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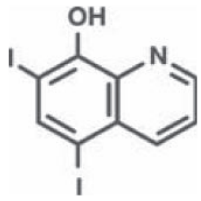
Alcortin®A and Aloquin®:

Topical Anti-infective Efficacy Enhanced with a Unique Delivery System, BAC™

Skin infections may be painful, lead to systemic sepsis and result in cosmetically unappealing scarring. Approximately 18% of patients have "mixed" infections consisting of combinations of bacteria, fungi and/or yeast.[1] Obesity predisposes mixed infections because friction and maceration of intertriginous skin provides fertile territory for fungal, yeast and bacterial colonies.[2] Up to 50% of obese people have cutaneous infections and ~23% have active skin-fold mycosis.[3] There is a clear clinical need for a broad-based anti-infective agent, which targets infectious lesions of unclear or mixed origin and has the ability to prevent infection in vulnerable, irritated skin. Iodoquinol (Figure 1), the anti-infective ingredient in **Alcortin®A** (1% iodoquinol, 2% hydrocortisone-acetate) and **Aloquin®** (1% iodoquinol, 1% aloe polysaccharides) acts by chelating metals[4] from all types of microbes, has no known microbial resistance and has an established history of topical use for common skin infections.

Figure 1



Killing Spectrum and Clinical Trials of Iodoquinol in Alcortin A and Aloquin

Trichophyton mentagrophytes and *Trichophyton rubrum* are the common microbial causes of tinea pedis, tinea corporis and onychomycosis. These dermatophytes can be resistant to antifungal treatments such as ketoconazole, bifonazole, griseofulvin and fluconazole.[5-7] Azoles and terbinafine also show limited effectiveness against *Malassezia* species, including *M. furfur*.[8] *Candida albicans* exhibits resistance to fluconazole, amphotericin-B and voriconazole.[9,10] Resistance is especially prevalent in skin bacteria.[11,12] *Propionibacterium acnes* is often resistant to both tetracycline and erythromycin. Methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa, Corynebacterium aquaticum, Streptococcus species* and *Micrococcus luteus* have shown resistance to common antibiotic classes.[13-17]

In a recent *in vitro* killing assay, 1% iodoquinol (Alcortin A) produced broader and better antimicrobial activity (by 3-log reduction) against fungi and bacteria compared to ciclopirox (Loprox®) and clotrimazole (Lotrisone®).[18] Iodoquinol had stronger and faster killing effects than both ciclopirox and clotrimazole on all fungi tested (*T. mentagrophytes*, *M. furfur*, *Microsporum canis*, *C. albicans*, *T. rubrum* and *E. floccosum*). Iodoquinol also showed the best killing effect against bacteria (*P. acnes*, MRSA, *P. aeruginosa* and *C. aquaticum*). Ciclopirox showed better killing effect on only one organism, *M. luteus*.[18]

Fungicidal Activity Against:
Trichophyton rubrum
Trichophyton mentagrophytes
Epidermophyton floccosum
Microsporum canis
Malassezia furfur
Candida albicans

Bactericidal Activity Against:
Corynebacterium aquaticum
Propionibacterium acnes
Micrococcus luteus
Pseudomonas aeruginosa

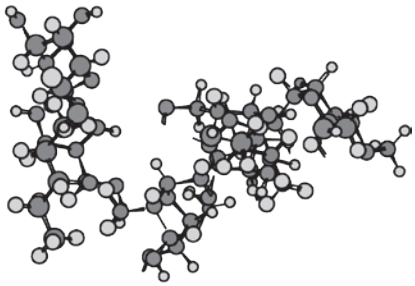
In large-scale, double-blind trials of patients with common dermatoses, iodoquinol and related compounds were effective *vs* placebo.[1,3,19] Presenting conditions varied, and included primary bacterial,

fungal and yeast infections, mixed infections and secondarily infected dermatitoses confirmed by culture. The most common pathogens recovered were *S. aureus*, *C. albicans*, *T. mentagrophytes* and *T. rubrum*. In each of these studies, clinical evaluation of lesion severity and patient ratings of comfort were significantly augmented in patients given an iodoquinol/steroid combination *(improvement rated as excellent or very good in 60-70% of cases)* compared to vehicle following 7-10 days of treatment. Importantly, the addition of the relatively low potency steroid hydrocortisone (HC) did not adversely affect microbiological conversion, suggesting that HC was not simply "masking" an active infection by suppressing active immune responses. A recent case study supported the notion that high potency steroids, even in combination with a topical azole antifungal can mask symptoms of tinea corporis, leading to long-lasting unresolved fungal infection.[20] Infections, especially those on non-intertrigous areas can be successfully treated with **Aloquin**. For infections accompanied by inflammation and/or pruritus, HC-acetate may provide symptomatic relief while the underlying infection is treated by iodoquinol. In such cases, **Alcortin A** would be the preferred option.

The Unique Delivery System in Alcortin A and Aloquin: Biopeptide Aloe Complex™ (BAC™)

Many different chemical solutions have been used to increase the delivery of active ingredients for treatment of a variety of skin disorders. Topically applied drugs can penetrate skin in three basic ways: *via* sweat glands, through hair follicles and sebaceous glands or directly through the stratum corneum. Most polar molecules, such as steroids, penetrate through follicles, sweat and sebaceous glands. Other formulations can aid even polar molecules in penetrating the stratum corneum. These include lipophillic ion pairing, in which charged drugs are complexed with lipids, and super-saturated solutions, in which the solvent containing the drug evaporates on the surface of the skin thereby increasing the effective local concentration of a drug which promotes a greater uptake into the stratum corneum. In addition, complexes with cyclodextrins and liposomes or lipid vesicles can chaperone drugs through the lipid bilayers into the stratum corneum. Finally, lipid disruption with solvents that interact with lipids or keratin (ie., alcohols, DMSO, fatty acids, terpenes, urea) have been shown to increase delivery of topically applied drugs. In all cases, hydration of the area by sealing with barrier such as petrolatum increases the residence of the drugs or drug complexes allowing increased delivery. The patented BAC (palmitoyl-peptide+aloe polysaccharide), contained in **Alcortin A** and **Aloquin (Figure 2)**, represents a unique approach for delivery of actives.

Figure 2



Aloe vera gel is composed of water, proteins, polysaccharides, lipids, simple sugars, fiber and minerals, and is known to soothe burns. A patented specific, highly purified, mannose-rich polysaccharide from aloe gel was shown to have both anti-inflammatory[23-27] and wound healing activity (Figure 2).[28] The purified polysaccharide has been shown to be immunomodulatory,[31-34] and to stimulate fibroblast growth and activity *in vitro*.[31] Additionally, the elegant aloe based vehicle offers many **patient-level benefits**:

- Elegant
- Easily spreadable
- Non tacky
- Non-greasy
- Dries quickly
- Absorbs easily
- Well suited to large BSA, intertriginous or hairy areas.

References

1. Konopka EA, Kimble EF, Zognans HC, and Heymann H (1975) Antimicrobial effectiveness of Locacorten-Vioform cream in secondary infections of common dermatoses. *Dermatologica* 151, pp. 1-8.
2. Hidalgo, LG (2002) Dermatological consequences of obesity. *American Journal of Clinical Dermatology* 3(7), pp. 497-506.
3. Scheinfeld NS (2004) Obesity and Dermatology. *Clinics in Dermatology* 22, pp. 303-309.
4. Healy J, Johnson S, Little MC, and MacNeil S (1998) An in vitro study of the use of chelating agents in cleaning nickel-contaminated human skin: an alternative approach to preventing nickel allergic contact dermatitis. *Contact Dermatitis* 39(4), pp. 171-181.
5. da Silva Barros ME, de Assis Santos D, Hamdam JS. Evaluation of susceptibility of *Trichophyton mentagrophytes* and *Trichophyton rubrum* clinical isolates to antifungal drugs using a modified CLSI microdilution method (M38-A). *J Med Microbiol.* 2007;56(pt 4):514-518.
6. Santos DA, Hamdan JS. In vitro activities of four antifungal drugs against *Trichophyton rubrum* isolates exhibiting resistance to fluconazole. *Mycoses.* 2007;50:286-289.
7. Aly R. Ecology and epidemiology of dermatophyte infections. *J Am Acad Dermatol.* 1994;31(3, pt 2):S21-S25.
8. Velegraki A, Alexopoulos EC, Kritikou S, et al. Use of fatty acid RPMI 1640 media for testing susceptibilities of eight *Malassezia* species to the new triazole posaconazole and to six established antifungal agents by a modified NCCLS M27-A2 microdilution method and Etest. *J Clin Microbiol.* 2004;42:3589-3593.
9. Cowen LE, Sanglard D, Calabrese D, et al. Evolution of drug resistance in experimental populations of *Candida albicans. J Bacteriol.* 2000;182:1515-1522.
10. Sabatelli F, Patel R, Mann PA, et al. In vitro activities of posaconazole, fluconazole, itraconazole, voriconazole, and amphotericin B against a large collection of clinically important molds and yeasts. *Antimicrob Agents Chemother.* 2006;50:2009-2015.
11. Weinstein RA, Nathan C, Gruensfelder R, et al. Endemic aminoglycoside resistance in gram-negative bacilli: epidemiology and mechanisms. *J Infect Dis.* 1980;141:338-345.
12. Gales AC, Jones RN, Turnidge J, et al. Characterization of *Pseudomonas aeruginosa* isolates: occurrence rates, antimicrobial susceptibility patterns, and molecular typing in the global SENTRY Antimicrobial Surveillance Program, 1997-1999. *Clin Infect Dis.* 2001;32(suppl 2): S146-S155.
13. Leyden JJ, McGinley KJ, Cavalieri S, et al. *Propionibacterium acnes* resistance to antibiotics in acne patients. *J Am Acad Dermatol.* 1983;8:41-45.
14. Eady EA, Coates P, Ross JI, et al. Antibiotic resistance patterns of aerobic coryneforms and furazolidone resistant gram-positive cocci from the skin surface of the human axilla and fourth toe cleft. *J Antimicrob Chemother.*2000;46:205-213.
15. Beckwith DG, Jahre JA, Haggerty S. Isolation of *Corynebacterium aquaticum* from spinal fluid of an infant with meningitis. *J Clin Microbiol.* 1986;23: 375-376.
16. Tendler C, Bottone EJ. *Corynebacterium aquaticum* urinary tract infection in a neonate, and concepts regarding the role of the organism as a neonatal pathogen. *J Clin Microbiol.* 1989;27:343-345.
17. Fridkin SK, Hageman JC, Morrison M, et al. Methicillin resistant *Staphylococcus aureus* disease in three communities. *N Engl J Med.* 2005;352:1436-1444.
18. Burnett BP and Mitchell CM. 2008. Antimicrobial activity of iodoquinol 1%–hydrocortisone acetate 2% gel against ciclopirox and clotrimazole. *Cutis* 82:273-280.
19. Maibach HI (1978) Iodochlorohydroxyquin-hydrocortisone treatment of fungal infections. *Archives of Dermatology* 114(12):1773-1775.
20. Oklota CA and Brodell RT (2004) Uncovering tinea incognito. *Postgraduate Medicine* 116(1), pp. 65-66.
21. Simeon A, Wegrowski Y, Bontemps Y and Maquart FX. 2000. Expression of glycosaminoglycans and small proteoglycans in wounds: modulation by the tripeptide-copper complex glycyl-L-histidyl-L-Cu(2+). J Invest Dermatol. 115(6):962-8.
22. Simeon A, Emonard H, Hornebeck W and Maquart FX. 2000. The tripeptide-copper complex glycyl-Lhistidyl-L-Cu(2+) stimulates matrix metalloproteinase-2 expression by fibroblast cultures. Life Sci. 67(18):2257-65.
23. Davis RH, Leitner MG, Russo JM. 1987. Topical anti-inflammatory activity of Aloe vera as measured by ear swelling. J Am Podiatr Med Assoc. 77(11):610-12.
24. Davis RH, Maro NP. 1989. Aloe vera and gibberellin. Anti-inflammatory activity in diabetes. J Am Podiatr Med Assoc. 1989. 79(1):24-6.
25. Davis RH, Leitner MG, Russo JM, Byrne ME. 1989. Anti-inflammatory activity of Aloe vera against a spectrum of irritants. J Am Podiatr Med Assoc. 79(6):263-76.
26. Davis RH, Rosenthal KY, Cesario LR, Rouw GA. 1989. Processed Aloe vera administered topically inhibits inflammation. J Am Podiatr Med Assoc. 79(8):395-7.
27. Davis RH, Parker WL, Samson RT, Murdoch DP. 1991. The isolation of an active inhibitory system from an extract of aloe vera. J Am Podiatr Med Assoc. 81(5):258-61.
28. Davis RH, Leitner MG, Russo JM, Byrne ME. 1989. Wound healing. Oral and topical activity of Aloe vera. J Am Podiatr Med Assoc. 79(11):559-62.
29. Davis RH, Parker WL, Murdoch DP. 1991. Aloe vera as a biologically active vehicle for hydrocortisone acetate. J Am Podiatr Med Assoc. 1991. 81(1):1-9.
30. Davis RH, DiDonato JJ, Johnson RW, Stewart CB. 1994. Aloe vera, hydrocortisone, and sterol influence on wound tensile strength and anti-inflammation. J Am Podiatr Med Assoc. 84(12):614-21.
31. Qiu Z, Jones K, Wylie M, Jia Q, Orndorff. 2000. Modified Aloe barbadensis polysaccharide with immunoregulatory activity. Planta Med. 66(2):152-6.
32. Strickland FM, Pelley RP, Kripke ML. 1994. Prevention of ultraviolet radiation-induced suppression of contact and delayed hypersensitivity by Aloe barbadensis gel extract. J Invest Dermatol. 102(2):197-204.
33. Jia Q, Qiu Z, Jones K, Zhao Y, Burnett BP. 2004. Up-regulating gene expression is a mechanism of action for immunomodulatory properties of a modified A*loe barbadensis* polysaccharide. 23rd International Aloe Science Council Annual Scientific Seminar Communications, 23:5-11.
34. Im SA, Oh ST, Song S, Kim MR, Kim DS, Woo SS, Jo TH, Park IP, Lee CK. 2005. Identification of optimal molecular size of modified Aloe polysaccharides with maximum immunomodulatory activity. International Immunopharmacol. 5:271-9.
35. Davis RH. 1998. Method of using aloe vera as a biological vehicle. US Patent # 5,708,038