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Calcipotriol and Betamethasone Dipropionate for the Treatment of Psoriasis: A 52-Week Study

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ABSTRACT

Psoriasis is a common skin disease affecting 1%-3% of the world's population with significant impacts on quality of life. There is a great need for therapies that are efficacious and safe, not only for the short-term, but also for long-term management. Dovobet®/ Daivobet®/ Taclonex® is a product combining two molecules, calcipotriol and betamethasone dipropionate, that may offer psoriatic patients with an option for maintenance therapy. The efficacy and safety of this combined formulation when used over a 4-week period is well documented. A recent publication in the British Journal of Dermatology *discusses the safety of this product when used for 52 weeks.*[1]

Key Words: *Calcipotriol, Betamethasone Dipropionate, Psoriasis*

Dovobet®(Leo Pharma)/ Daivobet®(Leo Pharma)/ Taclonex®(Warner Chilcott) is a two-compound ointment containing calcipotriol 50µg/gm and betamethasone dipropionate 0.5mg/gm. Hereafter, this ointment will be referred to as either "Dovobet®" or "combination product" in this article.

Calcipotriol

Calcipotriol is a Vitamin D analog with a broad range of pharmacologic activities. Like vitamin D, calcipotriol inhibits keratinocyte proliferation, promotes epidermal differentiation and has a significant impact on cytokines and T-cells in the skin. Calcipotriol, however, has much less effect on calcium levels as compared to vitamin D. Topical calcipotriol 50µg/gm has been used worldwide for over 15 years for the treatment of psoriasis vulgaris. A plethora of randomized controlled double-blind studies have confirmed its efficacy.[2,3]

Topical calcipotriol has a good long-term safety profile and again there are many studies documenting this.[3,4] Most adverse reactions relate to initial application, irritation to or aggravation of existing psoriatic lesions. There have been isolated case reports of hypercalcemia,[5] however this is uncommon when application is limited to <100gm/week in adults.

Corticosteroids

Topical corticosteroids have been the cornerstone of psoriasis therapy for many years. A recent study demonstrated that a super-potent steroid was used by 44% of psoriasis patients.[6] Their efficacy and limitations are well known. Apart from concerns relating to systemic absorption, the major concern relating to long-term topical steroid use is cutaneous atrophy and its various clinical presentations.

Betamethasone dipropionate has been categorized by the World Health Organization as a group III (mid-high) potency steroid. It has been shown to be safe and effective in treating psoriasis vulgaris.

Combined Formulation

Initially, combining betamethasone dipropionate and calcipotriol in a vehicle proved difficult as these two substances are incompatible in aqueous and alcoholic media. In Dovobet®, these molecules are combined in a water free vehicle, ensuring maximum stability and efficacy. It is also formulated to achieve optimal skin permeability.[7]

A recent study documented the effects of the molecules, in isolation and in combination, when used on psoriatic skin.[8] Calcipotriol alone had a major effect on the proliferation marker Ki-67 and differentiation marker keratin-10 (K-10) while reducing T-cell subsets CD 45RO (+) and CD8 (+). Betamethasone dipropionate produced a highly significant increase of the K-10 positive epidermal surface without an effect on Ki-67 positive nuclei, and the effect on T-cell subsets was a reduction of natural cell to cell receptors CD94 and CD161 in the epidermis. Therapy involving both molecules showed no added effect in relationship to proliferation marker Ki-67 and keratinization marker keratin-10, but when amalgamated, they had a profound effect on all T-cell subsets. This suggested a different mode of action of the two molecules on psoriatic plaques at the molecular level and points to evidence that supports a synergistic effect when they are combined.

Dovobet® has been proven to be highly effective in treating psoriasis vulgaris.[9] A recent study suggested PASI 50 and PASI 75 response in greater than 80% and 50% of patients respectively, regardless of initial disease severity. The report combined data from six phase III studies involving more than 6500 patients.[10,11]

Many recent reports have noted the profound effect that psoriasis has on the quality of life of patients. When applied once daily, Dovobet® has been shown to be superior to calcipotriol applied twice daily in improving the quality of life of patients with psoriasis vulgaris.[12]

The majority of studies documenting the efficacy and safety of Dovobet® have been limited to four-week periods of observation. As such, due to the chronic nature of psoriasis, detailed documentation to track long-term safety and efficacy is required by regulatory authorities.

Study Results

Recently, results of a 52-week randomized study of Dovobet® in the treatment of psoriasis vulgaris were published in the *British Journal of Dermatology*.[1] The primary objective of this study was to investigate the safety of two treatment regimens involving the "as needed" use of Dovobet® over 52 weeks. In particular, side-effects relating to the long-term use of a topical steroid were assessed by an adjudication panel consisting of three dermatologists not otherwise involved in the study.

Patients were randomized to one of the three double-blinded treatment groups:

(I) 52-weeks of combination product;

(II) 52-weeks of alternating 4-week periods of the combination product and calcipotriol ointment (alternating group); and

(III) 4-weeks of the combination product followed by 48 weeks of calcipotriol ointment (calcipotriol [non-steroidal control] group).

Treatment was limited to once daily application as required, and usage was limited to a maximum of 100gm/week per patient. Patients were seen every 4 weeks for assessment of adverse effects. A subset of 19 patients had adrenal function tests at baseline and after 4, 12, and 62 weeks.

The study was conducted from August 2002 to April 2004 and 634 patients were enrolled in 67 European centers and 10 Canadian centers. The treatment groups were similar with respect to age, sex, ethnic origin, duration of psoriasis, duration of previous topical steroid use and disease severity.

There were 21.7% of patients that developed adverse drug reactions in the Dovobet® group, 29.6% in the alternating group, and 37.9% in the calcipotriol group. In addition to the aggravation of existing psoriatic lesions, the most common adverse reaction was application-related irritation. The most common adverse reactions with calcipotriol treatment are known to be irritation and pruritus, as was reflected in the calcipotriol group. This study indicates that the steroid molecule reduces the irritative effect of calcipotriol in the Dovobet® group. The incidence of initial flare-ups of psoriatic lesions was similar in all groups.

There was one systemic event in the subset of 19 patients undergoing adrenal function testing. This one patient, who demonstrated adrenal insufficiency, was in the calcipotriol treatment group. Consequently, the event was considered unrelated to the therapy.

Skin atrophy was identified by the adjudication panel in 1.9% of the Dovobet® group, 0.5% of the alternating group, and 1.0% in the calcipotriol group. The four patients identified in the Dovobet® group demonstrated atrophy at 10–33 weeks of therapy and the condition resolved in three of the four patients. The fourth patient had used topical corticosteroids continuously for the previous 10 years prior to the study and continued to use Dovobet® every other day, as needed, in the remaining 40 weeks of the study following identification of the atrophy. In addition, he was prescribed Dovobet® once the study was completed. Folliculitis was noted by the adjudication panel in three patients in the Dovobet® group and in one patient in the alternating group, however all cases were mild. One patient in the calcipotriol group developed cellulitis. There were two cases of depigmentation in the Dovobet® group, one of which had resolved during the period of observation.

The study concluded that Dovobet®, when used for up to 52 weeks, was safe and well tolerated whether used as monotherapy, or alternating every 4 weeks with calcipotriol treatment.

Conclusion

The combination of calcipotriol and betamethasone dipropionate has been proven to be a very effective option for the topical treatment of psoriasis vulgaris.[8-12] Recently published findings indicate its safety and tolerability for continuous use as needed for up to 52 weeks.[1]

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Drug Treatments for Skin Disease Introduced in 2006

Drug Class	Generic/Trade Company Names	Indication	Approving Regulatory Agency
Actinic Keratoses	**Aminolevulinic Acid Hcl Topical Solution** *Levulan® Kerastick®* DUSA Pharmaceuticals/ Stiefel Laboratories	Approved for the treatment of precancerous actinic keratoses.	ANVISA Brazil
	Imiquimod *Aldara®* Graceway	Approval for expanded indication to include treatment of clinically typical, nonhyperkeratotic, nonhypertrophic actinic keratosis in adults.	EMEA
	Diclofenac Sodium 3% Gel *Solaraze®* SkyePharma	Approved for the treatment of actinic keratosis.	TGA Australia
Anesthetic (Topical)	**Lidocaine 7% & Tetracaine 7% Cream** *S-Caine®* ZARS Pharma	Approved as a topical local anesthetic for use on intact skin before various superficial dermatological procedures such as dermal filler procedures, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal. Indicated for use in adults.	US FDA
Antiacne	**Clindamycin Phosphate 1.2% & Tretinoin 0.025% Gel** *Ziana™* Medicis/Dow Pharmaceutical	Approved as the first and only combination product of clindamycin and tretinoin for the once daily treatment of acne vulgaris in patients 12 years of age or older.	US FDA
Antiaging Treatments	**Calcium Hydroxylapatite Microspheres in Water-based Gel** *Radiesse®* BioForm Medical	Approved for long-lasting correction of moderate-to-severe facial wrinkles and folds such as nasolabial folds. A second US FDA approval was granted for the long-lasting correction of facial fat loss (lipoatrophy) in patients with HIV.	US FDA
	Hyaluronic Acid Dermal Filler *Juvéderm™ Injectable Gel* Allergan	Approval for the treatment of facial wrinkles and folds.	US FDA
	Polymethylmethacrylate/ Bovine Collagen *ArteFill®* Artes Medical	This injectable implant was approved for the correction of facial wrinkles, folds, or smile lines. It is a nonresorbable dermal filler containing homogeneous precision-filtered microspheres suspended in purified collagen gel and 0.3% lidocaine to alleviate discomfort during injection.	US FDA
Antibacterial/ Antibiotic Agents	**Cephalexin Capsules** *Keflex®* Advancis Pharmaceutical	Approval letter issued by the US FDA to market two new strengths (333mg and 750mg) of the antibiotic capsules. Indicated to treat otitis media and infections of the respiratory tract, skin and skin structure, bone and genitourinary tract.	US FDA
	Retapamulin Ointment 1% *Altabax™* GlaxoSmithKline	The US FDA issued an approvable letter for this topical antibacterial for the treatment of secondarily-infected traumatic lesions that are most commonly caused by Staphylococcus aureus and Streptococcus pyogenes.	US FDA

Drug Class	Generic/Trade Company Names	Indication	Approving Regulatory Agency
Antibacterial/ Antibiotic Agents (cont)	**Tigecycline** *Tygacil®* Wyeth	Approved for the treatment of complicated infections of the skin, soft tissue, and intra-abdominal infections acquired in the hospital or community.	EMEA
Antihistamines	**Fexofenadine Hydrochloride Oral Suspension** *Allegra®* Sanofi-Aventis	The US FDA approved this twice daily treatment that provides non-impairing relief of symptoms related to seasonal allergies in children 2-11 years of age and for chronic idiopathic urticaria in children 6-11 years of age.	US FDA
Antimicrobial Agents	**Antimicrobial Barrier Dressing** *Acticoat™ Moisture Control with SILCRYST™ Nanocrystals* Nucryst Pharmaceuticals	This foam dressing was approved for the treatment of wounds with light-to-moderate exudates for up to 7 days.	EMEA
Antipsoriatic Agents	**Calcipotriene/Betamethasone Dipropionate** *Taclonex®* Warner Chilcott/Leo Pharma	Approved for the treatment of psoriasis vulgaris in adults.	US FDA
	Etanercept Enbrel® Amgen/Wyeth	Approved for the treatment of moderate-to-severe psoriasis in adults. Previously approved indications include rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis.	TPD Canada
	Infliximab *Remicade®* Schering-Plough	Approved for the treatment of moderate-to-severe psoriasis and psoriatic arthritis.	TPD Canada
	Infliximab *Remicade®* Centocor	Approved for the treatment of adult patients with chronic severe plaque psoriasis who are candidates for systemic therapy when other systemic therapies are not suitable.	US FDA
Antiviral Agents	**Zoster Vaccine Live** *Zostavax®* Oka/Merck	Approved for the prevention of herpes zoster (shingles) in people 60 years of age and older. Zostavax® is a live, attenuated varicella-zoster virus (VZV) vaccine and is given subcutaneously as a single dose of 0.65mL.	US FDA
	Quadrivalent Human Papillomavirus Vaccine (Types 6, 11, 16, 18) *Gardasil®* Merck	Approved for use in females aged 9 to 26 years of age for the prevention of cervical cancer, vulvar and vaginal pre-cancers, low-grade and pre-cancerous lesions and genital warts.	US FDA TPD Canada EMEA
	Famciclovir Single-Day *Famvir®* Novartis	Approval of supplemental new drug application (sNDA) for famciclovir tablets as a single-day treatment for immunocompetent patients with recurrent genital herpes or cold sores.	US FDA
	Green Tea Extract *Polyphenon® E Ointment 15%* MediGene AG/ Bradley	Approved for the topical treatment of external genital and perianal warts. The active ingredient is a concentrate of catechines with a defined composition, extracted from green tea leaves.	US FDA

Drug Class	Generic/Trade Company Names	Indication	Approving Regulatory Agency
Atopic Dermatitis/ Eczema	**Desonide Foam 0.05%** *Verdeso*™ Connectics	Approved for the treatment of mild-to-moderate atopic dermatitis.	US FDA
	Desonide Gel 0.05% *Desonate*™ SkinMedica	Approved for the treatment of mild-to-moderate atopic dermatitis in patients aged 3 months and older for up to 4 consecutive weeks. Desonate™ is a low-potency topical steroid formulated in a proprietary water-based vehicle. The formulation can be used on hair-bearing and non-hair-bearing skin.	US FDA
	Pimecrolimus *Elidel® Cream* Novartis	Labelling changes approved by the FDA include: a boxed warning about possible risk of cancer; recommendation as second-line treatments; and not recommended for use in children under 2 years of age.	US FDA
	Tacrolimus *Protopic® Ointment* Astellas		US FDA
	Miconazole Nitrate 0.25%, Zinc Oxide 15%, White Petroleum 81.35% *Vusion® Ointment* Barrier Therapeutics	Approved for the treatment of diaper dermatitis complicated by candidiasis.	US FDA
	Fluocinonide 0.1% Cream *VANOS*™ Medicis	Approval of additional indications for this Class I corticosteroid as primary therapy for all inflammatory and pruritic skin conditions, including eczema and poison ivy, in patients 12 years of age or older. Originally indicated for plaque-type psoriasis.	US FDA
Immuno-modulatory Agents	**Mycophenolate Mofetil** *CellCept®* Aspreva/Roche	This immunosuppressive agent was granted orphan drug designation for the treatment of pemphigus vulgaris.	US FDA
Medical Device	*Humira® Pen* Abbott Laboratories	This new device was approved for the administration of Humira®, a biologic treatment for moderate-to-severe rheumatoid arthritis and psoriatic arthritis. The device offers ease of use with its one-touch activation.	US FDA
Oncologic Agents	**Multi-subtype, Natural Human Alpha Interferon** Multiferon® Viragen International	Approved for the first-line adjuvant treatment of high-risk (Stages IIb-III) malignant melanoma following dacarbazine therapy (DTIC) after surgical removal of tumors.	MPA Sweden
	Oblimersen Sodium Injection *Genasense*™ Genta	Orphan Drug designation was granted for the treatment of patients with Stage IV malignant melanoma.	TGA Australia
	Vorinostat Capsules *Zolinza*™ Merck	The FDA approved this histone deacetylase inhibitor for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma who have progressive, persistent, or recurrent disease on or following two systemic therapies.	US FDA
Rosacea	**Doxycycline Capsules** *Oracea®* CollaGenex	Approval of doxycycline 40mg capsules for the treatment of inflammatory lesions (papules and pustules) of adult patients with rosacea.	US FDA

Drug Class	Generic/Trade Company Names	Indication	Approving Regulatory Agency
Psoriatic Arthritis Agents	**Adalimumab** *Humira®* Abbott	The FDA has approved an expanded indication for Humira® that includes inhibiting structural joint damage and improving physical function in patients with psoriatic arthritis. Previously approved indications include severe rheumatoid arthritis and active ankylosing spondylitis.	US FDA
	Infliximab *Remicade®* Schering-Plough	Revised indication to include the treatment of early rheumatoid arthritis and expanded new indication for psoriatic arthritis.	TGA Australia
	Infliximab *Remicade®* Centocor	FDA has extended its approval of infliximab for inhibiting progression of structural damage and improving physical function in patients with psoriatic arthritis, in addition to reducing signs and symptoms of active arthritis.	US FDA
Seborrheic Dermatitis	**Ketoconazole Gel 2%** *Xolegel™* Barrier Therapeutics	Approved for the topical treatment of seborrheic dermatitis in immunocompromised adults and children 12 years of age and older.	US FDA
Sunscreens	**Avobenzone 2%, Ecamsule 2% & Octocrylene 10% Cream** *Anthelios SX®* L'Oréal/ La Roche Posay	This OTC SPF15 broad spectrum sunscreen was approved for photoprotection and the prevention of sunburn.	US FDA

Class	Name/Company	Approval Dates and Comments
Biologics	**Adalimumab** *Humira*® Abbott Pharmaceuticals	The US FDA approved this biologic in February 2007 as a treatment for reducing the signs and symptoms and inducing and maintaining clinical remission in adults with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
Biologics	**Adalimumab** *Humira*® Abbott Pharmaceuticals	In April 2007 a supplemental Biologics License Application was submitted to the US FDA and a Type II Variation was submitted to the European Medicines Agency (EMEA) for approval to treat moderate-to-severe chronic plaque psoriasis.
Vaccines	**Human Papillomavirus Vaccine** *Cervarix*® GlaxoSmithKline	The US FDA received a Biologics License Application in March 2007 for this vaccine to be indicated for the prevention of cervical cancer and precancerous lesions associated with the most common cancer-causing human papillomavirus types. This vaccine is formulated with a proprietary adjuvant system called AS04, containing aluminum hydroxide and monophosphoryl lipid A, which has been shown to provide a stronger and longer lasting immune response.

Drug News

US FDA Cautions Drug Purchasing Online	The US FDA is launching a special web page to warn consumers about the dangers of buying isotretinoin (Accutane®, Roche Pharmaceuticals) online. Isotretinoin is approved for the treatment of severe recalcitrant nodular acne that does not respond to antibiotics. Improperly used, this drug can cause severe side-effects, including birth defects. Serious mental health problems have also been reported with isotretinoin use. The web page, http://www.fda.gov/buyonline/accutane, warns that the drug should only be taken under the close supervision of a physician or pharmacist, and provides links to helpful information, including ways to check that drugs purchased online come from legitimate pharmacies.
Eliminating Chagas Disease	The United Nations World Health Organization (WHO) is joining forces with Bayer HealthCare to expand global efforts aimed at eliminating Chagas, a parasitic disease that affects an estimated 9 million people, mostly children. The expanded WHO programme will be supported by funds and free tablets from Bayer HealthCare, which manufactures nifurtimox, a drug used to treat the disease, and these will allow the treatment of an estimated 30,000 patients over a period of 5 years. The disease is caused by the protozoan parasite, which enters the human body through broken skin, and can be passed on either by the bloodfeeding 'assassin bugs' that emerge at night to bite and suck blood, through transfusion with infected blood, or congenitally from infected mother to fetus. Usually a small sore develops at the site where the parasite enters the body. Within a few days, fever and swollen lymph nodes may develop. This initial acute phase may cause illness and death, especially in young children. However more commonly, patients enter a symptomless phase lasting several months or years, during which time parasites are invading most organs of the body, often causing heart, intestinal and esophageal damage and progressive weakness. In 32% of those infected, fatal damage to the heart and digestive tract occurs during this chronic phase.

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