

CLINICAL TRIAL SUMMARY

Phase III Clinical Trial - Dynamiclear Topical Solution

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Phase III Clinical Trial conducted by Apothecaries Clinical Research, 579, Devli, East Sainik Farms, New Delhi 110 062.
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CLINICAL TRIAL ORGANIZATION (CRO)

Apothecaries Clinical Research

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INVESTIGATOR SIGNATORY:

This report represents a description of the results of the study carried out by the listed Investigators. The study has been carried out in compliance with the ICH - GCP, "Guidelines for Clinical Trials on Pharmaceutical Products in India GCP Guidelines" issued by Central Drugs Standard Control Organization, Ministry of Health, Government of India, the ICMR guidelines on clinical trials and all the pertinent regulatory requirements in India. As a part of the compliance, the trial was conducted in accordance with the ethical principles originating from the Declaration of Helsinki. All the study personnel assisting in the conduct of study were informed regarding their obligations.

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1. STUDY SYNOPSIS

STUDY TITLE: A Prospective, Randomized, Multicenter, Comparative, Open label study to evaluate the Safety, Tolerability and Efficacy of Dynamiclear Topical Solution in patients suffering from Herpes Simplex Infection (HSV 1 & HSV 2) aged between 18 and 55 years.

PROTOCOL #: SC/111/06; Version 07, 31 May 06

STUDY PERIOD: June 2006 to December 2006.

REPORT DATE: August 2007

CLINICAL PHASE: III

STUDY PRODUCT: Dynamiclear Topical Solution

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1.1 INTRODUCTION

The Herpes simplex viruses comprise of 2 distinct types, HSV-1 and HSV-2. HSV-1 causes oral lesions in approximately 80% of cases and genital lesions in 20% of cases. The reverse is true for HSV-2, which causes genital lesions in 80% and oral lesions in

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20%. Herpes viruses cause a wide range of diseases, including the following:

- Gingivostomatitis
- Keratoconjunctivitis
- Encephalitis
- Genital disease
- Newborn infection

Primary infection

Primary infections are usually mild and in many cases asymptomatic. Patients who are immunocompromised may develop severe infections involving multiple organ systems. Immunocompetent individuals may also have severe primary infections.

Latency and recurrence

After the patient begins to produce antibodies, the infection becomes latent in the sensory ganglia. HSV-1 infection remains latent in the trigeminal ganglia, and HSV-2 in the sacral ganglia. The viruses become reactivated, secondary to certain stimuli, including fever, physical or emotional stress, ultraviolet light exposure, and axonal injury.

Recurrent infections tend to be less severe because of existing cellular and humoral immunity from prior exposures. Infection by HSV requires a break in the skin's barrier; intact skin is resistant to the virus.

Frequency

1. In the US: Approximately 70-90% of adults have antibodies to HSV-1, whereas antibodies to HSV-2 are found in approximately 22% of the population.
2. In sexually transmitted disease (STD) clinics, HSV-2 seropositivity approaches 40-50%.
3. Encephalitis develops in 1 per 250,000 to 500,000 patients per year.

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4. Neonatal HSV develops in 1 per 2,000 to 10,000 live births per year. The risk of maternal transmission is increased if vaginal delivery occurs when the mother is suffering from primary infection.

Mortality / Morbidity

Most cases of herpetic infection are limited to patient irritation and discomfort.

1. Infection occasionally may become life threatening.
2. Patients who are immunocompromised are at increased risk of developing severe HSV infections.

HSV-1 is a common cause of fatal encephalitis in the US. Mortality rate for encephalitis is 60-80%. Less than 10% of patients are left without significant neurological sequelae.

Keratoconjunctivitis may be caused by HSV-1. It is second to trauma as a cause of corneal blindness in the US.

Race

HSV-2 antibodies are present in approximately 20% of Caucasian adults and 65% of African American adults.

Sex

Men are 20% more likely to develop recurrences of HSV-2 than women.

Age

- Highest incidence of HSV-1 occurs in children aged 6 months to 3 years.
- HSV-2 most commonly occurs in those aged 18-25 years.

History

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Infection begins with chronological development of symptoms. First, the prodrome occurs, and then lesions appear along with constitutional signs and symptoms. The lesions coalesce, and tender bilateral lymphadenopathy develops. Lesions usually heal over the next several weeks. Lesions usually are vesicular or ulcerative on an erythematous base and are very painful. Many primary infections are asymptomatic. Recurrent lesions are common.

- Patients may give a history that includes the following:
 1. Occupational exposure
 - i) Herpetic whitlow, found in health care workers (especially medical or dental)
 - ii) Herpes gladiatorum on bodies of wrestlers
- Previous history of herpetic diseases
- Apparently undiagnosed episodes
- Immune status
 1. HIV
 2. Malnourishment
 3. Hematological malignancies
 4. Bone marrow
 5. Renal transplant
 6. Cardiac transplant
- Neurological symptoms
 1. Headache
 2. Confusion
 3. Fever

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- Lesions
 1. Location varies
 2. May be very painful
 3. Tenesmus, itching with anal/perianal lesions
 4. Dysuria with genital lesions
 5. Sore throat with oral lesions
- Constitutional symptoms (usually present with development of herpes lesions)
 1. Anorexia
 2. General malaise
- Prodromal symptoms (present in advance of herpes lesions)
 1. Burning
 2. Itching

PATHOPHYSIOLOGY

HSV-1 infections spread either by respiratory droplets or by direct exposure to infected saliva. HSV-2 usually is transmitted via genital contact.

Herpes viruses cause cytolytic infections; therefore, pathological changes are due to cell necrosis as well as inflammatory changes. Fluid accumulates between the dermis and the epidermal skin layers and causes vesicle formation. Then fluid is absorbed, scabs are formed, and healing is completed without evidence of scarring. Shallow ulcers form after the vesicles rupture on mucous membranes.

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1.2 PRODUCT CLAIM

Dynamiclear is a topical antiseptic for infectious skin lesions and is found to be very effective against the herpes virus. Dynamiclear offers confidence in controlling the outbreaks and in some cases users have reported that they have not had any further outbreaks after using Dynamiclear.

Long and short term sufferers have reported dramatic relief from symptoms of herpes and cold sores after using Dynamiclear. It has been shown to improve the quality of life, alleviating discomfort of cold sore and herpes breakouts.

With the application of Dynamiclear, the infected area will immediately begin to dry out and wound begins to heal, speeding up the recovery time dramatically. If symptoms return, the recurrence is typically less severe and far less frequent, with longer intervals between each outbreak. Frequency of recurrences reduce with each application and it is reported in many cases that little to no further symptoms occur after treatment.

Dynamiclear is a natural remedy to be used by human beings as a topical antiseptic in following conditions:

Herpes Simplex Infedction, Tinea, Cold Sores, Open Wounds, HIV skin lesions, Psoriasis lesions, any form of skin lesion that's caused by bacterial or viral activity.

1.3 OBJECTIVES: The objectives of the study were to evaluate the safety, tolerability and efficacy of Dynamiclear as a therapy for the treatment of Herpes Simplex infection (HSV 1 & HSV 2) in adult patients.

1.4 STUDY DESIGN: Multi-center, Prospective, Randomized, Comparator-controlled, Open-labeled study.

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1.5 RATIONALE OF STUDY DESIGN AND PLAN:

1.5.1 This trial was a prospective, randomized, multi-center, comparative, open label clinical trial. Patients had received their medication on an out-patient basis.

No blinded comparator product (placebo or active formulation) was available for the study. Blinding was considered not feasible without placebo, as the formulations and dosage forms of IP and comparator were completely different. While IP was a topical solution, the comparator product was a topical cream available in the market. Besides, any placebo solution would also have contributed to local soothing effect, altering the perception of itching, burning and stinging sensations, thereby skewing local cutaneous assessments. At each site, only investigator himself assessed all the patients throughout the study.

1.5.2 Patients with diagnosis of Herpes simplex infection (HSV1 or HSV2) who were eligible to receive the therapy as per the inclusion criteria were included in the study. The trial had enrolled 149 herpes simplex patients (HSV 1 & HSV 2) aged 18-55 years, having active lesions on external genitalia and skin. Subjects were randomized into two groups (A and B).

1.5.3 Subjects in Group A applied investigational product (Dynamiclear Topical Solution) by taking 2-4 drops (depending upon the affected area) to a wet cotton swab (enough to saturate it) on the affected part only once at clinic while in Group B, 0.5 - 1.5 grams of the comparator article (Acyclovir 5% cream) was applied five times daily to cover the affected area for 7 days.

The study assessed the safety, tolerability and efficacy of Dynamiclear Topical Solution as a therapy for the treatment of Herpes Simplex (HSV 1 & HSV 2) in adult patients.

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1.6 NUMBER OF PATIENTS: 149 (75 on Investigational Product and 74 on Comparator Product)

1.7 DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Patients between 18 to 55 years of age, presenting with symptoms of Herpes Simplex Infection HSV 1 & HSV 2 (lesions on external genitalia and skin).

1.8 TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION:

1.8.1 Investigational Product (IP):

Single Dose Topical Application;

1. Cotton swab was immersed in water and lightly squeezed out to remove most of its water,
2. 2-4 drops of IP (depending upon the affected area) were transferred to the cotton swab (enough to saturate it).
3. The cotton swab was then applied to the location of active condition making sure the entire lesion was swabbed thoroughly with Dynamiclear.

1.8.2 Comparator Product:

Five times daily application; 0.5 to 1.5 gm of Acyclovir 5% cream was applied on the affected area.

1.9 DURATION OF TREATMENT: Single application of investigational product, 7 days application of comparator product.

1.10 CRITERIA FOR EVALUATION: Safety evaluations consisted of vital signs, clinical laboratory investigations (chemistry, hematology, and urinalysis), physical examination findings and occurrence of adverse events. The efficacy evaluations consisted of local cutaneous evaluations i.e. assessments of erythema, induration,

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itching, vesiculation and stinging sensation besides the assessment of crust/scab formation in ulcers and disappearance of pain.

1.11 STATISTICAL METHODS:

1.11.1 Test of Hypothesis: In this trial the study population was calculated on the hypothesis that the difference between the two treatments was 30%, with the group on study drug showing more efficacy than the comparator group. The results of the treatment group were evaluated to test the “null hypothesis” that there is no difference between the treatment groups in all the safety, tolerability and efficacy parameters.

1.11.2 Safety: Safety parameters were assessed statistically as well as clinically including adverse events and laboratory values. All tabulations regarding safety parameters were displayed using treatment received approach.

1.11.2.1 Laboratory Safety

Predefined clinically significant limits of change are the primary display of results for the laboratory safety parameters. A patient has been considered as having a clinically significant laboratory abnormality if:

- Any of his/her values fell outside the predefined limits and;
- That value was more abnormal than the baseline value.

1.11.3 Efficacy: The main efficacy evaluation was based on the following efficacy endpoint evaluations measured at different time points:

1. Appearance of crusting or healed rash of Herpes.
2. Disappearance of pain.
3. Local cutaneous assessments such as erythema, induration, itching, vesiculation and stinging sensation.

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1.11.3.1 Comparison of proportion of the efficacy parameters between the treatment were done using the Chi – Square test. The results were reported as proportion at different time points and the difference in the proportion of change (95% CI) over a period of time for all the efficacy parameters between the two treatment groups and OR (95% CI) by using logistic generalized estimating equation.

1.11.3.2 LOCF (last observation carry forward method) was applied for the handling of the missing data.

1.11.3.3 Adjustment of covariates was not done for the efficacy analysis as well as safety parameters since these covariates were balanced in both the groups.

1.11.3.4 Subjects' demographic and screening characteristics were summarized for the cohort of the subjects evaluable for the efficacy and the safety analysis. These demographic characteristics were then reported in tables.

1.12 SUMMARY- CONCLUSIONS:

1.12.1 Efficacy Results: In this multicenter, randomized, prospective, open label study to evaluate the efficacy of Dynamiclear in the treatment of Herpes Simplex (Type 1 & 2) in adult patients, a total of 149 patients were analysed. In all the efficacy parameters, significantly higher percentage of patients in the Dynamiclear group were relieved of symptoms after single application of the drug by both ITT and PP analysis.

1.12.2 Safety Results: The overall safety of the Dynamiclear is assessed in 75 patients who received single dose of the drug.

CONCLUSION: This study establishes the safety, tolerability and efficacy of Dynamiclear for symptomatic management of Herpes Simplex Infection (HSV 1 and HSV 2) in adult patients.

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