Drug Corner

Safety & Efficacy of the FLUCOLD Uncoated Tablet in the Treatment of Common Cold and Flu Syndrome : Postmarketing Surveillance Study

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Background : Common cold and flu syndrome generally affects the upper respiratory tract in alliance with a low fever and some systemic symptoms such as sore throat, cough, nasal decongestion headache, etc. Different clinical studies showed that a combination of analgesics, antihistaminic and decongestant offers better symptomatic relief in the common cold. The current post-marketing surveillance study was conducted to investigate the safety and efficacy of marketed FLUCOLD tablets in the Indian population.

Methodology : In a prospective, interventional, single arm, multicenter, post-marketing clinical study 200 subjects were included out of which 199 completed the study. All patients were treated with FLUCOLD uncoated tablets for three days and follow-up performed for the next 6 days. The incidence of Adverse Events (AE) and Serious Adverse Events (SAE) was evaluated during the study. Efficacy of FLUCOLD uncoated tablet assessed by using VAS score changes from baseline to end of the treatment. The safety of the product was also assessed by evaluating blood biomarkers such as hemoglobin, platelet, SGOT, SGPT, and creatinine level.

Results : Results show the reduction in symptomatic score of common cold and flu syndrome observed after 3rd follow-up visit (11.141 ± 5.564 to 2.663 ± 3.699). During the study, no intervention-related adverse events were observed. Furthermore, no Serious Adverse Events (SAE) were observed during the study and follow-up period. No changes in levels of the blood biomarkers (Hemoglobin, Platelet, SGOT, SGPT and Creatinine) were observed in the study.

Conclusions : FLUCOLD tablet is safe and effective in the treatment of common cold and flu syndrome in the Indian adult population.

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***Key words* : FLUCOLD tablet, common cold, flu syndrome, congestion, haemoglobin, etc.**

Acute respiratory infections are frequent in the general population, with common cold, flu-like syndromes, tracheobronchitis, sinusitis, laryngitis, and pneumonia being among the most common. When the etiology is suspected to be bacterial, medications and symptomatic alleviation are used. The most prevalent clinical entities, common cold, and flu-like sickness, both have a viral etiology, therefore symptomatic therapy is still the conventional approach in most situations. In medical practice, the common cold is the most prevalent sickness[1]. It generally affects two to four times a year and leads to 40% of work absences among the adult population.

The cold and flu syndrome usually disturbs upper respiratory airways in combination with low-grade fever and one or more symptoms such as dysphonia, throat, cough, nasal decongestion, sore throat, headache, etc. Symptoms of the syndrome generally reach to peak at 2 to 3 days with a mean duration of 7 to 10 days[3,4]. The flu-like syndrome is characterized by the sudden appearance of headache, fever, sore throat, nasal congestion, loss of appetite, and weakness. If remained untreated, complications like otitis, pneumonia, sinusitis may appear[4].

The medical treatment options available for the common cold are anticholinergics, antihistaminic, alpha-adrenergic agonist, NSAIDS, ascorbic acid, zinc & herbal medications. The clinical study was conducted to investigate the effect of high doses of Vitamin C in common cold treatment and found that no clinical benefits were shown by Vitamin C in common cold[5]. In another study, the effect of *Echinacea purpurea* on the common cold was evaluated and no clinical benefits were observed during the study[6-8].

In Cochrane meta-analyses, the symptomatic treatment of the common cold has been assessed. The first meta-analyses examined the use of

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antihistamines in the treatment of the common cold and comprised 32 trials with a total of 8930 individuals. Monotherapy did not affect symptoms in either children or adults, according to the findings[9]. The results of the combined antihistamines and decongestants may improve symptoms in the adult population, but the results are diverse[8,10]. In another investigation, meta-analyses show that the combination of antihistaminic, decongestants, and analgesics provided some benefit in adults and children[11].

The majority of influenza infections necessitate the use of medications to alleviate symptoms. Treatment focused on targeting the etiological agent is not common in clinical practice, although it has become much more common after the 2009 H1N1 pandemic [12].Because of the epidemiological importance and severity of symptoms of flu-like syndromes and the common cold, patients continue to take drugs that provide symptomatic relief.

The current study investigated the safety and efficacy of FLUCOLD tablet [Fixed dose combination of paracetamol (500 mg), phenylephrine (10 mg), and chlorpheniramine maleate (2 mg)] in the treatment of common cold and flu syndrome in the adult population.

Currently, no clinical trial assessed for the efficacy and safety of FLUCOLD tablet or fixed-dose combination for common cold and flu syndrome in an adult. This was the first clinical trial conducted in India designed to assess the adverse events associated with fixed-dose combination.

Material and Methods

Study Design & Participant :

We conducted a prospective, interventional, single-arm, multicenter, post-marketing clinical study to determine the efficacy & safety of the FLUCOLD tablet. A total of 200 eligible participants with common flu and cold symptoms were included in the study. At the end of the study 199 participants were treated with FLUCOLD tablets(one tablet four hourly for three days) & completed the study. The total duration of the study for the patient was 9 days (03 days medications with 6 days of follow-up).

Patients or their families were asked to fill the printed questionnaire form in relation to the study. Informed consent to participate was obtained from all participants. Study was conducted in accordance with the ICMR guidelines, New Drugs and Clinical Trial Rules 2019 India, & the Declaration of Helsinki (Brazil 2013) & the ICH E6, R2, "Guidance on Good Clinical Practice" (GCP). Furthermore,the trial was approved by Royal Pune Independence Ethics Committee, Prakash Institutional Ethics Committee & SPARSH Hospital Institutional Ethics Committee(ICBio/CR/WPPL/0309/110).

Inclusion Criteria :

The study comprised the volunteers of both genders aged between 18 to 55 years who are presented symptoms less than 72 hours. The common cold was described by the following symptoms: sneezing, rhinorrhea, nasal congestion, headache, muscle pain, discomfort in the throat, sore throat, dysphonia, cough, fever, the latter being of moderate to severe intensity through a symptom severity scale of 4 points (0 = none, 1 = mild, 2 = moderate, 3 = severe). The flu syndrome should consist of a fever of at least 38.1°C and a headache of moderate or severe intensity or myalgia/arthralgia moderate or severe using a scale of severity of symptoms of 4 points (0 = none, 1 = mild, 2 = moderate, 3 = severe).

Exclusion Criteria :

Subjects were excluded form the study if they met any of the following condition: Patients who are not willing to give written informed consent; any known hypersensitivity to the study products; any history of seasonal or perennial allergic rhinitis; patients who have taken treatment for the presenting symptom within 7 days of screening; any history of drug abuse/chronic alcoholism; use of monoamine oxidase inhibitors or barbiturates; use of Vitamin C/ascorbic acid or taking supplements or fruits rich in vitamin C; Presenting the diagnosis of any disease activity in acute or chronic disease exacerbated (uncompensated), including hypertension, ischemic heart disease, narrow- angle glaucoma, symptomatic prostatic hyperplasia, chronic renal failure, liver diseases, infectious tracheobronchitis presumably bacterial pneumonia, pharyngitis strep, asthma or chronic obstructive pulmonary disease and any disease or condition that in the opinion of the investigator can modify the results of their study is not due to the drug under investigation or that puts the patient at significant risk; Patients who received influenza vaccine within 7 days of screening; patients who in the opinion of attending physician may need to receive antibacterial drugs for the treatment of acute respiratory infection; any lab findings or clinical findings that in the opinion of treating physician may appear as risk to the patient; participation in any clinical trials within 12 months of screening; any finding of clinical observation (clinical history or physical examination) that is interpreted by the physician investigator as a risk to the patient's participation in the study; severely immune compromised patients; patients with positive serology laboratory values; use of any investigational drug currently or within 30 days prior to study entry.

Participant Removal or Withdrawn Criteria :

The patient can be withdrawn from the study by the investigator for any of the following : occurrence of an adverse event associated with the administration of the IP and requiring its cancellation; the emergence of any diseases or conditions during the study that worsens the prognosis of the patient, as well as makes it impossible for the patient to continue his/her participation in the clinical study; the need for a forbidden concomitant therapy; pregnancy of the patient; violation of the study protocol; improper inclusion of the patient who did not meet the inclusion criteria and/or met the relevant exclusion criteria; other violations of the protocol, which, according to the investigators, are significant; withdrawal of the informed consent by the patient. One subject withdrew his consent because of a personal problem.

Recruitment :

Suitable subjects, who agree to participate in the study were recruited from 3 sites (Jyothi Multispecialty Clinic, Prakash Institute of Medical Science & Research & SPARSH Hospital). Each site recruited the participants who have voluntarily visited each trial site for enrollment.

Intervention :

After selection of the subjects, all were treated with FLUCOLD uncoated tablet (consisting of a fixed-dose combination of Paracetamol 500 mg + Phenylephrine HCl 10 mg + Chlorpheniramine maleate 2 mg) (Wallace Pharmaceutical Pvt. Ltd.) for three days and follow up of performed for the next 6 days (Fig 1).

Outcome Measures :

Primary outcome measure —

To evaluate the safety of fixed-dose combination of Paracetamol 500 mg + Phenylephrine HCl 10 mg + Chlorpheniramine maleate 2 mg uncoated tablet of Wallace Pharmaceutical Pvt Ltd in the treatment of common cold and flu syndrome in the adult population. Treatment-Emergent Adverse Events (TEAE) and serious adverse events were assessed during the study.

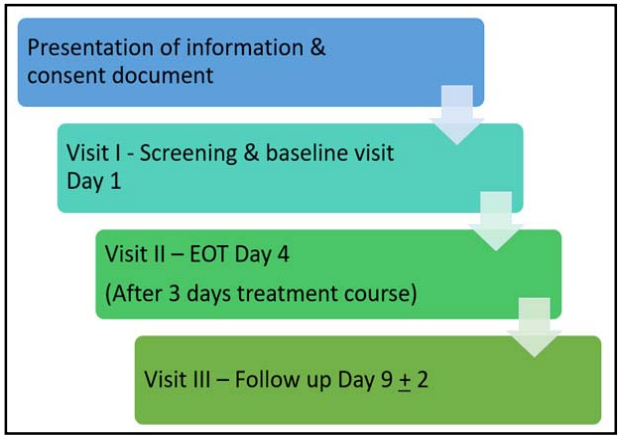

Fig 1 — Study Flow Chart

Secondary Outcome Measures :

Secondary outcome measurement includes assessment of symptomatic relief of common cold and flu syndrome, changes inthe Visual Analogue Score (VAS) from baseline to end of the treatment & assessment of safety of FLUCOLD (Biomarker evolution such as hemoglobin, platelet, SGOT, SGPT and serum creatinine).

Statistical Analysis :

A statistical analysis of the data was performed using statistical software SAS version 9.1 INC, CARY, USA. Descriptive statistics were presented for all continuous efficacy and safety indicators obtained during the study and frequency distribution is presented for all categorical variables available in the data. To test the hypothesis of significance, change from baseline to end of the treatment, the ANOVA and $\div^2$ test was used (for internal parameters with normal distribution in the population under consideration). Efficacy analysis was performed for the per-protocol (PP) population. Primary efficacy was based on PP patients' samples.

Results

During the study, total of 200 patients were enrolled in the study from 3 sites out of which 1 patient withdrew from the study (Fig 2).

The mean age of the participants included in the study was31.9 ± 8.5 years whereas average weight & height was 63.61 ± 11.18 kg & 162.19 ± 6.240 cm respectively. The average BMI calculated during the study was found to be at 24.139 + 3.81 kg/m^2 (Table 1).

During the study, no intervention-related adverse events were observed. Furthermore, no Serious Adverse Events (SAE) were observed during the study and follow-up period.

The assessment reduction in total symptom score from day 1 to day 4 and follow-up visit was performed by using a 4-point scale (0- no symptom, 1-Mild, 2-Moderate, 3-severe). The statistical difference was observed in scores from baseline to end of treatment (significance at 0.05). The reduction in symptomatic score of common cold and flu syndrome was observed after 3rd follow-up visit (11.141 ± 5.564 to 2.663 ± 3.699) (Fig 3).

Visual Analog Score (VAS) was used to assess the effect of the intervention on the severity of the common cold and flu syndrome. The VAS score was

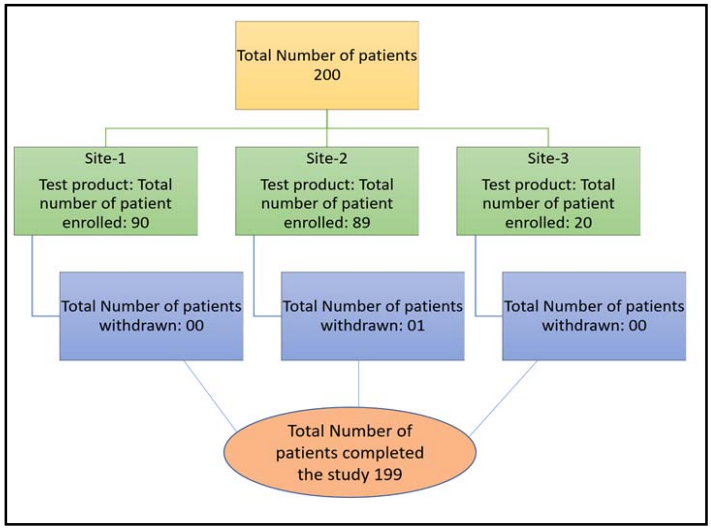

Fig 2 — Deposition of the patient

Table 1 — *Demographic data of the patient*

Statistics	Age (in years)	Weight (in Kg)	Height (in cm)	BMI (kg/m-2)
N	199	199	199	199
MIN	18	36	146	13.3
MAX	55	106	182	34.3
MEAN	31.930	63.614	162.196	24.139
STD	8.569	11.180	6.240	3.810

found to be decreased after the intervention in visit 2 (5.472 ± 0.920 to 2.111 ± 1.132) (P< 0.001). Findings showed that statistically significant difference was observed from baseline to End of the Treatment (EOT) for VAS score (Fig 4).

During the study, subject-wise data for intervention tolerability was analysed using the tolerability scale (Side effect observed or any change of treatment). Based on the values reported in the study (Table 2 & 3) no side effects were observed during the study. The data shows that FLUCOLD was well tolerated during the entire study period.

No treatment-related adverse events or serious adverse events were observed in the subject after the

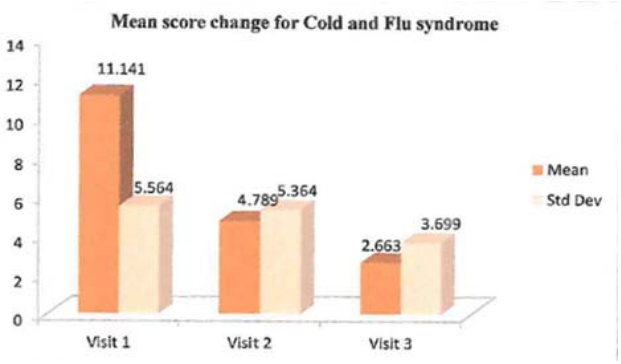

Fig 3 — Mean score change for cold and flu syndrome

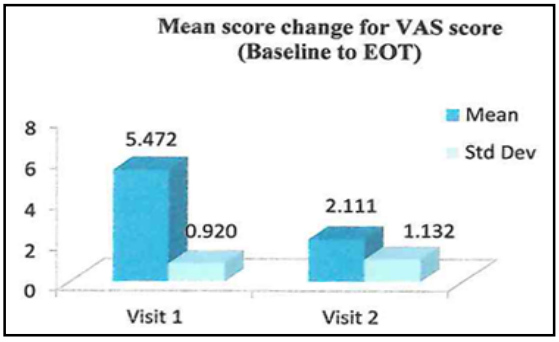

Fig 4 — Significant changes in VAS score from baseline to EOT

administration of FLUCOLD. The systemic biomarker values were assessed to evaluate the safety of FLUCOLD & no changes in mean scores of the serum values of haemoglobin, platelet count, SGOT, SGPT & creatinine was observed. The haematological test, liver function & kidney function test shows that tablet does not exert any adverse effect on their mean score. All test resultswere found to be normal (Table 4).

Table 2 — *Descriptive statistics for FLUCOLD tablet tolerability*

Visit	Statistics	Results
Visit	N	199
	MIN	1
	MAX	3
	MEAN	1.305
	STD	0.578

Discussion

Although the common cold is a self-limiting disease with symptomatic treatment, it is also responsible for considerable absence from work, school, and daily life. By addressing the symptoms of the common cold, the patient can reduce the number of days missed due to the common cold.The occurrence of common cold and other viral infections is highly prevalent and often their treatment requires the use of drugs for symptomatic relief.

The prospective, interventional, single arm, multicenter, post-marketing clinical study was

Table 3 — *Frequency count for product tolerability*

Scale	No of Subjects
Very good (no side effects)	151
Good (insignificant side effects which do not cause serious problems to the patient)	37
Statisfactory (side effects which affect the patient's condition, but do not necessitate discontinuation of the formulation)	12
Unsatisfactory (adverse effects which significantly affect the patient's condition and necessitate discontinuation of the formulation)	00
Highly Unsatisfactory (adverse effects which necessitate discontinuation of the formulation & use of additional clinnical measures)	00

Table 4 — *Biomarkers of systemic safety after FLUCOLD treatment*

Serum biomarker	Values at the EOT
Haemoglobin	14.043 ± 1.576
Platelet count	248.671 ± 99.960
SGOT	27.594 ± 5.845
SGPT	24.949 ± 10.184
Creatinine	0.804 ± 0.160

performed to assess the efficacy and safety of the FLUCOLD Tablet which contains paracetamol (500 mg), phenylephrine (10 mg), and chlorpheniramine maleate (2 mg). No treatment-related side effects were observed during the study. Furthermore,the FLUCOLD tablet is effective in relieving common cold and flu syndrome.The decline in symptomatic score of common cold and flu syndrome was observed after 3rd follow-up visit (11.141 ± 5.564 to 2.663 ± 3.699). The VAS score was found to be declined after the treatment with FLUCOLD in visit 2 (5.472 ± 0.920 to 2.111 ± 1.132).

During the study total of 200 patients from 3 sites were enrolled in the study out of which only 199 subjects completed the trial. The efficacy analysis was executed to assess the incidence rate of treatment-related adverse events and serious adverse events. Study findings indicate that there were no treatment-related adverse events observed during the study. Furthermore, FLUCOLD tablet is found to be effective in the treatment of common cold and flu syndrome in an adult.

Picon et al investigated the effectiveness and safety of chlorpheniramine maleate, paracetamol, and phenylephrine for the treatment of common cold in phase III trial (n=146). At the end of the treatment (after 10 days), symptom scores were reduced from 14.09 to 3.54 (74.87% improvement) for the treatment group. The adverse events were comparable in both groups[13].

In another phase IV open-labelled multicentric-study, efficacy and safety of the triple combination of paracetamol, chlorpheniramine maleate, and phenylephrine in the common cold were evaluated in adults. Reduction in total symptom score from 5.91 on day 1 to 3.57 on day 3 & 1.47 on day 5 was observed. The study concludes that combination is safe and effective in the treatment of common cold and allergic rhinitis[14].

Our study results showed that symptoms of common cold and flu syndrome were resolved mostly on the second visit and no drug-related side effects were observed during the treatment and follow-up.

Conclusion

After 4 days of treatment with FLUCOLD tablet, significant improvement in symptomatic relief of common cold and flu syndrome was observed. The safety results depict that FLUCOLD uncoated tablet is safe and well-tolerated by oral route.

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Conflict of Interest : The author has no conflict of intrest to declare.

References

1 Mossad SB — Treatment of the common cold. *BMJ* 1998; 317: 33-6.
2 Kirkpatrick GL — The common cold. *Prim Care* 1996; **23:** 657-75.
3 Jackson GG, Dowling HF, Spiesman IG, Boand AV — Transmission of the common cold to volunteers under controlled conditions. I. The common cold as a clinical entity. *AMA Arch Intern Med* 1958; **101:** 267-8.
4 Roll S, Nocon M, Willich SN — Reduction of common cold symptoms by encapsulated juice powder concentrate of fruits and vegetables: a randomized, double-blind, placebo-controlled trial. *Br J Nutr* 2011; **105:** 118-22.
5 Audera C, Patulny RV, Sander BH, Douglas RM — Mega-dose vitamin C in treatment of the common cold: a randomised controlled trial. *Med J Aust* 2001; **175(7):** 359-62.
6 Barrett BP, Brown RL, Locken K, Maberry R, Bobula JA, D'Alessio D — Treatment of the common cold with unrefined Echinacea. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2002; **137:** 939-46.
7 Yale SH, Liu K — Echinacea purpurea therapy for the treatment of the common cold: a randomized, double-blind, placebo-controlled clinical trial. *Arch Intern Med* 2004; 164: 1237-41.
8 Linde K, Barrett B, Wölkart K, Bauer R, Melchart D — Echinacea for preventing and treating the common cold. *Cochrane Database Syst Rev* 2006; 1 CD000530.
9 Sutter AI, Lemiengre M, Campbell H, Mackinnon HF — Antihistamines for the common cold. *Cochrane Database Syst Rev* 2005; 3 CD001267.
10 Schroeder K, Fahey T— Over-the-counter medications for acute cough in children and adults in ambulatory settings. *Cochrane Database System Rev* 2004; 4 CD001831.
11 Sutter AI, Lemiengre M, Kumar AA, Lesslar O, Skrt A — Oral antihistamine-decongestant-analgesic combinations for the common cold. *Cochrane Database Syst Rev* 2012; 2 CD004976.
12 Panasiuk L, Lukas W, Paprzycki P, Verheij T, Godycki-Æwirko M, Chlabicz S— Antibiotics in the treatment of upper respiratory tract infections in Poland. Is there any improvement? *J Clin Pharm Ther* 2010; **35:** 665-69.
13 Picon PD, Costa MB, da VeigaPicon R, Fendt LC, Suksteris ML, Saccilotto IC, *et al* — Symptomatic treatment of the common cold with a fixed-dose combination of paracetamol, chlorphenamine and phenylephrine: a randomized, placebo-controlled trial. *BMC Infectious Diseases* 2013; **13(1):** 1-8.
14 Kiran M, Pawaskar L, Sheikh S, Waghambare P — Efficacy And Safety for The Combination of Paracetamol, Phenylephrine And Chlorpheniramine Maleate In Indian Paediatric Patients Of Common Cold And Allergic Rhinitis-Post-Marketing Surveillance Study. International Journal of Medical Science and Diagnosis Research, 5(7).