INTRODUCING

CSI 0909

Potent Anti-Acne Agent

EXECUTIVE SUMMARY

The Situation

With a prevalence of over 17 million people, acne is the most common skin condition in the United States. Acne is especially problematic for adolescents and young adults with nearly 85 percent of people between the ages of 12 and 24 afflicted with the disorder. Both cause and severity are multifactorial with contributions from microbial infection, inflammation and hormone imbalance.

The Challenge

Current agents for the prevention and treatment of acne include antimicrobials, anti-inflammatories and hormones. However, over the last decade, the emergence of drug resistant bacteria has limited the effectiveness of OTC and prescription drugs for the prevention and treatment of acne[i]. In addition, commonly used antimicrobial and anti-inflammatory agents can often cause skin irritation, dryness and other unwanted side effects[ii].

The Solution

CSI0909 is a broad spectrum antimicrobial plus anti-inflammatory agent that safely and effectively treats bacterial skin infection and the associated inflammation. The product contains Bakuchiol (or drupanol) which has been shown to inhibit the growth of bacteria and to inhibit the COX/LOX inflammatory pathways.

Key Benefits*

- Potent antimicrobial proven to inhibit growth or to sterilize pathogenic microorganisms.
- Balanced inhibition of the COX-1 and COX-2 enzymes Inhibits pro-inflammatory LOX pathway
- Human and *in vitro* safety testing with no adverse effects
- Safe, well-tolerated mixture
- Easily formulated with other ingredients
- Patent pending

* Indications and claims related to the health benefits or property of an ingredient or product are governed in accordance with country-specific laws and regulations. In the United States, it is your responsibility to ensure that product claims and indications are in compliance with all applicable laws and regulations, including the Federal FD&C Act and the FTC Act. In all other countries, please consult with a local regulatory or legal professional who may provide you with competent advice and guidance.

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BACKGROUND

Summary

- Acne is the most common skin disease in the US, affecting 17 million people. Microbial
- infection, inflammation and hormone imbalance contribute to cause chronic acne.
- Current treatment regimens can be ineffective due to increasing drug resistance and lack of compliance due to serious side effects.

What causes Acne?

Acne is a chronic skin disease of the pilosebaceous unit characterized by excess production of sebum by the sebaceous glands, follicular epithelial desquamation, bacterial proliferation and inflammation. Hormone imbalance, microbial infection and inflammation are the major factors associated with the onset of acne[iii].

What is the size of the market?

Acne is most common during adolescence, affecting more than 85% of teenagers, and frequently continues into adulthood. Approximately 1 in 16 or 17 million people in the US suffer from acne. Global sales of acne treatments in 2008 were estimated at $561 million, an increase of 22% from 2003. (Source: Euromonitor)

What are the limitations with existing treatment options?

Current agents for the prevention and treatment of acne include anti-inflammatories, such as salicylic acid, antimicrobials such as benzoyl peroxide and hormonal drugs such as retinoids[iv]. The topical application of an antimicrobial agent, such as benzoyl peroxide[v] in combination with the COX inhibitor salicylic acid[vi] has been clinically demonstrated to be an effective and safe therapy for the treatment of acne. While safe and effective, this treatment regimen produces cutaneous irritation and/or dryness in many affected individuals, which leads to noncompliance, mitigating effectiveness. Additionally, salicylate avoidance is advised during lactation, due to the risk of promoting bleeding in nursing infants[vii] Antibiotics are no longer recommended as first line therapy due to risk of resistance among causative organisms, e.g., Propionibacterium acnes and among commensals, e.g., Staphylococcus epidermidis, Satphylococcus aureus, Streptococccus pyrogenes[viii].

What is the opportunity?

The threat of antibiotic resistant bacteria has prompted interest in natural product antimicrobials with mechanisms of action that do not overlap those of antibiotics. Traditional healers have long used plants and plant derived substances to prevent or cure infectious disease. Many of these plants have been investigated scientifically for antimicrobial activity and a large number of botanical natural products have been shown to inhibit the growth of pathogenic microorganisms. Bakuchiol from Psoralea species is one such antimicrobial botanical. Bakuchiol has been reported as a useful compound for development of antibacterial agents[ix] against oral pathogens and has great potential for use in food additives and mouthwash for preventing and treating dental caries[x].

The major problem preventing the use of bakuchiol compositions extracted from the seeds of Psoralea plants is the presence of psoralen and isopsoralen toxins, Also known as furanocoumarins, psoralens are well known to be phototoxic agents, which increase the sensitivity of skin to ultra violet radiation[xi],[xii],[xiii]. As described in the following pages, our scientists have developed a proprietary[xiv], cost effective process for removing these toxic materials from Psoralea extracts, while maintaining the desired Bakuchiol antimicrobial activity in high yield.

PRODUCT PROFILE

What is ?

CSI0909 is a broad spectrum antimicrobial plus anti-inflammatory agent that safely and effectively treats skin infection and the associated inflammation. **CSI0909** contains Bakuchiol (or drupanol), a well-documented broad spectrum antimicrobial and anti-inflammatory, extracted from *Psoralea* plants (*Psoralea corylifolia* or *Psoralea glandulosa*) using a proprietary (patent pending) process that eliminates toxic coumarin contamination**. **CSI0909** has been shown in both human and *in vitro* studies to inhibit the growth of bacteria implicated in acne and to significantly reduce inflammation.

Key Benefits*

- Potent antimicrobial proven to inhibit growth of pathogenic microorganisms.
- Balanced inhibition of the COX-1 and COX-2 enzymes Inhibits pro-inflammatory LOX pathway
- Human and *in vitro* safety testing with no adverse effects
- Safe, well-tolerated mixture without coumarin contamination**
- Easily formulated with other ingredients
- Patent pending

Plant Origin

Contains a unique form of Bakuchiol (or drupanol) derived from the seeds of *Psoralea corylifolia* or *Psoralea glandulosa*

Applications

Potent anti-acne agent for addressing microbial infection and inflammation

Formulation

Can be used as an active agent in topical skincare products

Physical Properties

Brownish-red viscous liquid and dissolves in ethanol and other common organic solvents

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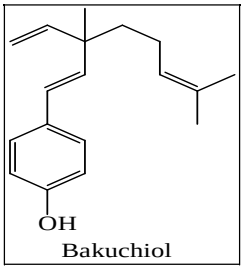
**NMT 100 PPM

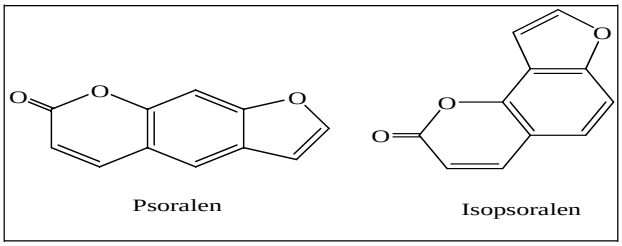
DISCOVERY PROCESS

Bakuchiol (or drupanol) is a phenolic compound having a single hydroxyl group on the aromatic ring and an unsaturated hydrocarbon chain (see structure below). It has been isolated from the seeds of *Psoralea. corylifolia* L. (Luguminosae) and the aerial part of *Psoralea. glandulosa* L. (Papilionaceae).



Bakuchiol

Bakuchiol compositions isolated from plants in the *Psoralea* genus include the presence of psoralens, such as psoralen and isopsoralen. Psoralens, also known as furanocoumarins, are naturally occurring secondary metabolites in plants, including many fruits and vegetables.



Psoralen Isopsoralen

A number of health risks have been associated with the handling, topical application and ingestion of psoralen-containing plants and synthetic psoralens. Psoralens are well known to be phototoxic agents, which increase the sensitivity of skin to ultra violet radiation. Unlike other Bakuchiol preparations, our Company's proprietary **CSI0909** composition is produced by a patent pending process that removes harmful Psoralens to a level not more than 100PPM.

PRE-CLINICAL EFFICACY DATA

Summary

- **CSI0909** shows broad spectrum anti-microbial activities with MIC at single digit ppm concentration.
- **CSI0909** shown to inhibit COX1/COX2 pro-inflammatory pathways.
- **CSI0909** also inhibits pro-inflammatory 5-LOX pathway

ANTI-MICROBIAL ACTIVITY

Table 1: Anti-Microbial Activity of CSI0909

ORGANISM	CLASS	CONCENTRACTION	POSITIVE CONTROL/ CONCENTRATION
Propionibacterium acnes (ATCC6919)	Anaerobe	1ug/ml	Ampicillin (0.1 ug/ml)
Staphylococcus epidermis ATCC 12228)	Gram Positive	1ug/ml	Gentamicin (0.1 ug/ml)
Trichophyton mentagrophytes (ATCC 9533)	Fungi (mammalian)	30ug/ml	Amphotericin B Solubilized (0.1 ug/ml)
Staphylococcus aureus (ATCC10390)	Gram Positive	3ug/ml	Gentamicin (0.3 ug/ml)
Actinomyces viscosus (ATCC 15987)	Anaerobe	3ug/ml	Ampicillin (0.03 ug/ml)
Aspergillus niger (ATCC 8740)	Fungi (general)	30ug/m	Amphotericin B Solubilized (0.3 ug/ml)

Additional testing on **CSI0909** antimicrobial properties was conducted to test activity against gram positive organisms associated with respiratory tract infections, *Streptococcus pyogenes* (ATCC 19615) and *Streptococcus pneumoniae* (ATCC 6305).

The MIC (lowest concentration of test substance that completely inhibited visible organism growth) and the MBC (the lowest concentration that demonstrated no recoverable growth of test organism) was determined, as shown in **Table 2**.

Table 2: Anti-Microbial Activity of CSI0909

Test Substance Identification	Test Organism	MIC (Test substance concentration)	MBC (Test substance concentration)
CSI0909	*Streptococcus pyogenes* (ATCC 19615)	1.56 ug/mL	3.13 ug/mL
	Streptococcus pneumoniae (ATCC 6305)	0.78 ug/mL	1.56 ug/mL

ug = microgram

CSI0909 activity meets the current FDA guidelines for penicillin in the treatment of pneumoccocall pneumonia. (www.fda.gov/cder/foi/label2008/050638s012lbl.pdf)

penicillin	Susceptible(S)	Intermediate(I)	Resistant (R)
MIC (ug/ml)	<2	4	8

ANTI-INFLAMMATION OF CSI0909

Table 3: Inhibition of COX and LOX Enzymes by CSI0909

Compound Name	COX-1 (IC_{50})	COX-2 (IC_{50})	5 LOX (IC_{50})
MH-258-08 (99% bakuchiol)	2.34 μM	5.78 μM	3.41 μM

The COX-1 and COX -2 activity of **CSI0909** listed above compared to published activity of aspirin at COX-1 IC_{50} =0.35 μM and COX-2 IC_{50} at 2.4μ M demonstrates that **CSI0909** has a good anti-inflammation profile.[xv]

CLINICAL DATA

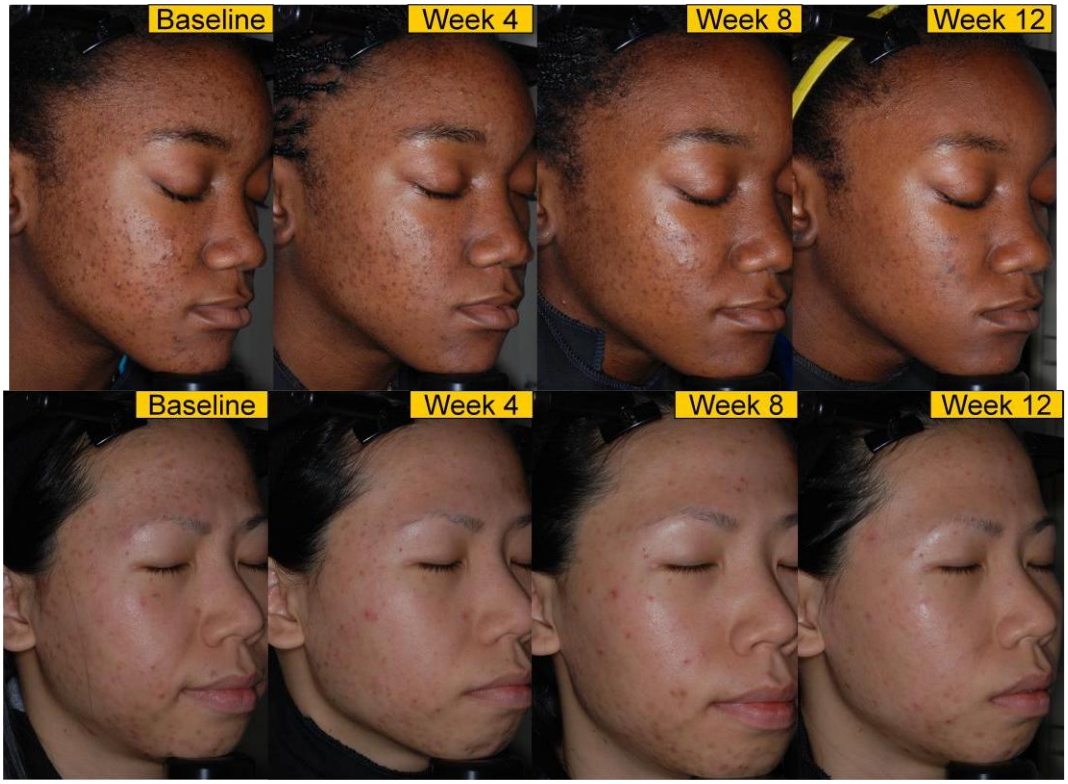
Clinical Evaluation

A pilot, open label study to evaluate the antimicrobial and anti-inflammatory properties of **CSI0909** 0.5% is currently on going. The study will recruit a least 15 subjects meeting the exclusion /inclusion criteria for a study duration of 12 weeks. The subjects are instructed to apply the cream twice a day, morning and night, and return to the site for a total of 9 visits including the screening visit.

The efficacy evaluation is based on the Investigator Assessment, Global Response to product (relative to baseline).

The following evaluation procedures are included in the study, Subject questionnaires, Physician, Global Assessment, Lesion Counts, Safety and Tolerability and photographs at baseline, Week 4, Week 8 and Week 12.

Photos of two study participants who have completed the 12 week study protocol are shown below. Substantial clearing of affected facial skin sites is clearly evident in both subjects with progressive improvement seen with increasing exposure to the **CSI0909** cream.



SAFETY DATA

Summary

- **CSI0909** shows no eye irritation, no skin irritation and no skin allergic contact sensitization, and no phototoxicity.
- **CSI0909** has a solid safety profile at a broad range of purity levels (20% to 99% purity).
- **CSI0909** has a good skin penetration

Several safety tests were performed. Tests are listed with results in **Table 4** below.

Table 4: Safety tests revealed that CSI0909 has a solid safety profile

NAME	BRIEF DESCRIPTION OF THE TEST PROCEDURE	RESULT
AMES	This is a biological assay to assess the mutagenic potential of chemical compounds. The test uses strains of the bacterium that carry specific mutations. The variable being tested is the mutagen's ability to cause a reversion of these mutations.	Test product was not associated with any mutagenic changes at doses up to 3 mg/plate
EPIOCULAR MTT VIABILITY ASSAY	This is a biological assay to evaluate ocular toxicity or irritating potential of a test article by determining the ET50 for MTT viability of EpiOcular samples.	Test Product at the 1% concentration was classified as minimal to non-irritating category.
CHAMBER SCARIFICATION	This is a clinical test to assess the irritating potential of chemical compounds. The test is performed on human subjects whose skin was sensitized by scratching. The variable being tested is the compound's ability to cause irritation of compromised skin.	The effects of 0.5% of the test product on scarified skin were comparable to the saline control at 72 hours
REPEATED INSULT PATCH	This is a clinical test to assess both irritating and allergenic potentials of chemical compounds. The test is performed by repetitive application of the compounds to the skin of healthy volunteers. The variables being tested are the compound's ability to cause erythema or edema.	Under study conditions the test product did not indicate a potential for dermal irritation or allergic contact sensitization.
PHOTO-TOXICITY	This is a clinical test to assess phototoxic potential of test compounds. The test is performed on human subjects by application of the compounds to the skin, followed by UV-irradiation, and up to 1 week post-irradiation period. The variables being tested are the compound's ability to cause adverse or unexplained reactions.	The test product was considered non-phototoxic according to reference at 0.5% concentration tested.
PERCUTA-NEOUS ABSORBTION	This is an ex-vivo test to assess skin penetration of chemical compounds. The test is performed by single application to cadaver skin. The variable being tested is percentage of test compound that is absorbed into skin over certain period of time.	At 0.5% formulation, the data indicates a good penetration profile and absorption into skin over 48 hours

SPECIFICATIONS & OTHER INFORMATION

Available upon request – Please contact your representative

SCIENTIFIC REFERENCES/BIBLIOGRAPHY

Additional reference on antimicrobials

Species	MIC(ug/ml) Bacteriostatic	Sterilizing Conc (ug/ml)Bactericidal
Streptococcus mutans (JCM5175)	1	20
Streptococcus mutans (GS5)	1.2	20
Streptococcus mutans (JC2)	1.4	5
Streptococcus mutans (IFO 13955)	1.8	10
Streptococcus sobrinus 6715	1.6	10
Phorphyromonas gingivalis(ATCC 33277)	4	20
Enterococcus faecalis (IFO 3989)	2	10
Enterococcus faecalis (IFO 3926)	2	10
Lactobacillus acidophilus(AKU 1122)	1	10
Lactobacillus acidophilus(AKU 1124)	1	5
Lactobacillus plantarum (AKU 1130)	1	5
Streptococcus sanguis (179-3)	ND*	10
Streptococcus sanguis (254-4)	ND	5
Streptococcus salivarius (70-2)	ND	5
Streptococcus salivarius (160-2)	ND	5
Actinomyces viscosus (19246)	ND	5
Lactobacillus plantarum (AKU 8016	ND	20
Lactobacillus casei (4646)	ND	5
	* ND, not determined	

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[iii] Toombs (2005) Dermatol. Clin. 23(3):575-581; Nishijima et al. (2000) J. Dermatol. 27(5):318-323

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[xi] Epstein, Semin. Cutan. Med. Surg. 1999: 18(4);274-284

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