERAKOS® Photopheresis System) were primarily related to hypotension secondary to changes in extracorporeal volume (>1%). In study CTCL 3 (UVADEX®), six serious cardiovascular adverse experiences were reported in five patients (5/51, 10%). Five of these six events were not

related to photopheresis and did not interfere with the scheduled photopheresis treatments. One patient (1/51, 2%) with ischemic heart disease had an arrhythmia after the first day of photopheresis that was resolved the next day. Six infections were also reported in five patients. Two of the six events were Hickman catheter infections in one patient, which did not interrupt the scheduled photopheresis. The other four infections were not related to photopheresis and did not interfere with scheduled treatments.

POSTMARKETING: An analysis of postmarketing data shows the following events occurred with an incidence of <0.01%: rash, allergic reaction, pyrexia, nausea, dysgeusia.

OVERDOSAGE

There are no known reports of overdosage with extracorporeal administration of methoxsalen. However, in the event of overdosage, the patient should be kept in a darkened room for at least 24 hours.

DRUG DOSAGE AND ADMINISTRATION

Each UVADEX® treatment involves collection of leukocytes, photoactivation, and reinfusion of photoactivated cells. UVADEX® (methoxsalen) Sterile Solution is supplied in 10 mL vials containing 200 mcg of methoxsalen (concentration of 20 mcg/mL). The THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System Operator's Manual should be consulted before using this product. UVADEX® should not be diluted. The contents of the vial should be injected into the THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System immediately after being drawn up into a syringe. Do not inject directly into patients. The UVADEX® vial is for single use only. Any UVADEX® that is not used during a procedure should be immediately discarded. UVADEX® can adsorb onto PVC and plastics, therefore only THERAKOS® UVAR XTS® or THERAKOS® CELLEX® photopheresis procedural kits supplied for use with the instrument should be used to administer this medicinal product. Once UVADEX® is drawn into a plastic syringe it should be immediately injected into the photoactivation bag. UVADEX® exposed to a plastic syringe for more than one hour should be discarded.

During treatment with the THERAKOS® UVAR XTS® or THERAKOS® CELLEX® Photopheresis System, the dosage of UVADEX® for each treatment will be calculated according to the treatment volume.

- The prescribed amount of UVADEX® should be injected into the recirculation bag prior to the Photoactivation Phase using the formula:

$$\text{TREATMENT VOLUME} \times 0.017 = \text{mL of UVADEX}^{\circledR} \text{ for each treatment}$$

$$\text{Example: Treatment volume of 240 mL} \times 0.017 = 4.1 \text{ mL of UVADEX}^{\circledR}$$

Frequency/Schedule of Treatment:

Normal Treatment Schedule: Treatment is given on two consecutive days every four weeks for a minimum of seven treatment cycles (six months).

Accelerated Treatment Schedule: If the assessment of the patient during the fourth treatment cycle (approximately three months) reveals an increased skin score from the baseline score, the frequency of treatment may be increased to two consecutive treatments every two weeks. If a 25% improvement in the skin score is attained after four consecutive weeks, the regular treatment schedule may resume. Patients who are maintained in the accelerated treatment schedule may receive a maximum of 20 cycles. There is no clinical evidence to show that treatment with UVADEX® beyond six months or using a different schedule provides additional benefit. In study CTCL 3, 15 of the 17 responses were seen within six months of treatment and only two patients responded to treatment after six months.

HOW SUPPLIED

UVADEX® (methoxsalen) Sterile Solution 20 mcg/mL in 10 mL amber glass vials (NDC 64067-216-01), and cartons of 12 vials (NDC 64067-216-01). One vial of 10 mL contains 200 micrograms methoxsalen. The drug product must be stored between 59°F (15°C) and 86°F (30°C)

REFERENCES

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4. Clinical Oncological Society of Australia, Guidelines and Recommendations for Safe Handling of Antineoplastic Agents. Med J Australia, 1983; 1:426–428.
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