

Skin Therapy Letter[©]

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Focus on Diane-35[®]

Diane-35[®], known as Dianette[®] in some countries, is a combination of cyproterone acetate 2 mg and ethinyl estradiol 0.035 mg. It has recently received regulatory clearance in Canada, but has not yet been approved by the US FDA. The Canadian indication is for the treatment of women with severe acne that is unresponsive to oral antibiotics and other available treatments, and is associated with symptoms of androgenization including seborrhea and mild hirsutism.¹ When Diane-35[®] is used in a cyclic manner it also functions as an oral contraceptive.¹

Some of the early studies of cyproterone combined with ethinyl estradiol utilized Diane[®], which is a preparation containing 0.050 mg of ethinyl estradiol. Studies have shown that compared to Diane, Diane-35[®] with the estrogen component reduced to 0.035 mg of ethinyl estradiol, is as effective in treating acne and hirsutism, and is as reliable as a contraceptive. As well, it has the added advantage of a 30% reduction in the amount of estrogen it contains.^{2,3}

Pharmacology

Some experts believe that in female acne, hypersensitivity of the target tissue is related to an excessive conversion of androgen precursors to active metabolites and of ovarian or adrenal hyperandrogenism. This topic remains a matter of debate. Others believe that in both women and men, there may be a hypersensitivity of the end organ to androgens. This is related to an increase in the

activity of 5 α -reductase type 1 which converts testosterone into active dihydrotestosterone. The production and the plasma transport of androgens may also be involved.⁴ Cyproterone acetate is antiandrogenic, (i.e., blocking androgen receptors) and antigonadotrophic, (i.e., inhibiting the hypothalamopituitary ovarian axis reducing androgen synthesis). In addition, the estrogen component increases the level of sex hormone binding globulin, which in turn reduces the plasma level of free androgens. These actions reduce the androgen stimulated increase in sebum associated with seborrhea.⁵ Sebaceous gland activity decreases over a period of three to six months, leading to diminution and even clearance of the acne.

Cyproterone can produce unwanted side effects including menstrual irregularities, but the presence of the estrogen circumvents this problem.

Cyproterone also has progestogenic activity. When the cyproterone-estrogen combination is taken as recommended, it provides reliable contraception, but should not be prescribed solely for this purpose.¹

Clinical studies

In 144 women, most of whom were suffering from moderately severe androgenization, six cycles of Diane-35[®] significantly improved or healed their acne and seborrhea. After 12 treatment cycles, the treatment success rate was almost 90%.⁷ In another study of 26 women, acne was in remission in 82% of patients after three cycles. As well, seborrhea was reduced in 86% of the women after three cycles and

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in 96% after six cycles.⁸ Between 1968 and 1995, 143 women were treated with Cyproterone 50 mg (combined with estrogen in most cases). The results for acne were good or very good in more than 90% of patients.⁹

Adverse effects

Diane-35[®] has many properties in common with estrogen/progestogen combination oral contraceptives, and the same contraindications, warnings and precautions should be considered. In a prospective, two year follow-up study in 35 of the 143 patients mentioned above⁹, hematological, clinicochemical, and metabolic parameters before and after, suggest that cyproterone acetate, with or without ethinyl estradiol, is an effective and safe long term treatment of hirsutism and/or acne in women.

Practical experience with Diane-35[®]

A panel of experts in the treatment of acne was questioned about their experiences using Diane-35[®]. The questions they were asked, and their responses are summarised below:

1. *If the patient fails to respond to antibiotics, would a hormonal combination such as Diane-35[®] be your treatment of choice?*

If it was only tetracycline that was used, one could try minocycline before trying a hormonal combination such as Diane-35[®].¹⁰ However, when patients have failed to respond to antibiotics, most¹¹⁻¹⁵ of our panel advise the use of this hormonal combination. This is true, especially if the symptoms are not severe enough to consider prescribing isotretinoin, and when contraception is indicated or already being taken.¹⁴

Not everyone agrees. One of the panel members feels that used alone, hormonal combinations are not sufficiently effective.¹⁶ Another stated that after antibiotic treatment fails, he uses isotretinoin, unless the patient wants birth control long term.¹⁷

We should remember that women with SAHA-syndrome (seborrhea, acne, hirsutism and possibly also androgenetic alopecia) require the hormonal combination rather than antibiotics to clear their acne. Also, 30-35 year old females with persistent acne may also exhibit dysmenorrhea. In such instances, using Diane-35[®] would be helpful, especially as polycystic ovary disease (PCO) is often an underlying disease in these cases.¹⁸

2. *For what period of time should hormonal treatment be continued for acne, and what percentage of patients relapse when treatment is discontinued?*

Use Diane-35[®] for three months and then review.^{10,13,16} Usually, clinical improvement will be clearly visible after about three¹⁸ to six months. For the longer term, when such treatment proves to be appropriate, some advisors prescribe hormonal combinations for months¹⁵ to years.^{11,12,17} The percentage of patients whose acne relapses when treatment is discontinued depends on the age of the patient, the severity of the disease and the duration of treatment.¹⁸ Some felt that there was insufficient data to accurately answer the question.¹⁰⁻¹² One panel member believed that the percentage of patients who relapse, is lower than that seen following discontinuation of birth control pills with a higher estrogen content.¹² Estimates of relapse ranged from 3%¹⁴, to 60-70% on a long term basis^{13,15}, to more than 90%.¹⁶

3. *Has the occurrence of any side effects limited the usefulness of such treatment?*

Most of the side effects are also seen with standard oral contraceptives.¹⁰ All of the side effects are minor and uncommon and rarely necessitate discontinuation of treatment.¹⁷

Side effects that have been reported include dysmenorrhea (including breakthrough and premature bleeding in 1-2% of cases),¹⁴ some breast tension and hardness found in 10-15% of

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Psoriasis Treatments Under Development

A review of this list of agents that are presently undergoing clinical trial, should dispel any idea that psoriasis is not considered a major therapeutic priority. Although only a few of the drugs on this list will gain regulatory approval, what is exciting is the likelihood that some new agents will be approved and will radically alter the way we treat psoriasis.

Product	Status
ABX-IL8, ABX-EGF Monoclonal antibody products Abgenix Inc.	Monoclonal antibody which targets IL-8 for the treatment of moderate to severe psoriasis. Multicentre trial.
AE-941 Psovascar [®] Aeterna Laboratories Inc.	This is an angiogenesis inhibitor. Phase II trials are scheduled for 1999.
AGN-4310 Allergan Specialty Therapeutics Inc.	A topical retinoic acid receptor antagonist for the treatment of psoriasis. Undergoing Phase I clinical trials.
APC-2059 Axys Pharmaceuticals Inc.	A tryptase inhibitor, in topical cream formation for the treatment of mild to moderate psoriasis. Phase I trial.
CTLA4-Ig Antibodies BMS 188667 Bristol-Myers Squibb Co.	A fusion protein to be used in the treatment of psoriasis and autoimmune disorders. Ready to market.
Hu 1124 Xoma Ltd.	A humanized monoclonal antibody for treatment of moderate to severe psoriasis. Undergoing clinical trials.
ICM 3 Icos Corp.	This anti-psoriasis agent blocks the ICAM-3 receptor on T-cells and antigen-presenting cells. Undergoing clinical trials.
IR-502, T-cell receptor (TCR) peptide therapeutic psoriasis vaccine Hoffmann-La Roche	An immunomodulator for treatment of patients with moderate to severe psoriasis. Undergoing clinical trials.
LFA3-TIP Biogen Inc.	This is an immunosuppressive agent for psoriasis treatment. Phase III trial will be getting underway in late 1999.

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Product	Status
<p><i>Mometasone furoate 0.1% and salicylic acid 5%</i> Combisor <i>Schering-Plough Corp.</i></p>	<p>This combination awaiting regulatory approval for the treatment of chronic, moderate to severe psoriasis.</p>
<p><i>Mycophenolate Mofetil</i> Cell Cept® <i>Hoffmann-La Roche</i></p>	<p>This agent was recently approved in Europe as an immunosuppressant to be used in combination with Cyclosporin (Neoral) or as monotherapy in transplant procedures. Clinical trials for psoriasis are being considered.</p>
<p><i>22-oxacalcitrol</i> Maxacalcitol <i>Schering-Plough Corp. and Chugai Pharmaceutical Co. Ltd.</i></p>	<p>A vitamin D3 analog for topical treatment of psoriasis. Undergoing phase III clinical trials in Europe.</p>
<p><i>Paclitaxel gel</i> <i>Angiotech Pharmaceuticals Inc.</i></p>	<p>An anti-neoplastic, in topical gel formulation. It appears to inhibit normal skin growth while being non-toxic to healthy cells. It inhibits inflammatory cell response and angiogenesis. For the treatment of mild to moderate psoriasis. Phase II trial.</p>
<p><i>Porfimer sodium</i> Photofrin® Benzoporphyrin® <i>QLT PhotoTherapeutics Inc.</i></p>	<p>This product is for patients with psoriasis and psoriatic arthritis. Phase II studies to take place in 1999.</p>
<p><i>SU 5271</i> <i>Sugen</i></p>	<p>A potent and selective small molecule transduction inhibitor of epidermal growth factor receptor for the treatment of psoriasis. Clinical trials are continuing.</p>
<p><i>Tacalcitol</i> Bonealfa® <i>Teijin and Hermal, E. Merck</i></p>	<p>This product is for the treatment of psoriasis. Undergoing clinical trials.</p>
<p><i>VX-497</i> <i>Vertex Pharmaceuticals, Inc.</i></p>	<p>An inosine monophosphate dehydrogenase (IMPDH) inhibitor for treatment of severe plaque psoriasis and other chronic autoimmune diseases. Undergoing clinical trials.</p>

cases,¹⁴ and very sporadic reports of headache^{16,14} and nervousness.^{18,14}

Other reports include possible or occasional chloasma¹⁵ which may become more of a problem in countries with greater sun exposure.¹⁸ There are some reports of depression¹⁴ and decreased libido,¹⁸ however, increased libido and decreased depression have also been noted.^{14,18}

5. *Does the monthly cost of the medication create a problem for patients?*

The answer was a unanimous NO! Many other acne treatments are more expensive.¹⁷

6. *Do you usually recommend the use of topical anti-acne medications in combination with hormonal therapy?*

The majority of our panel said yes, although one would only use topical anti-acne medications during the initial phase of treatment.¹² Unlike the isotretinoin treatment for acne, complete clearing is unusual with hormonal combinations, and additional topical therapy may be helpful.¹⁷ The choice of product depends on whether the acne is inflammatory or comedonal.¹⁰ A sebostatic drug may cause skin dryness, and this can confuse women used to seborrheic skin.¹⁸ They may be helped by skin cleaning products which help maintain the skin's water content.

Ortho Tri-cyclen[®], a combination of ethinyl estradiol with norgestimate, one of the newer less androgenic progestins, was approved by the US FDA in December, 1996, and the Canadian HPB in March, 1998. The indication is for the treatment of *moderate acne vulgaris* in women with no known contraindications to oral contraceptive therapy. Ortho Tri-cyclen[®] was reviewed in a focus article in the *Skin Therapy Letter*, Volume 2, Number 3.

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Product	Diane-35 [®]	Ortho Tri-cyclen
Dosage	First treatment course: 1 tablet daily for 21 days; subsequent courses consist of 21 days on and 7 days off.	21-Pill Pack: 21 active pills taken daily for 3 weeks followed by no pills for 1 week. 28-Pill Pack: 21 active pills taken daily for 3 weeks and then 7 "reminder" pills with no hormones taken for 1 week.
Supplied	Blister pack units consisting of 21 tablets; each tablet contains 2mg cyproterone acetate and 0.035mg ethinyl estradiol.	Each tablet contains ethinyl estradiol 0.035mg. The white tablets contain 0.18mg of norgestimate; the light blue tablets contain 0.215mg of norgestimate; the green tablets contain inert ingredients.
Cost	\$19.00 (CDN) £5.52 (UK)	21-Pill Pack: \$28.70 (US), \$18.26 (CDN) 28-Pill Pack: \$28.85 (US), \$18.26 (CDN)

Update on Drugs

Class	Name/Company	Approval Dates and Comments
Anticancer	Methoxsalen Uvadex <i>Therakos</i>	In April, 1999, the FDA approved this drug for extracorporeal administration with the UVAR Photophoresis system in the palliative treatment of skin manifestations of cutaneous T-cell lymphoma that are unresponsive to other forms of treatment.
Diabetic ulcers	Becaplermin 0.01% Regranex [®] <i>Janssen-Ortho</i>	FDA approved for the treatment of full thickness, lower extremity diabetic ulcers.
Metastatic melanoma	Aldesleukin Proleukin [®] <i>Chiron</i>	Approved in February, 1999, by the US FDA for the treatment of metastatic melanoma in adults.
Post-herpetic neuralgia	Lidocaine 5% Lidoderm [®] patch <i>Endo Pharmaceuticals</i>	Approved in March, 1999, by the US FDA to treat the pain associated with post-herpetic neuralgia (PHN) complication of shingles. This is the first product approved by the FDA for the treatment of PHN.
Anti-inflammatory dermatoses	Betamethasone valerate foam Luxiq [®] 0.12% <i>Connetics Corporation</i>	Approved in March, 1999, by the US FDA for the relief of inflammatory and pruritic manifestations of corticosteroid-responsive dermatoses of the scalp.
Drug news		
Anticancer	Paclitaxel Taxop [®] <i>Bristol-Myers Squibb Co.</i>	Nail disorders or changes may occur more often than was at first thought. These changes can include discoloring, nailthickening, onycholysis, and paronychia.
Dietary supplements	Labels must now list all ingredients in order of quantity, suggested serving, percent daily value and amount of calories. Vitamin and mineral product labels must state the quantity of specific nutrients and herbal products must specify the actual plant parts used.	
Malignant melanoma	Temozolomide Temodal [®] <i>Schering-Plough</i>	The FDA's Oncologic Drugs Advisory Committee <i>recommended against approval</i> of temozolomide because of an inability to demonstrate any superiority over dacarbazine for this condition.
Tinea pedis	Terbinafine HCl cream 1% Lamisil [®] <i>Novartis</i>	In March, 1999, the FDA approved the switch from prescription status to over-the-counter availability of terbinafine cream for tinea pedis.

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