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 0.05 mL, glacial acetic acid 0.0012 mL, and Water for Injection q.s. to 1.0 mL. UVADEX® is used in combination with the UVAR™ XTS™ Photopheresis System 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.

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 extra-corporeal 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 8 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.

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Response % Within Six Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTCL 3 (UVADEX™)</td>
<td>17/51 (33)</td>
</tr>
<tr>
<td>CTCL 2 (oral methoxsalen)</td>
<td>16/57 (28)</td>
</tr>
<tr>
<td>CTCL 1 (oral methoxsalen)</td>
<td>21/39 (54)</td>
</tr>
</tbody>
</table>

Although the response rate with UVADEX® in CTCL 3 was similar to that 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 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 reactions to psoralen compounds. 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 protoporphyrin, 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.

WARNINGS

Concomitant Therapy: Special care should be exercised in treating 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, maldixid acid, halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides, and certain organic staining dyes such as methyl blue, toluidine blue, rose bengal and methyl orange.
Absorbing, wrap-around sunglasses for twenty-four (24) hours after UVADEX® treatment. Safety in children has not been established. Potential hazards of long-term therapy include the possibilities of carcinogenicity and cataractogenesis as described in the Warnings Section as well as the probability of actinic degeneration which is also described in the Warnings Section.

Adverse Reactions:
Side effects of photopheresis (UVADEX® used with the THERAKOSTM 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.

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 UVARM™ XTS™ or THERAKOS® CELLEX® Photopheresis System Operator’s Manual should be consulted before using this product.

During treatment with the UVARM™ 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 Photactivation Phase using the formula:

\[
\text{TREATMENT VOLUME X 0.017 = mL of UVADEX}^\text{® for each treatment}
\]

Example: Treatment volume of 240 mL X 0.017 = 4.1 mL of UVADEX®

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 vials (NDC 64067-216-01), and cartons of 12 vials (NDC 64067-216-01). The drug product must be stored at 2° to 8°C (36° to 46°F).

References:
3. National Study Commission on Cytotoxic Exposure- Recommendations for Handling Cytotoxic Agents. Available from Louis P. Jeffrey, ScD., Chairman, National Study Commission on Cytotoxic Exposure, Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, Massachusetts 02115.

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