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Oral Contraceptives in the Treatment of Acne

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ABSTRACT

Oral contraceptives (OCs) can reduce acne by lowering the production of adrenal and ovarian androgens, by inhibiting 5-alpha-reductase, which in turn, reduces the levels of dihydrotestosterone, and by stimulating sex hormone binding globulin (SHBG), thus reducing the levels of free testosterone. In newer OCs, such as Tricyclen *and* Diane-35, *the progestin component is minimally androgenic and anti-androgenic respectively, thereby enhancing the favorable profile of these products in the treatment of hyperandrogenic disorders, including acne. The efficacy of these agents and their long-term safety profile supports their use in various grades of acne in females:*

- *as adjunctive therapy to topical agents for women with mild non-scarring acne desiring oral contraception*
- *as primary therapy for patients with moderate non-scarring acne in combination with topical therapy and systemic antibiotics*
- *as one of two preferred methods of contraception in patients with scarring and severe inflammatory acne being treated with systemic isotretinoin.*

KEY WORDS: *acne, oral contraceptives, progestin*

Acne is initiated by the effect of androgens on pilosebaceous units resulting in sebaceous hypersecretion and follicular occlusion. Hormonal therapy in acne is, therefore, rationally directed at interrupting this initial phase in the sequence of acne pathogenesis.

Oral contraceptives have been available since 1960, and have evolved to contain less estrogen, thus minimizing the risk of thromboembolic events, hepatic tumors, hypertension, and altered glucose metabolism. As well, present day OCs include progestins, which have less intrinsic androgenicity. These developments in OC pharmacology also led to their usefulness in treatment across the spectrum of acne severity in females.[1]

Hormonal Pathways in Acne Pathogenesis

Androgens that are relevant in acne pathogenesis include dihydrotestosterone (DHT), testosterone (T), androstenedione (A) and dehydroepiandrosterone-sulfate (DHEA-S). The production of these androgens from ovaries and adrenal glands is mediated by gonadotrophins. Testosterone is converted to the biologically more potent 5-dihydrotestosterone (5-DHT) by 5-alpha-reductase. The bioavailable testosterone fraction is considered to be biologically active and comprises the free fraction of testosterone and the fraction bound by albumin. Levels of free testosterone are inversely related to levels of sex hormone binding globulin (SHBG).

Oral Contraceptives

OCs, which contain estrogen and progestins, directly affect androgen physiology and can therefore impact acne. Potential mechanisms of the therapeutic effect of estrogens include:

- decreased production of adrenal (DHEA-S) and ovarian androgens (A, T)
- inhibition of 5-alpha-reductase leading to the reduction of DHT levels
- stimulation of SHBG, reducing levels of free T.

19-nortestosterone derivatives		Progesterone derivatives
Gonanes (norgestrel related)	Estranes (norethindrone related)	
Norgestrel	Norethindrone	Cyproterone acetate
Levonorgestrel	Norethindrone acetate	
Desogestrel	Ethynodiol diacetate	
Gestodene	Lynestrenol	
Norgestimate		

Table 1: Overview of Progestins

Progestins vary in their androgenic potential and may therefore have variable effects on acne. The most commonly used progestins in OCs are 19-nortestosterone derivatives (see Table 1).[2] Progestins with the lowest androgenic potential (e.g., desogestrel, norgestimeate, cyproterone acetate) are more appropriate in the treatment of acne and other hyperandrogenic disoders.

Hormonal Preparations Approved for Treatment of Acne

1. **Ethinyl estradiol 0.035mg with norgestimate in increasing doses of 0.180mg/0.215mg/0.250mg *(Tricyclen):***

   Norgestimate has low intrinsic androgenicity with low binding affinity for androgen receptors, whereas it is strongly selective and avidly bound to progesterone receptor sites. Two 6-month, randomized, double-blind placebo-controlled trials involving 507 females with moderate acne showed clinically and statistically significant reduction of inflammatory lesions and total lesion counts.[3,4] Moderate acne was defined as 6-100 comedones, 10-50 papules or pustules, and no more than 5 nodules. The mean decrease in inflammatory lesion count was 12, or 62% from baseline (compared to 8 lesions or 39% for placebo), and the decrease in total lesion count was 29, or 53% (compared to 14, or 27% in placebo). No significant changes for nodules were noted. A 50% reduction in total lesion count was attained between the 4th to 6th month of treatment, with a plateau of effect attained at 6 months.

	Erkkola et. al (1990)[12]	Aydinlik et. al (1990)[13]	Gollnick et. al. (1998)[14]
Randomized?	Yes	No	No
Placebo-controlled?	No Compared to desogestrel/ethinyl estradiol*	No	No
Blinded?	No	No	No
Standard Dermatological Assessment and Outcome Endpoints	No "healing/improvement" "complete healing"	No "healing/improvement" "definitive healing" "complete healing"	Yes: Lesion counts and acne grading
Sample Size At Start/At Completion	162/133	1161/1071 (after 6 months); 850 (after 12 months); 192 (after 36 months)	890/794
Duration of Treatment	9 months	Maximum 36 months	6 months
Efficacy	Complete healing: 60% Healing/Improvement: 81%	Healing/improvement: 72% (at 6 months); 90% (at 12 months)	Lesion count reduction 73%; reduction in acne grade in 64%
Adverse Events		Headache (7%), nausea (5%), breast tension (13%), melasma (7%)	Breast tenderness (12%), headache (9%), nausea (6%), nervousness (4%), dizziness(3%)

Table 2: Summary of Pivotal Studies for *Diane-35*
* desogestrel 0.15 mg with ethinyl estradiol 0.03 mg

2. **Ethinyl estradiol 0.035mg and cyproterone acetate 2mg *(Diane-35):***

Cyproterone acetate (CPA) is an analogue of hydroxyprogesterone and has progestational activity. It acts as a potent antiandrogen by competitive inhibition of T and DHT binding to the androgen receptors, and by inhibiting gonadotropin secretion. It is currently available in a dose of 2mg CPA in combination with ethinyl estradiol *(Diane-35).* Higher doses of CPA (50-100mg/d) may be required in treatment of more refractory acne or if associated with hyperandrogenization.[5]

The effectiveness of *Diane-50* (containing 0.05mg of ethinyl estradiol and 2mg of CPA) for the treatment of acne has been demonstrated in placebo-controlled and antibiotic-comparative trials. Two randomized controlled trials compared *Diane-50* to systemic antibiotics in the treatment of acne. In a 6-month trial of 78 patients randomized to minocycline 50mg po bid or *Diane-35,* papules were reduced by 73% and 70%, and pustules by 77% and 83%, respectively.[6] A similar 6-month trial evaluating *Diane-50* compared to tetracycline 500mg po bid in 92 women showed reduction in lesion counts of 74% and 68% respectively[7].

Two randomized controlled trials compared *Diane-35* to *Diane-50,* one for 9 months and the other for 12 months. They demonstrated that these preparations were similarly effective in the treatment of acne.[8,9] In a 6-month study of 133 patients randomized to treatment with *Diane-35, Diane-50* or levonorgestrel 0.15mg/ethinyl estradiol 30mg, the reduction in acne lesions from baseline was 72%, 70%, and 35% respectively.[10]

The three pivotal studies referred to in the Canadian product monograph[11] for *Diane-35* are summarized in Table 2.[12-14] One trial was randomized, comparing *Diane-35* to desogestrel 0.15 mg/ethinyl estradiol 0.03mg, but was unblinded, introducing the potential for observer or patient bias. Standard dermatological outcome parameters for acne, such as lesional counts or change in acne grade, were used in only one study. In that study fifty percent reduction in lesion counts was attained between the 2nd to 4th month of treatment.[14] Two studies used non-standard, subjective outcome parameters such as "healing/improvement", "complete healing" and "definitive healing" which are of limited utility in outcome assessment across studies.

Summary

Currently available OCs such as *Tricyclen* and *Diane-35,* containing progestins with minimal androgenic and anti-androgenic potential respectively, provide an important therapeutic option for women with acne. Their proven efficacy and long-term safety profile support their use for various grades of acne in females.

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Drug Treatments For Skin Disease Introduced in 2000

Drug Class	Generic/Trade/ Company Names	Labelled Indication	Approving Regulatory Agency
Anti-acne Agent	**Chloramphenicol, Sulphur, Hydrocortisone Acetate, 2-butoxyethyl Nicotinate, Allantoin** *Actinac* Aventis Pharma	• For the treatment of mild to moderate acne	TPP - Canada
	Clindamycin Phosphate & Benzoyl Peroxide *Clindoxyl Gel* Stiefel Canada	• For the treatment of mild to moderate acne	TPP - Canada
	Clindamycin Phosphate *Clindasol Cream 1% & Clindets Pledgets* Stiefel Canada	• For the treatment of mild to moderate acne	TPP – Canada
Antibacterial Agent	**Levofloxacin Tablets/Injection** *Levaquin Tablets/Injection* Ortho Pharmaceuticals	• Additional indication for the treatment of complicated skin and skin structure infections at a higher dose of 750mg once daily	US FDA
	Linezolid *Zyvox* Pharmacia & Upjohn	• For the treatment of complicated skin/skin structure infections, infections caused by vancomycin resistant *Enterococcus,* and hospital acquired pheumonia	US FDA
	Silver Sulfadiazine *Flamazine* Smith & Nephew	• Previously available for superficial skin infections	TPP – Canada
Antifungal Agent	**Amphotericin B Liposome for Injection** *Ambisome* Fujisawa Canada	• For the treatment of systemic or disseminated infections due to *Candida, Aspergillus* or *Cryptococcus* in patients refractory to, or intolerant of conventional amphotericin B therapy, or suffer renal impairment.	TPP – Canada
	Ciclopirox Olamine 1% *Loprox Cream, Loprox Lotion* Dermik Laboratories	• For the treatment of fungal infections	TPP – Canada
	Ketoconazole 2% Cream Teva Pharmaceuticals	• For the treatment of fungal infections	US FDA
	Terbinafine HCl 1% Solution *Lamisil* Novartis	• For the treatment of interdigital athlete's foot, jock itch and ringworm. Switched from prescription to OTC status	US FDA
	Terbinafine HCl *Gen-Terbinafine 250mg Cap* Genpharm	• For the treatment of interdigital athlete's foot, jock itch and ringworm. Switched from prescription to OTC status	TPP – Canada
	Terbinafine HCl *Novo-Terbinafine 125-250mg Cap* Novopharm	• For the treatment of interdigital athlete's foot, jock itch and ringworm. Switched from prescription to OTC status	TPP – Canada
	Terbinafine HCl *Terbinafine – 250* Pro Doc Limitée	• For the treatment of fungal infections	TPP – Canada
Antihistamines	**Loratadine** *Claritin* Schering-Plough	• For the treatment of chronic idiopathic urticaria and seasonal allergies in children $\geq$ 2 years of age	US FDA
	Trimeprazine Tartrate *Panectyl* Aventis Pharma	• Antipruritic	TPP – Canada
Anti-inflammatory Agent	**Amlexanox 5% Paste** *Apthera* Access Pharmaceuticals	• For the treatment of aphthous ulcers (canker sores)	TPP – Canada
Antipsoriatic Agent	**Calcipotriol** *Dovonex Cream & Ointment* Leo Pharma	• New indication for the treatment of psoriasis, used in combination with topical corticosteroids, cyclosporin A, acitretin, and phototherapy (PUVA or UVB)	TPP – Canada

Drug Class	Generic/Trade/ Company Names	Labelled Indication	Approving Regulatory Agency
Antirejection Agent	**Cyclosporin** *Gengraf* Abbott Laboratories	• For the prevention of organ rejections in kidney, liver and heart transplants. It is the bioequivalent to *Neoral* (Novartis Pharmaceuticals)	US FDA
Antirosacea Agent	**Metronidazole** *Rosasol Topical Cream, 1%* Stiefel	• For the treatment of rosacea	TPP – Canada
Antiviral Agent	**Docosanol Cream 10%** *Abreva* Glaxo Smith Kline	• For the treatment of recurrent oral facial herpes simplex infections	US FDA (OTC)
	Interferon-Alpha *Veldona* Amarillo Bioscience	• For the treatment of papillomavirus warts in the oral cavity of HIV positive patients	US FDA (Orphan Drug Designation)
Corticosteroids	**Flumethasone Pivalate** *PMS-FLUMETHASONE-CLIOQUINOL* Pharmascience	• For the treatment of otitis externa, and otomycosis due to *aspergillus niger.* It is the generic form of *Locacorten Vioform* (Novartis)	TPP – Canada
	Prednicarbate 0.1% *Dermatop Emollient Cream & Dermatop Ointment* Dermik Laboratories	• For the relief of the inflammatory and pruritic manifestations of acute and chronic corticosteroid-responsive dermatoses	TPP – Canada
Dermatosclerosis Agent	**Halofuginone** Collgard Biopharmaceuticals	• For the treatment of scleroderma	US FDA (Orphan Drug Designation)
HIV/AIDS	**Amprenavir** *Agenerase* Glaxo Wellcome	• For use in combination with other anti-retroviral agents for the treatment of PI-experienced HIV infected adults and children ≥ 4 years of age	CPMP – Europe
	Lamivudine, Zidovudine & Abacavir *Trizivir* Glaxo Wellcome	• For the treatment of HIV infection	US FDA
Hormonal Preparations	**Testosterone Gel** *AndroGel 1%* Unimed Pharmaceuticals	• For the treatment of low testosterone levels linked with reduced sex drive/impotence, reduced lean body mass, reduced bone density, and lowered mood/energy levels in men who have not had breast or prostate cancer.	US FDA
Immunomodulators	**Tacrolimus Ointment** *Protopic* Fujisawa	• For the treatment of moderate-to-severe atopic dermatitis or eczema	US FDA
Keratolytic Agent	**Diclofenac Sodium** *Solaraze (US)* *Solarase (Canada)* SkyePharma PLC	• For the treatment of actinic keratosis	US FDA TPP – Canada
	5-fluorouracil Microsponge *Solex* Advanced Polymer Systems / Dermik Laboratories	• For the treatment of actinic keratoses	US FDA
Neurotoxin	**Botulinum Toxin Type B** *Myobloc* Elan Corporation	• For the treatment of patients with cervical distonia to reduce the severity of associated abnormal head position and neck pain. Past experience suggests that it will likely attract off-label use for wrinkle correction.	US FDA
Oncologic Agent	**Alitretinoin 0.1% Gel** *Panretin* Ligand Pharmaceuticals	• For the treatment of cutaneous lesions from AIDS-related Kaposi's sarcoma.	CPMP – Europe
	Bexarotene Capsules *Targretin* Ligand Pharmaceuticals	• For the treatment of all stages of cutaneous T-cell lymphoma in patients who are refractory to > 1 prior systemic therapy.	US FDA
	Bexarotene 1% Gel *Targretin* Ligand Pharmaceuticals	• For the treatment of cutaneous lesions in patients with early-stage cutaneous T-cell lymphoma who cannot tolerate other therapies.	US FDA

Drug Class	Generic/Trade/ Company Names	Indication	Approving Regulatory Agency
Oncologic Agent	**Bleomycin** Gensia Sicor Pharmaceuticals	• This generic injection form of Bristol-Myers Squibb's bleomycin *(Blenoxane)* tentatively approved for the management of squamous cell carcinoma, lymphomas and testicular carcinoma	US FDA
	Cyclophosphamide 25mg and 50mg Tablets Roxane Laboratories	• For treatment of certain forms of cancer to be used in combination with other antineoplastic therapies	US FDA
	Hydroxyurea Barr Laboratories	• This generic formulation approved for use in the treatment of melanoma	US FDA
	Paclitaxel *Paxene* IVAX/Bristol-Myers Squibb	• For the treatment of AIDS-related Kaposi's sarcoma in patients who have failed prior liposomal anthra-cycline therapy.	TPP – Canada
Pediculocides	**Piperonyl Butoxide/Pyrethrins** *Rid Mousse* Soltec Research	• For the treatment of head, pubic (crab), and body lice	US FDA
Photo-aging	**Tretinoin Cream** *Renova 0.02%* Ortho Pharmaceuticals	• For reducing fine facial wrinkles associated with chronic sun exposure and the natural aging process.	US FDA
	Tretinoin Cream *Renova 0.05%* Ortho Pharmaceuticals	• For use in the mitigation of fine wrinkles, mottled hyperpigmentation and tactile roughness of facial skin	US FDA
Scalp Dermatoses	**Clobetasol Propionate** *Olux Foam 0.05%* Connetics	• For the short-term topical treatment of inflammatory and pruritic manifestations of moderate-to-severe corticosteroid-responsive dermatoses of the scalp.	US FDA
Topical Anesthetic	**Lidocaine & Procaine** *EMLA Cream & Patch* AstraZeneca	• Topical anesthetic for dermal analgesia	TPP - Canada
Transdermal Agent	**Estradiol Transdermal System** *Vivelle* Novogyne Pharmaceuticals	• For the additional indication of postmenopausal osteoporosis for this transdermal estrogen patch	US FDA
Urticaria	**Fexofenadine HCl** *Allegra* Aventis Pharmaceuticals	• For the additional treatment of uncomplicated skin manifestations of chronic idiopathic urticaria in adults and children ≥ 6 years of age	US FDA
Vaginal Preparations	**Butoconazole Nitrate** *Gynazole 2% Vaginal Cream* KV Pharmaceuticals	• For the treatment of vaginal yeast infections using only one dose.	US FDA
	Clotrimazole 2% *Clotrimazole 2% Three Day Vaginal Cream* Taro Pharmaceuticals	• OTC for the treatment of vaginal yeast infections	US FDA
	Estradiol Vaginal Ring *Estring* Pharmacia and Upjohn	• For the treatment of urogenital symptoms associated with post-menopausal vaginal atrophy	US FDA
Wound Care	**Tissue Engineered Collagen Matrix** *Oasis Wound Dressing* COOK's	• For the treatment of full-thickness skin injuries	US FDA
	Graftskin *Apligraf* Novartix Pharmaceuticals	• For expanded use with conventional diabetic food ulcer care in the treatment of diabetic food ulcers > 3 weeks in duration	US FDA
	"Intelligent" Dressing *Acemannan Hydrogel* Carrington Laboratories	• For the management of postsurgical incisions, first- and second-degree burns, arterial and venous stasis ulcers, pressure ulcers, and foot ulcers	US FDA

TPP: Health Canada, Ottawa – Therapeutic Products Program

FDA: United States Food and Drug Administration

CPMP: European Union's Committee for Proprietary Medicinal Products

Roche Introduces New Drug Warnings for *Accutane* in US

As a result of recent meetings held by the US FDA, Roche has introduced further steps to inform doctors and patients about possible side effects by their anti-acne drug *Accutane* (isotretinoin), such as birth defects, mental disorders and suicide.

Doctors must now make sure their patients sign a consent form that explains the drug's possible risks before they can write the prescription for this drug. As well, each prescription for *Accutane* will include a consumer-friendly pamphlet that details the benefits and the possible side effects.

Accutane labelling already includes both birth defects and mental disorders. Roche has taken several steps to publicize the drug's potential teratogenic effects, including an elaborate pregnancy prevention program, as well as a tracking program monitored by the Slone Epidemiology Unit in Boston, Massachusetts. However, in spite of this, some women who were taking *Accutane* became pregnant each year.

In addition to addressing birth defects as a possible side effect, the new consent forms also advise patients to look for signs of depression, e.g., feelings of sadness, irritability, fatigue or loss of appetite. Health officials are not certain whether *Accutane* does indeed cause problems with depression, suicidal thoughts and mood disorders.

American Academy of Dermatology Issues Policy Statement on *Accutane*

In November 2000, the American Academy of Dermatology (AAD) issued a new policy statement on *Accutane* (isotretinoin, Roche), which reads as follows:

- The Academy is committed to the safe and responsible use of isotretinoin.
- The Academy calls on the FDA not to limit the ability of qualified patients, in consultation with their physician, to receive isotretinoin.
- The Academy supports more education for physicians and patients on potential pregnancy hazards.
- The Academy opposes the inclusion of isotretinoin on a list of drugs that can only be obtained by registered physicians and patients.
- The Academy calls for a study designed to determine if there is a direct causative link between isotretinoin and psychiatric events.
- The Academy calls upon the American Medical Association to support its efforts to ensure the continued accessibility to, and medically appropriate use of, isotretinoin.

The AAD indicated that patient safety is its primary concern, and feels that education of physicians and their patients, rather than regulation, is the best way to ensure safe and effective results with this medication.

Update on Drugs

Class	Name/Company	Approval Dates and Comments
Antihistamine	**Loratidine** *Claritin* Schering-Plough	Schering-Plough submitted an abridged application to the US FDA and to the European Regulatory Committee (CPMP) in January 2001, to market their non-sedating antihistamine in a rapidly disintegrating tablet form for the treatment of seasonal allergic rhinitis and chronic idiopathic urticaria in adults and children ≥12 years of age.
Antiviral Agent	**Varicella Zoster Immune Globulin** *VariZIG* Cangene	TPP-Canada approved this hyperimmune product in January 2001. *VariZIG* is a highly purified and specialized antibody against the varicella zoster virus that causes chicken pox.
Antihistamine	**Levocetirizine** *Xyzal/Xusal* Sepracor	The German Health Authorities approved this new generation antihistamine in January 2001, for the treatment of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria.
Enzyme Replacement Therapy	**Agalsidase Beta** *Fabrazyme* Genzyme General	The US FDA completed its review of the biologics licensing application in December 2000, for this investigational enzyme replacement therapy for Fabry disease. Genzyme must supply additional data and conduct a Phase IV trial before the US FDA will give their approval.
Atopic Dermatitis Agent	**ASM 981 Cream 1%** Novartis Pharmaceuticals	An NDA was submitted to the US FDA in December 2000, for this non-steroid, skin-specific cytokine inhibitor for the treatment of atopic dermatitis or eczema.

Drug News

Antiviral Agent	Docosanol 10% Cream *(Abreva)* was launched in January 2001, by SmithKline Beecham. It is the first OTC cold sore medication to be approved by the US FDA for reducing the healing time and duration of symptoms.
Antiviral Agent	Novartis Pharmaceuticals has acquired the antiviral products *Famvir* (famciclovir) and *Denavir* (penciclovir) from SmithKline Beecham for the treatment of herpes.
Atopic Dermatitis Agent	According to results presented at the annual meeting of the American College of Asthma, Allergy and Immunology in October 2000, topically applied strontium salts may be effective for treating itch and sensory irritation. Dr. G.S. Hahn from Cosmederm Technologies stated that when atopic subjects were treated with 20% strontium nitrate in a 5% ethanol/water vehicle vs. the vehicle alone, 70% of strontium treated sites had less itch than the vehicle treated sites. Topically applied strontium is very safe and can be found in more than 30 cosmetic and dermatological products sold around the world.
Allergic Contact Dermatitis	French researchers report that skin painting, also known as pseudo-tatooing, can lead to allergic contact dermatitis. Skin painting is done using henna, a hair dye preparation, and C.J. Le Coz, et al* stated that when henna is used on the skin, it can cause sensitization to chemical coloring agents, such as p-phenylenediamine and diaminobenzenes or diaminotoluenes. **Arch Dermatol* 136(12):1515-7 (2000 Dec)

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