

PRODUCT MONOGRAPH

OXSORALEN-ULTRA CAPSULES 10 mg,

Methoxsalen Capsules 10 mg, USP

TO FACILITATE REPIGMENTATION IN VITILIGO

TO INCREASE TOLERANCE TO SOLAR EXPOSURE

FOR USE IN PHOTOCHEMOTHERAPY OF PSORIASIS AND ATOPIC DERMATITIS

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CAUTION

This new dosage form of methoxsalen exhibits significantly greater bioavailability and earlier photosensitization onset time than previous methoxsalen dosage forms. Each patient should be evaluated by determining the minimum phototoxic dose (MPD) and phototoxic peak time after drug administration prior to onset of photochemotherapy with this dosage form.

Oxsoralen-Ultra is a potent drug and should be used only under supervision of a physician with special training and experience in photochemotherapy (PUVA).

ACTION

Psoralens are a group of structurally related photoactive compounds. They are called "photoactive" because they are activated selectively in the presence of longwave ultraviolet light (UVA). They may be ingested orally or applied topically but without UVA are totally inactive.

OXSORALEN-ULTRA (methoxsalen), when activated by long wavelength ultraviolet radiation (UVA) in the range of 320-400 nm, is strongly erythemogenic, melanogenic, and cytotoxic in the epidermis; the maximal erythemogenic activity occurs in the range of 330-360 nm.

Following photoactivation, methoxsalen forms covalent bonds with DNA to produce monofunctional (addition to a single strand of DNA) and bifunctional adducts (crosslinking to both strands of DNA).

The photochemical reaction between activated psoralens and DNA has been shown to inhibit epidermal DNA synthesis and this is the rationale for the use of psoralen (P) and UVA irradiation (PUVA) therapy in the treatment of psoriasis.

While the mechanism of action of methoxsalen in inducing repigmentation of vitiliginous skin has not been established, it is considered that repigmentation depends on the presence of functioning melanocytes and UV light. One group of investigators feels that the psoralens have a specific effect on the epidermis, or more specifically, on the melanocytes. Another group feels that the primary response to the psoralens is an inflammatory one and that the process of melanogenesis is secondary.

Erythema resulting from therapy with a psoralen (P) and UVA radiation (320-400 nm) (PUVA) differs from sunburn or the erythema produced by middle wavelength ultraviolet radiation (UVB, 290-320 nm), since UVA radiation penetrates more deeply into the skin and the photochemical reaction occurs deeper within skin tissue. Since the maximum erythemogenic activity of psoralens occur in the range of 330-360 nm, the drugs increase the patient's sensitivity

to primarily UVA light but not to UVB light.

PUVA-induced erythema may begin to appear 24 hours after initiation of therapy which peaks at 48 to 72 hours; however, exposure to UVB radiation may produce erythema which reaches its peak effect at 24 hours.

Four hours after ingestion of methoxsalen, the skin is much less reactive to UVA and after 8 hours, most patients will no longer experience an enhanced erythematous response to UVA.

PHARMACOKINETICS

Absorption: methoxsalen appears to be well, but variably, absorbed from the GI tract following oral administration. When oral methoxsalen is administered with food, the extent of absorption and the peak serum concentration appear to be increased.

Considerable interindividual variations in peak serum concentrations of methoxsalen after intake with food have been reported. Following oral administration of a single dose of methoxsalen in a liquid-filled capsule (Oxsoralen-Ultra) with low-fat milk, peak serum drug concentrations occur with a mean T_{max} of 1.8 hours (range: 0.5-4.0 hours) and serum concentrations decline to low levels within 8-10 hours. Peak serum methoxsalen concentrations are approximately 2-3 times higher and the area under the serum concentration-time curve is approximately 1.5-2 times greater with Oxsoralen-Ultra than with Oxsoralen (crystalline, hard gelatine capsule). In most instances, peak photosensitivity occurs within 1.5-2.1 hours after administration of Oxsoralen-Ultra.

Distribution: Distribution of methoxsalen into human tissues and fluids has not been fully

characterized. Methoxsalen distributes into the lens of the eye in concentrations proportional to the serum concentrations. The drug is 75 to 91 % bound to serum proteins, principally albumin. It is not known whether methoxsalen crosses the placenta or is distributed into milk.

Elimination: The elimination half-life of methoxsalen has been estimated to be 0.75-2.4 hours. Following oral administration of methoxsalen, 80-90 % of the drug is excreted in urine within 8-12 hours as hydroxylated, glucuronide, and sulfate metabolites; less than 0.1 % of a dose is excreted in urine as unchanged drug. About 95 % of the drug is excreted in urine within 24 hours as metabolites.

INDICATIONS AND CLINICAL USE

Idiopathic Vitiligo

Oxsoresalen-Ultra (methoxsalen) is used orally in conjunction with controlled exposure to long wavelength ultraviolet radiation (UVA) or sunlight to repigment vitiliginous skin in patients with idiopathic vitiligo. Clinical response to methoxsalen is erratic and unpredictable and is cosmetically acceptable in only a small percentage of patients with vitiligo. Complete cures following psoralen therapy are infrequent; only about one-third of patients with vitiligo have an appreciable amount of pigmentation restored.

Repigmentation varies among patients in completeness, time of onset, and duration. Methoxsalen-induced repigmentation occurs more rapidly on fleshy areas such as the face, abdomen, and buttocks than on bony areas such as the dorsa of the hands and feet.

Repigmentation of vitiliginous lesions may begin after a few weeks of treatment (approximately

25 exposures with facial lesions and 50 exposures with disease elsewhere), but substantial changes usually require 6-9 months (50 to 300 exposures) of therapy. If follicular repigmentation is not apparent after 3 months of treatment, methoxsalen therapy should be discontinued. To retain new pigment, periodic treatment with the drug and UVA light exposure is often required. Because individual responses are highly variable, there are no fixed schedules for maintenance.

Increasing Tolerance to Sunlight

In blond persons and those with fair complexions who suffer painful reactions when exposed to sunlight, **Oxsoralen-Ultra** (methoxsalen) aids in increasing resistance to solar damage. Certain persons who are allergic to sunlight or exhibit sun sensitivity may benefit from the protective action of **Oxsoralen-Ultra** (methoxsalen). In albinism, **Oxsoralen-Ultra** (methoxsalen) will increase the tolerance of the skin to sunlight, although no pigment is formed. This protective action seems to be related to the thickening of the horny layer and retention of melanin which produces a thickened, melanized stratum corneum and formation of a stratum licidum.

Psoriasis

Oxsoralen-Ultra (methoxsalen) is used in conjunction with controlled exposure to long wavelength ultraviolet radiation (UVA, 320-400 nm) for the symptomatic treatment of severe, recalcitrant, disabling psoriasis confirmed by biopsy and unresponsive to other forms of therapy. The dosage of **Oxsoralen-Ultra** (methoxsalen) is based upon the patient's body weight (please refer to Table 2). In several studies, psoriatic lesions cleared in about 90 % of patients treated with a mean of 20 exposures to PUVA therapy (psoralen and UVA light). To obtain acceptable therapeutic results in the treatment of psoriasis, it is necessary to activate the **Oxsoralen-Ultra**

(methoxsalen) 1 to 2 hours after ingestion with high intensity UVA light of 320-400 nm with a peak emission of 340-365 nm. Patients should be clear of psoriasis by the 30th treatment. Patients who are not clear by this time should only be subjected to further treatment after reevaluation by the physician.

Maintenance therapy will probably be required to maintain the patient clear of psoriasis. The frequency of maintenance therapy will vary from patient to patient and should be determined on an individual basis.

Atopic Dermatitis

The dosage of **Oxsoralen-Ultra** (methoxsalen) is based on the patient's body weight (Table 2). To obtain acceptable therapeutic results in the treatment of atopic dermatitis, it is necessary to activate the **Oxsoralen-Ultra** (methoxsalen) 1 to 2 hours after ingestion with high intensity UVA light, 320-400 nm with peak emission of 340-365 nm. Maintenance therapy will probably be required to maintain the patient clear of atopic dermatitis. The frequency of maintenance therapy will vary from patient to patient and should be determined on an individual basis.

CONTRAINDICATIONS

Oxsoralen-Ultra (methoxsalen) is contraindicated in

- * patients exhibiting idiosyncratic reactions to psoralens or with a history of a sensitivity reaction to the drug;
- * patients with diseases associated with photosensitivity (e.g., lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum,

albinism, hydroa vacciniforme, leukoderma of infectious origin, polymorphous light eruptions);

- * patients with a history of skin cancer, e.g., melanoma or a history of melanoma and in patients with invasive squamous cell carcinoma;
- * patients with aphakia (absence of lenses) or early signs of cataracts because of the increased risk of retinal damage;
- * poor compliance with directions;
- * history of exposure to arsenic or ionizing radiations;
- * patients with severe cardiovascular, hepatic or renal disorders;
- * patients who are significantly immunosuppressed;
- * pregnant or lactating women;
- * patients with many dysplastic nevi;
- * concomitant use of other photosensitizing drugs;
- * children under 12 years of age since safe use of methoxsalen in this age group has not been established.

WARNINGS

Dermatologic Effects: Phototoxic reactions including severe edema and erythema, and painful blistering, burning and peeling of skin may occur with methoxsalen and conventional UV light. In addition, PUVA therapy has produced severe burns requiring hospitalization, and marked hyperpigmentation and aging of skin. Phototoxic reactions to methoxsalen occur most commonly when the skin is overexposed to UV light or when dosage is excessive. Severe burns may occur

if treated skin is accidentally exposed to additional UV light.

Cataract Potential: Prior to the initiation of PUVA therapy and yearly thereafter, patients should have an ophthalmologic examination because of the cataractogenic potential of psoralens.

Carcinogenic Potential: The overall incidence of basal cell carcinoma found in one long-term study in psoriatic patients showed a risk factor of 1.7 and the overall incidence of cutaneous squamous cell carcinoma was about 9 times higher as compared to normal subjects. The risk of cutaneous squamous cell carcinoma developing at least 22 months after the initial PUVA exposure was approximately 12.8 times higher in patients receiving high-dose PUVA than in those receiving low-dose PUVA. Reduction in PUVA dose substantially reduces the risk. A substantial dose-related increase in the risk of basal cell carcinoma was not observed. Malignant melanoma has developed rarely in patients receiving PUVA therapy.

PRECAUTIONS

Oxsoralen (crystalline methoxsalen) and **Oxsoralen-Ultra** (liquid methoxsalen) capsules exhibit substantially different rates and extents of absorption, minimum phototoxic doses, and peak photosensitivity times and **should not be used interchangeably**.

Oxsoralen-Ultra (methoxsalen) is a strong photosensitizer capable of producing severe burns if used improperly, the drug should be used only under supervision of a physician with special training and experience in photochemotherapy. Because of the potential for serious adverse effects (e.g., ocular damage, aging of the skin, and skin cancer, including melanoma) resulting from PUVA therapy, the patient should be fully informed by the physician of the risks associated with the treatment. To prevent serious adverse effects, the physician should carefully instruct the patient to adhere to the prescribed methoxsalen dosage regimen and

schedules for UVA exposure.

Considerations before Oxsoralen-Ultra (methoxsalen) administration:

Because psoralens have caused photoallergic contact dermatitis and may precipitate sunlight allergy, methoxsalen should be used with caution in patients with a family history of sunlight allergy. The drug should also be used with caution in patients with GI diseases or chronic infection.

For at least 24 hours prior to methoxsalen administration and UVA exposure, patients should avoid prolonged exposure to sun light, including extended outdoor activities, since the presence of sunburn may prevent an accurate evaluation of patient response to photochemotherapy.

Before and 6-12 months after oral methoxsalen therapy is initiated, a complete blood count, antinuclear antibody titer, and hepatic and renal function tests should be performed.

Considerations before PUVA (methoxsalen & UVA) administration:

Exposure to sunlight and/or UVA may result in premature aging of the skin or skin cancer. In patients with multiple basal cell carcinomas or history of basal cell carcinomas, careful observation during treatment with methoxsalen is recommended. Patients with a history of radiation therapy or treatment with arsenic compounds should be carefully observed for signs of carcinoma. The total cumulative dose of UVA that can be given over long periods of time with safety has not been established.

Patients with cardiac disease or those unable to tolerate prolonged standing or exposure to heat stress should not be treated in a vertical UVA chamber.

Considerations during PUVA (methoxsalen & UVA) administration:

Total UVA-absorbing/blocking goggles must be worn during PUVA therapy. Failure to do so may increase the risk of cataract formation. Skin of the abdomen, breasts, genitalia, and other sensitive areas should be protected during PUVA therapy for about one-third of the initial exposure time until sufficient tanning occurs; unless affected by disease, male genitalia should be shielded.

Considerations following PUVA (methoxsalen & UVA) administration:

Following PUVA therapy, wrap-around sunglasses with UVA-absorbing properties should be worn by patients during daylight hours for 24 hours. The protective eyewear must be designed to prevent entry of stray radiation into the eyes, including that which may enter from the sides of the eyeglasses. Protective eyewear is used to prevent irreversible binding of methoxsalen to proteins and DNA components of the lens.

Mild, transient erythema occurring 24-48 hours after PUVA therapy is an expected cutaneous reaction, and indicates that a therapeutic interaction between methoxsalen and UVA has occurred. Areas of skin showing fiery erythema with edema should be shielded during subsequent UVA exposures until the erythema has resolved. Fiery erythema with edema which occurs within 24 hours following UVA exposure may indicate a potentially severe burn, since the peak erythematous reaction usually occurs 48-72 hours following PUVA therapy. If burning or blistering of skin or intractable generalized pruritus occurs, therapy should be discontinued until these effects subside.

Following PUVA treatment, patients must avoid additional, direct or indirect (through window glass or cloud cover) exposure to sunlight for at least 8 hours. If exposure to sunlight cannot be avoided, the patient should wear protective clothing (e.g., hat, gloves) and/or apply sunscreens that filter out UVA radiation (e.g., sunscreens with a sun protective factor greater than or equal to 15). Sunscreens should be applied to all areas of the body that may be exposed to the sun (including lips).

Following PUVA therapy, patients should avoid prolonged exposure to sun light including extended outdoor activity since erythema and/or burning resulting from photochemotherapy and sunburn are additive.

Pregnancy, Fertility, and Lactation: Animal reproduction studies have not been performed with oral methoxsalen. It is not known whether methoxsalen can cause fetal harm when administered to pregnant women. Methoxsalen should be used during pregnancy only when clearly needed.

It is not known whether methoxsalen affects fertility in humans.

Since it is not known whether methoxsalen is distributed into milk, the drug should be used with caution in nursing women.

Drug Interactions

Photosensitizing Agents

Concomitant therapy with Oxsoresalen-Ultra (methoxsalen) and other systemic or topical photosensitizing agents (e.g., anthralin, coal tar or coal tar derivatives, griseofulvin, nalidixic acid, halogenated salicylanilides (bacteriostatic soaps), sulfonamides, tetracyclines, thiazides, or

certain organic staining dyes such as methylene blue, toluidine blue, rose bengal, and methyl orange) may produce additive photosensitizing effects. Particular caution is necessary if methoxsalen is administered concomitantly with any topical or systemic photosensitizing agent.

Concurrent use of systemic methoxsalen with phenothiazines may potentiate intraocular photochemical damage to the choroid, retina, and lens.

Food Interaction

Furocoumarin-containing foods, such as limes, figs, parsley, parsnips, mustard, carrots, and celery should be avoided when OxSORALEN-ULTRA is initiated because of the risk of additive phototoxicity.

ADVERSE REACTIONS

Dermatologic Effects: Pruritus occurs in about 10 % of patients. In most cases, pruritus is relieved by frequent application of bland emollients or other topical agents; severe pruritus may require systemic treatment. When pruritus is unresponsive to these measures, pruritic area should be shielded from further UVA exposure until the condition resolves. If pruritus refractory to treatment is generalized, PUVA therapy should be discontinued until the pruritus disappears.

Other adverse dermatologic effects associated with PUVA therapy include: skin freckling, hypopigmentation, uneven or excessive tanning, dry skin, vesiculation and bullae formation, generalized exfoliation, nonspecific rash, urticaria, miliaria, folliculitis, acneiform eruption, aggravation or extension of psoriasis, hyperpigmentation of psoriatic lesions, cutaneous tenderness, severe skin pain (lasting 1-2 months), and exacerbation of latent photosensitive dermatoses (e.g., lupus erythematosus).

Gastrointestinal Effects: Nausea occurs in about 10 % of patients. Nausea and other adverse GI effects may be minimized by administering methoxsalen with lowfat milk or food, or in 2 divided doses approximately 30 minutes apart, or by reducing dosage.

CNS Effects: Nervousness, dizziness, headache, vertigo, insomnia, mental depression or excitation have been reported.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage of methoxsalen or overexposure to UV light following methoxsalen administration may result in serious burning and blistering of skin. In acute methoxsalen overdose, the stomach should be emptied immediately by inducing emesis; emesis is beneficial only within the first 2-3 hours after the ingestion. The patient should be placed in a darkened room for at least 24 hours or until cutaneous reactions subside, and supportive measures for the treatment of burns should be initiated.

DOSAGE AND ADMINISTRATION

Administration: Oral methoxsalen may be administered as a single dose on a full stomach, or in 2 divided doses approximately 30 minutes apart, to minimize adverse GI effects.

Dosage: Methoxsalen therapy must be accompanied by some form of UVA irradiation. Initial UV light exposure times should be based on the minimum phototoxic dose (MPD) for the

specific light source being used. MPD can be determined by irradiating several skin areas on the patient's back, 2 cm in diameter with varying light exposure times and determining the exposure time that produces erythema at 72 hours. To prevent serious burns following administration of methoxsalen, patients should be carefully instructed not to exceed the recommended dosage and UV light exposure time.

Before using PUVA therapy with Oxsoralen-Ultra (methoxsalen), the MPD and peak photosensitivity time after drug administration should be evaluated in each patient.

Vitiligo

To repigment vitiliginous areas in adults and children older than 12 years of age, the oral dosage of **Oxsoralen-Ultra** (methoxsalen) is 20 mg (2 capsules) daily, given as a single dose on a full stomach 1 to 2 hours before measured periods of sunlight or UVA exposure (See Sun Exposure Guide). Therapy should be on alternate days and never on 2 consecutive days. Oral dosages greater than 0.6 mg/kg should not be used, since severe burns may result. Repigmentation of vitiliginous lesions may begin after a few weeks of treatment, but substantial changes usually require 6-9 months of therapy. If follicular repigmentation is not apparent after 3 months of treatment, Oxsoralen-Ultra (methoxsalen) therapy should be discontinued.

To Increase Tolerance to Sunlight

Two capsules (20 mg) daily taken on a full stomach 1 to 2 hours before measured periods of exposure to sun or ultraviolet irradiation. Therapy is not to be continued for longer than 14 days. The dosage should **not** be increased as severe burning may occur. (Follow suggested Sun Exposure Guide in Table 1)

Suggested Sun Exposure Guide

(for the treatment of vitiligo and to increase tolerance to sunlight)

The exposure time to sunlight should be limited according to the following plan:

Table 1:

Basic Skin Colour

	<u>Light</u>	<u>Medium</u>	<u>Dark</u>
Initial Exposure	15 min	20 min	25 min
Second Exposure	20 min	25 min	30 min
Third Exposure	25 min	30 min	35 min
Fourth Exposure	30 min	35 min	40 min

Subsequent Exposure: Gradually increase exposure based on erythema and tenderness.

Psoriasis

For the symptomatic treatment of severe, recalcitrant, disabling psoriasis, the appropriate oral dose of **Oxsoralen-Ultra** (methoxsalen) is administered on a full stomach 1 to 2 hours before exposure to high-intensity UVA radiation (320-400 nm). Treatments may be administered 2 or 3 times weekly but at least 48 hours apart. The initial dose of **Oxsoralen-Ultra** (methoxsalen) capsules is based on the patient's weight (Table 2) according to the following schedule:

Table 2:

Weight (kg)	Dose (mg)
< 30	10
30-50	20
51-65	30
66-80	40
81-90	50
91-115	60
> 115	70

The number of methoxsalen doses per week is determined by the patient's schedule of UVA exposures (Table 4). PUVA therapy should not be administered more frequently than once every other day, since the full extent of phototoxic reactions to therapy may not be evident until 48 hours after each exposure. Subsequent treatment with UVA after the initial exposure and provided the patient exhibits **no greater than 1** (Table 3) on the erythema scale (minimally perceptible erythema, faint pink), the following schedule of light treatments is recommended (Tables 4 & 5). Before each exposure, the patient is examined for degree of erythema (Table 3). If areas are observed to have greater than grade 1 erythema, treatment should not be continued until the situation is resolved.

TABLE 3 - ERYTHEMA SCALE

Grade	Erythema
0	no erythema
1	minimally perceptible erythema - faint pink
2	marked erythema but no edema
3	fiery erythema with edema
4	fiery erythema with edema and blistering

Table 4

INITIAL UVA EXPOSURE SCHEDULE FOR OXSORALEN-ULTRA

(1-2 hours after ingestion of **Oxsoralen-Ultra** (methoxsalen))

Skin Type	History	Exposure Dose (Joules/cm ²) For 2-3 treatments/week		
		Init.	Increm.	Final
I	always burn, never tan	1.5	0.5	5.0
II	always burn, sometimes tan	2.5	0.5	8.0
III	sometimes burn, always tan	3.5	0.5-1.0	12.0
IV	never burn, always tan	4.5	1.0	14.0
V	moderately pigmented individuals; American Indians, Asiatics, Mexicans, Puerto Ricans and Orientals	5.5	1.0	16.0

VI Black 6.5 1.0-1.5 20.0

NOTE: Joules/cm² is the radiant energy delivered per square centimeter of skin surface in a given exposure time.

Init. =initial treatment
 Increm.=incremental increase of exposure
 Final =total J/cm² per week

The Exposure Time can be calculated following the formula below:

$$\text{Time (minutes)} = \frac{16.67 \times (\text{prescribed UVA dose in J/cm}^2)}{\text{Energy output of UVA delivery system in milliwatts/cm}^2}$$

Example: If your measured output is 10 milliwatts/cm² and you wish to deliver a dose of 5 joules, exposure time would be 16.67 x 5/10 = 8.3 minutes or 8 minutes 18 seconds.

Table 5:

SCHEDULE OF LIGHT TREATMENTS FOR PSORIASIS

For Skin Type	Frequency
I, II, III, IV	2 or 3 times/week
V, VI	3 times/week

If the weight of the patient changes during therapy such that the patient would be in a different weight range/dose category, a dose change is usually not necessary; however, if the change in weight is considered sufficiently great, adjustment of methoxsalen dosage and exposure to UVA

light should be made accordingly (Table 2). If there is no response or only minimal response after 15 PUVA treatments, the dose of methoxsalen may be increased by 10 mg (a one-time increase); the increased dose may be continued for the remainder of the course of treatment but should not be exceeded. Patients should be clear of psoriasis by the 30th treatment. Patients who are not clear by this time should only be subjected to further treatment after reevaluation by the physician. Maintenance therapy will probably be required to maintain the patient clear of psoriasis. The frequency of maintenance therapy will vary from patient to patient and should be determined on an individual basis.

Extra UVA Exposure to the Lower Legs

Psoriasis present on the lower legs is slow to clear. After the 6th treatment, if psoriasis is present there, the lower legs may receive "extra" UVA. Initially, 0.5 J/cm² to 1.0 J/cm², depending on the skin type, should be given but as tanning occurs, this may be gradually increased to a maximum of 1/3 of the whole body-UVA dose. The "extra" UVA may be given either before or after the total body treatment, with the rest of the body carefully shielded in order to avoid overexposure.

Atopic Dermatitis

As for the treatment of psoriasis, the dosage of **Oxsoralen-Ultra** (methoxsalen) is based upon the patient's body weight (Table 2). To obtain acceptable therapeutic results in the treatment of atopic dermatitis, it is necessary to activate the **Oxsoralen-Ultra** (methoxsalen) 1 to 2 hours after ingestion with high intensity UVA light 320-400 nm with peak emission of 340-365 nm. Maintenance treatment will probably be required to maintain the patient clear of atopic dermatitis. The frequency of maintenance therapy will vary from patient to patient and should be

determined on an individual basis. Duration of therapy and the maintenance therapy have to be decided on the condition of the patient and the response to PUVA therapy.

Maintenance Therapy

After patients are cleared, they may be assigned a maintenance schedule of treatment once-a-week, once-every-two-weeks, or once-every-three-weeks. The UVA exposure time for the maintenance treatment is the same as the patient's last treatment of the clearing phase and is not changed during maintenance therapy unless the patient develops erythema, psoriasis or atopic dermatitis.

1. Erythema: during maintenance therapy, the patient's tan and threshold for erythema may gradually decrease. If maintenance treatments produce erythema, the exposure to UVA should be decreased by 0.5 J/cm^2 to 1.0 J/cm^2 per treatment until treatments no longer produce erythema.
2. Psoriasis and Atopic Dermatitis: If the patient develops new areas of psoriasis or atopic dermatitis during maintenance therapy, the exposure to UVA is increased by 0.5 J/cm^2 per treatment for patients with a Grade 1-2 tanning response (Table 6); by 1.0 J/cm^2 per treatment for patients with a Grade 3-4 tanning response; and by 1.0 J/cm^2 to 2.0 J/cm^2 per treatment for patients with skin types V and VI (Table 4). This is continued until the psoriasis or atopic dermatitis is brought under control and the patient is again clear.

Table 6:

Tanning Response

0 = no change in pigmentation

1 = minimally perceptible tan, light brown

2 = moderate tan, medium brown pigmentation

3 = dark brown pigmentation

4 = black pigmentation

Concomitant Therapy:

Emollient creams and bath oils: these are to be used regularly during therapy. They will help to remove scales and also prevent excessive dryness.

Topical steroids, tar preparations, salicylic acid and other keratolytics: these preparations may be used on the scalp but are not to be used on the body, except in areas shielded from UVA exposure (e.g., intergluteal folds, soles of feet when upright unit is used, etc.). After exposure to measured periods of sunlight or UVA listed in the above schedule, the skin should be protected from further exposure by applying sunscreens or sun blocker. Sunglasses should be worn during exposure and the lips protected with a light-screening lipstick.

PHARMACEUTICAL INFORMATION

Drug Substance : Methoxsalen USP

Chemical Name : 7H-Furo(3,2-g)(1)Benzopyran-7

-one,9-Methoxy,9-Methoxy-7H-Furo(3,2-g) (1) Benzopyran-7-one

Structural Formula:

Molecular Formula : $C_{12}H_8O_4$

Molecular Weight : 216.19

Description : methoxsalen occurs as white to cream-coloured, fluffy, odourless needles
insoluble in water, soluble in acetone and chloroform

Stability : Oxsoralen-Ultra (methoxsalen) capsules should be stored in well- closed, light-
resistant containers at controlled room temperature (15-30° C)

Composition : Oxsoralen-Ultra soft gelatine capsules are filled with a clear, straw-coloured
liquid with no odor, contained in a green, oval size # 6 soft gelatine capsule,
and contain methoxsalen, USP and polyethylene glycol.

AVAILABILITY

Each Oxsoralen-Ultra green soft gelatine capsule contains 10 mg methoxsalen USP. Bottles of
50 and 100.

INFORMATION TO THE CONSUMER

Eating certain foods while using **Oxsoralen-Ultra** (methoxsalen) capsules may increase the skin's sensitivity to sunlight. In order to prevent increasing the sensitivity of skin **DO NOT EAT** limes, figs, parsley, parsnips, mustard, carrots and celery.

For at least 24 hours prior to methoxsalen administration and UVA exposure (PUVA), avoid prolonged exposure to sun light, including extended outdoor activity, since the presence of sunburn may prevent an accurate evaluation of your response to photochemotherapy.

Before taking other medications consult with your physicians, since some medications may increase the sensitivity of your skin to sunlight or UVA exposure.

Following PUVA treatment, avoid additional, direct or indirect (through window glass or cloud cover) exposure to sunlight for at least 8 hours. If exposure to sunlight cannot be avoided, wear protective clothing (e.g., hat, gloves) and/or apply sunscreens that filter out UVA radiation (e.g., sunscreens with a sun protective factor greater than or equal to 15). Sunscreens should be applied to all areas of the body that may be exposed to the sun (including lips).

Following PUVA therapy, wear wrap-around sunglasses with UVA-absorbing properties during daylight hours for 24 hours. The protective eyewear must be designed to prevent entry of stray radiation into the eyes, including that which may enter from the sides of the eyeglasses. Protective eyewear is used to prevent damage to the eye-lens.

PHARMACOLOGY

Pigment formation with Oxsoralen-Ultra: the normal pigmentation of the skin is due to melanin, which is produced in the cytoplasm of the melanocytes located in the basal layers of the epidermis at its junction with the dermis. Melanin is formed by the oxidation of tyrosine to DOPA (dihydroxyphenylalanine) with tyrosinase as catalyst. This enzymatic reaction, however, must be activated by radiant energy in the form of ultraviolet light, preferably between 290 and 380 nm (black light).

The exact mechanism of action of psoralens in the process of melanogenesis is not known. It has been suggested that methoxsalen may activate the few functional and dihydroxyphenylalanine-positive melanocytes present in vitiliginous skin. An increase in the activity of tyrosinase, the enzyme that catalyzes the conversion of tyrosine to dihydroxyphenylalanine (a precursor of melanin), has been shown in melanin-producing cells exposed *in vitro* to trioxsalen and UVA light. Other mechanisms of increased pigmentation may include an increase in the number of functional melanocytes, and possibly activation of dormant melanocytes; enhancement of melanin granule synthesis; stimulation of the movement of melanocytes up hair follicles resulting in melanocytic repopulation of the epidermis; and/or hypertrophy of melanocytes and increased arborization of their dendrites. Psoralens may also increase melanin formation by producing an inflammatory reaction in the skin.

The photosensitizing property of psoralen is related to the ability of the photoactivated psoralen

molecules (triplet state) to transfer the absorbed ultraviolet energy to DNA. This results in monofunctional single-strand photoadducts with thymine bases and interstrand cross links (bifunctional adducts) between opposite pyrimidine base pairs. This presumably leads to an inhibition of DNA synthesis and thus, of cell division within the rapidly dividing psoriatic epidermis. Whether this is the mechanism responsible for the regression of psoriatic lesions is still unknown.

Orally ingested psoralens are rapidly metabolized in the liver and over 90 % of the administered dose is excreted within 8-12 hours in the urine. Psoralens are detoxified as hydroxylated and glucuronide derivatives and are not accumulated in any detectable quantity either in the skin, liver or any other organ. The maximum concentration of the photosensitizing methoxsalen within the blood is found 1-3 hours after ingestion and this corresponds with the peak of the UVA-induced erythema response after oral administration. Therefore, the optimum treatment period is 1 to 3 hours after ingestion of methoxsalen. Four hours after ingestion of methoxsalen, the skin is much less reactive to UVA, and after 8 hours, most patients will no longer experience an enhanced erythematous response to UVA.

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