American Journal of

Biochemistry and Molecular Biology

ISSN 2150-4210

Academic
Journals Inc.

www.academicjournals.com

OPEN ACCESS American Journal of Biochemistry and Molecular Biology

ISSN 2150-4210
DOI: 10.3923/ajbmb.2024.10.17

Research Article
Evaluation of Safety and Efficacy of Clevira Tablets Against Influenza Viruses: Randomized Open Label Clinical Study

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Abstract

Background and Objective: Viral flu and influenza are seasonal ailments in winter season most commonly. Scientifically validated drug is needed and with this objective the study was planned and compared for the efficacy of Clevira tablets in human adult patients with influenza A&B and vital flu. The objective of this study was to compare the efficacy of Clevira tablets in Human adult patients, with influenza A&B and viral flu. **Materials and Methods:** An open label, balanced, randomized, multi-dose, two-treatment, parallel, comparative phase III clinical trial to determine the safety and efficacy of Clevira tablets. Twenty patients were enrolled and received Clevira tablet along with standard treatment for influenza A&B and other respiratory viral infections. Enrolment was based upon the diagnosis of haematology, biochemistry, serology, RT-PCR and chest x-ray and inclusion and none of the exclusion criteria and included in the study. **Results:** A total of 20 patients were enrolled into the study and received Clevira tablet along with standard treatment for influenza. All haematology parameters were found to be normal and within limits at the end of the study period of day 10. There were no adverse events and serious adverse events reported during course of the study. The patients demonstrated safety measures with respect to blood pressure and pulse rate. Also, statistically significant ($p<0.0001$) improvement showed in temperature from baseline (102.03 ± 0.64) and at the end of the study period (98.14 ± 0.70). **Conclusion:** The study demonstrated an expedited clinical cure with normal vital signs and haematological results which validated that Clevira is safe and efficacious in patients with influenza A&B and vital flu. The data's further entrusted that Clevira can be used in infected patients with influenza A&B and viral flu and relieve the signs and symptoms, with a rapid recovery, without any adverse side effects.

Key words: Clevira, influenza virus, phase III clinical trial, RT-PCR, adverse events

Citation: Austin, A., Abiraamasundari and E.R. Selvan, 2024. Evaluation of safety and efficacy of clevira tablets against influenza viruses: Randomized open label clinical study. Am. J. Biochem. Mol. Biol., 12: 10-17.

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Clevira, a polyherbal combination of many substances with antiviral efficacy against both HSV-1 and HSV-2. Its antiviral effectiveness against fever of viral origin has also been demonstrated by pre-clinical, clinical and docking tests. A proprietary ayurvedic medication is called Clevira. Each of the individual herbal constituents has been shown to offer a range of therapeutic benefits against viral fever and to have potent antipyretic, analgesic, antiviral and immune-modulator properties. It was found to be important to study the efficacy of Clevira in order to use the formulations in treatment of viruses like influenza. In a country like India, a rich source of herbs with antviral and anti pyretic activity[1].

The ingredients of the exclusive Ayurvedic medicine Clevira tablet are *Carica papaya, Melia azedarach Andrographis paniculata*, *Vetiveria zizanioides*, *Trichosanthes dioica*, *Cyperus rotundus*, *Zingiber officinale*, *Piper nigrum*, *Mollugo cerviana* and *Tinospora cordifolia*. The specific herbal medications that are employed have been shown to have a range of therapeutic benefits, including the ability to effectively treat viral fever and increase immunity[2,3]. These ingredients were found to have anti-inflammatory, anti-pyretic, antibacterial, antimicrobial, anti-cancer, antihelmintic, larvicidal, hepato-protective, antidiabetic, antiobesity and hypolipidemic activity[4-7].

Reports from the World Ethno Botanical indicated that 70-80% of people worldwide depend on traditional medical care[8]. Herbal remedies have gained widespread acceptance and significant medicinal value in India. The majority of the therapeutic plants in the mixture exhibited pharmacological effects and had been the subject of years of research[9]. There are still restrictions on the safety and effectiveness of the preparations but new goals and an efficacy profile for the advantages of these medicinal plants have been established and supported by scientific data[10].

Traditional medicine uses CSPHF, a concoction of 10 components, to treat viral infections and other illnesses. Anti-inflammatory, anti-pyretic, antibacterial, anti-microbial, anti-cancer, antihelmintic, hepatoprotective, anti-diabetic, anti-obesity and hypolipidemic properties were discovered for these compounds[11-13].

The objective of this study was to compare the efficacy of Clevira by apex laboratories private limited, India with Standard Supportive Care Treatment in human adult patients with influenza.

MATERIALS AND METHODS

Study area: The study was conducted in Medisecure Superspeciality Hospital, Plot No-10 B, Sector-07, Kamothe, Maharashtra, India during the period of June to August 2023.

Study design: This study was an Open label, balanced, randomized, Multi-dose, two-treatment, parallel, comparative phase III clinical trial to determine the safety and efficacy of Clevira tablets.

Ethical conduct of the study: The study was conducted as per the Ethical guidelines for biomedical research on human participants, ICMR (2017), ICH (Step 5) 'Guidance on Good Clinical Practice. The study was initiated after obtaining proper ethical committee approvals and registered in clinical trial registry of India (CTRI/2023/02/050004).

Patient information and consent: The enrolled 20 Patients were asked to read the informed consent document which was followed by a presentation by the trained study personnel. All the queries of the patients were resolved before obtaining their consent. Copy of the informed consent documents (English and vernacular language versions) used for obtaining consent for participation in the study. Patients were under medical supervision throughout their stay in the clinical facility to ensure safety and well-being of the patients.

Diagnosis and main criteria for inclusion and exclusion: Patients who met all of the following inclusion criteria was considered for enrolment in the study:

Before enrolling in the Study haematology, biochemistry, serology, RT-PCR will be done to the patients for diagnostic purpose/conformation of infection.

Inclusion criteria:

- Patients who fulfilled each of the subsequent requirements were given consideration for trial enrolment
- Patients may engage in between the ages of 18 and 75. They may also have an oral temperature more than 38.0°C (100.4°F), along with accompanying symptoms such as rash, joint and body discomfort, excruciating headache, nausea and vomiting
- Mild to other respiratory viral infections linked to influenza and other illnesses as classified by WHO

- Viral fever combined with thrombocytopenia and a platelet count of 80,000-100,000 µL, as well as stable vital signs including blood pressure and pulse
- Female patients who tested negative for pregnancy (up to two weeks prior to the study)

Exclusion criteria

Patients with the following conditions were not enrolled in the study:

- With dengue hemorrhagic fever grade III and IV
- Platelet count less than 80,000 µL
- Pregnant/lactating women
- Patients who undergone transfusions of blood or blood products when they are unwell
- Thrombocytopenia Purpura (ITP), leukemia and hemophilia
- Patients with impaired renal function, defined as serum creatinine levels greater than 1.5 mg/dL (for men) and >1.4 mg/dL (for females) and serum ALT levels three times higher than the top limit of the normal range (>165 U/L)
- Patient who exhibited hypersensitivity to any of the formulation's ingredients

Primary selection of patients: The primary selection was to assess the efficacy of Clevira from day one of enrolment/treatment initiation, soon after the confirmation of illness, which is defined as time taken for clinical recovery. Patient enrolment was confirmed by RT-PCR/ CT value with symptoms of influenza and other respiratory viral infections.

Sample size and treatment: Totally 22 patients were screened and 20 patients were enrolled and received Clevira tablet along with standard treatment for influenza A&B, viral flu. Twenty patients were received the daily dose of 01 or 02 Clevira tablets along with Standard Treatment, in twice a day for 7-10 days, based on the severity of infection.

Data analysis

Analysis sets: The statistical evaluation was performed using Chi-square test or Fisher exact test between the treatment groups. The proportion of patients with influenza and flu, a contagious respiratory illness caused by influenza viruses that infect the nose, throat and sometimes the lungs on day 10 and the percentage of patients receiving rescue therapy during the treatment period were analysis by using Pearson correlation coefficient or Spearman rank correlation. Statistical analysis was performed using the SAS® Version 9.4 (SAS® Institute Inc., USA).

Safety analysis: A total of 20 patients were dosed successfully recovered from the infections. There were no adverse events and serious adverse events reported during course of the study. The planned safety analyses consisted of descriptive summaries of the data as relevant to the scale of data, e.g., frequency and percentage for recovered days and mean changes from baseline as appropriate. Frequency and percentage of patients were to be provided for each categorical variable by treatment group.

Efficacy and safety assessment

Evaluation schedule: The first visit (Visit 01) is the screening Visit, followed by the second visit (Visit 02) which is a randomization visit/study enrolment visit (day 00). The third visit (Visit 03) is subdivided into two viz., (I) Evaluation visit on day 01 to 10 (Treatment Arm 0) and (ii) Evaluation visit for one month (Treatment Arm 03) if required and followed by the final fourth visit (Visit 04) which is a follow up visit after one month, if required. The visit is based upon the patient's signs and symptoms, which are reduced between the treatment days and based on the investigator's decision.

RESULTS

Out of 22 patients 02 were found to be negative for RT- PCR, out of twenty enrolled patients fifteen were positive for influenza A virus, four were positive for influenza B virus and was diagnosed with viral fever (Fig. 1).

Some common symptoms were observed from the patients like: Fever runny nose, headache, fatigue, sneezing, cough, sore throat, body ache, weakness, loss of appetite, nasal congestion and stuffy nose.

Demographic and other baseline characteristics: A total of 20 patients were enrolled into the study and their mean age, height, weight and BMI were recorded (Table 1).

All patients included in the study were Asians. Table 2 explains the summarized demographic details of patients who were enrolled in the study.

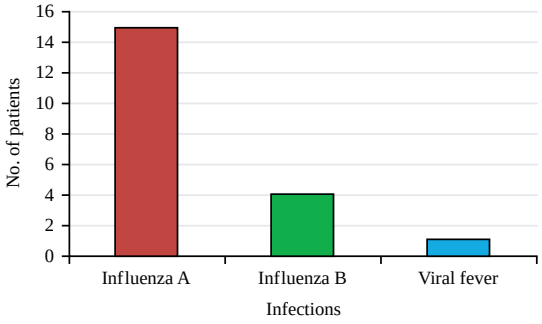

Fig. 1: RT-PCR interpretation of the patients

Table 1: Demographic details of patients enrolled

Patient enrolment code	Gender	Race	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
S002-01-001	F	Asian	42	158.0	62.0	24.8
S002-01-002	F	Asian	29	149.0	56.0	25.2
S002-01-003	F	Asian	32	153.0	60.0	25.6
S002-01-004	F	Asian	58	158.0	58.0	23.2
S002-01-005	M	Asian	27	160.0	65.0	25.3
S002-01-006	F	Asian	28	155.0	59.0	24.5
S002-01-007	M	Asian	71	159.0	60.0	23.7
S002-01-008	F	Asian	41	151.0	59.0	25.8
S002-01-009	F	Asian	19	148.0	48.0	21.9
S002-01-010	M	Asian	21	162.0	66.0	25.1
S002-01-011	F	Asian	49	157.0	56.0	22.7
S002-01-012	M	Asian	20	155.0	58.0	24.1
S002-01-013	M	Asian	57	158.0	60.0	24.0
S002-01-014	F	Asian	29	151.0	53.0	23.2
S002-01-015	M	Asian	53	157.0	61.0	24.7
S002-01-016	F	Asian	43	153.0	58.0	24.7
S002-01-017	M	Asian	65	159.0	59.0	23.3
S002-01-018	F	Asian	19	145.0	44.0	20.9
S002-01-019	M	Asian	27	160.0	57.0	22.2
S002-01-020	M	Asian	62	155.0	56.0	23.3

Table 2: Summarized demographic details of patients

Parameters	Mean	SD	Min.	Max.	CV (%)
Age (years)	39.60	16.82	19.00	71.00	42.47
Height (cm)	155.15	4.53	145.00	162.00	2.92
Weight (kg)	57.75	5.06	44.00	66.00	8.76
BMI (kg/m^2)	23.91	1.32	20.90	25.80	5.53

SD: Standard deviation, Min.: Minimum and Max.: Maximum

Table 3: Mean value for age and BMI

Treatments	(Clevira tablet along with standard treatment) day 10
Number of subjects	20
Gender (female:male)	11 F:09 M
Mean age	39.60±16.82
Mean BMI	23.91±1.32

±: Plus or minus

Efficacy evaluation

Statistical analysis of phase III clinical trial of clevira tablet: Primary and secondary end point efficacy evaluations were performed for Clevira Tablet. Primary and secondary end point of recovery analysis data from day 01 to 10 and safety measure analysis data for the all the patients (demographic data, haematology and vital signs) were performed by SAS software.

Demographic data: There is no statistically significant ($p = 0.6006$) difference was observed between Clevira tablet (39.60±16.82) of age (Table 3 and 4).

Hematology parameters: All hematology parameters were found to be normal and within limits and at the end of the study period of day 10 (Table 5).

Vital signs: During the course of study at Day 01 and 10, blood Pressure, radial pulse rate, temperature and wellbeing status was enquired and recorded (Table 6). Paired sample t-test example baseline vs end of treatment comparison given in Table 7.

Patients in Treatment with Clevira tablets clearly illustrated the safety aspects with respect to blood pressure and pulse rate. Also, statistically significant ($p<0.0001$) improvement showed in temperature from baseline (102.03±0.64) to end of the study treatment (98.14±0.70). (Fig. 2).

Recovery analysis: Mean recovery day (Mean±SD) of Treatment (Clevira tablet were found to be 8.00±1.30) (Table 8). The overall clinical efficacy shows healthy recovery rate found from 20 patients.

Table 4: ANOVA procedure for dependent variable; age and BMI

Source	DF	ANOVA SS	Mean square	F-value	Pr> F
Clevira tablet	1	75.62500000	75.62500000	0.28	0.6006

DF: Degree of freedom

Table 5: Comparison of hematology parameter between baseline and end line (day 00 vs 10)

		Hematology								
Patient enrolment code	Time of evaluation	RBC count ($\times 10^{12}$/µL)	Packed cell volume (%)	Total WB Count (µL)	Lymphocytes (%)	Neutrophils (%)	Eosinophil (%)	Monocyte (%)	Basophils (%)	Platelet count ($\times 10^{9}$/L)
S002-01-001	Day 00	4.40	36.8	10000	45	50	2	3	0	139.0
	Day 10	5.30	38.1	6650	39	59	1	1	0	184.0
S002-01-002	Day 00	4.60	37.2	9710	37	59	1	2	1	125.0
	Day 10	5.20	39.3	6920	38	56	2	4	0	178.0
S002-01-003	Day 00	4.30	39.5	10307	32	60	0	8	0	152.3
	Day 10	5.60	40.8	7900	39	54	1	5	1	245.0
S002-01-004	Day 00	4.40	40.7	9950	36	57	1	5	1	164.0
	Day 10	4.62	41.2	6542	36	57	3	3	1	214.3
S002-01-005	Day 00	5.10	42.4	10850	54	40	3	3	0	160.7
	Day 10	5.01	43.9	7843	37	56	0	6	1	210.0
S002-01-006	Day 00	4.94	36.6	10763	58	38	0	3	1	154.0
	Day 10	5.10	39.2	7204	38	56	1	5	0	204.6
S002-01-007	Day 00	4.30	41.8	8612	52	44	2	2	0	98.1
	Day 10	4.92	43.4	6250	34	63	0	2	1	122.0
S002-01-008	Day 00	4.23	39.7	9624	37	57	1	4	1	160.0
	Day 10	5.30	41	6471	35	59	2	3	1	219.0
S002-01-009	Day 00	4.70	40.9	8007	51	39	3	6	1	151.0
	Day 10	5.60	42.3	5913	37	57	1	5	0	207.0
S002-01-010	Day 00	4.10	43.6	8730	43	46	5	5	1	120.4
	Day 10	5.32	43.2	5849	33	63	1	3	0	191.0
S002-01-011	Day 00	4.00	38.9	8040	44	51	1	4	0	134.0
	Day 10	5.21	42.7	5981	38	59	0	3	0	235.0
S002-01-012	Day 00	4.60	41.6	9562	52	43	2	2	1	164.0
	Day 10	4.80	42.4	6007	34	62	1	2	1	217.0
S002-01-013	Day 00	5.20	42.2	9145	50	46	0	3	1	167.0
	Day 10	4.92	44.7	6143	31	66	1	2	0	227.0

Day 00: Screening baseline

Table 6: Vital signs (blood pressure, radial pulse rate and temperature day 00 vs 10)

		Day 01			Day 10		
Patient enrolment code	Treatment group	Blood pressure (mm Hg)	Radial pulse rate (per min)	Body temperature (°F)	Blood pressure (mm Hg)	Radial pulse rate (per min)	Body temperature (°F)
S002-01-001	Influenza A	116/80	78	102.20	121/79	79	98.24
S002-01-002	Influenza A	121/76	74	101.60	119/82	75	98.78
S002-01-003	Influenza A	130/76	70	102.38	126/80	72	97.88
S002-01-004	Influenza A	114/80	65	102.02	118/83	68	98.96
S002-01-005	Influenza A	120/80	80	102.20	120/84	83	98.06
S002-01-006	Influenza A	127/85	82	101.84	125/81	78	98.42
S002-01-007	Viral fever	122/80	87	103.10	123/78	76	98.60
S002-01-008	Influenza A	128/87	81	102.20	126/85	82	97.70
S002-01-009	Influenza B	129/78	79	102.38	130/80	80	99.14
S002-01-010	Influenza A	126/79	71	101.46	129/82	75	98.24
S002-01-011	Influenza A	126/81	84	102.32	124/82	81	98.42
S002-01-012	Influenza B	132/84	80	102.20	130/80	83	96.98
S002-01-013	Influenza A	124/84	76	102.38	125/83	80	97.16
S002-01-014	Influenza A	130/81	72	102.74	127/79	77	98.42
S002-01-015	Influenza A	120/86	81	101.00	122/85	83	98.78
S002-01-016	Influenza A	126/79	77	101.90	128/78	79	98.24
S002-01-017	Influenza A	132/81	78	100.90	131/80	84	96.26
S002-01-018	Influenza B	120/82	82	102.46	122/83	80	98.42
S002-01-019	Influenza B	119/81	74	102.74	120/78	78	97.70
S002-01-020	Influenza A	123/84	76	100.60	125/85	81	98.42

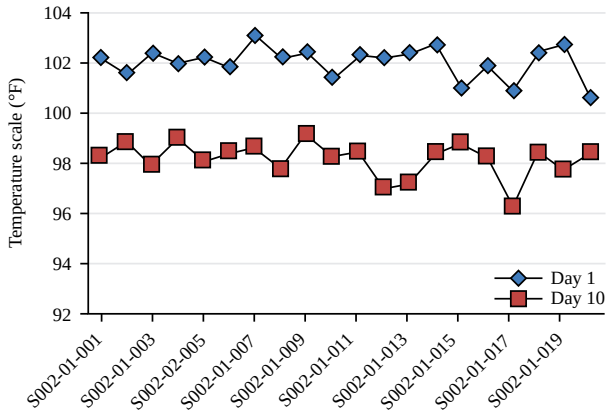

Fig. 2: Comparison of fever scale between baseline and end line (day 01 vs 10)

Table 7: Paired sample t-test example (baseline vs end of treatment comparison) Clevira tablet

Difference	DF	t-value	Pr>|t|
Systolic blood pressure	19	-0.55	0.5906
Diastolic blood pressure	19	-0.24	0.8142
Pulse rate	19	-1.54	0.1391
Temperature	19	19.26	<0.0001

DF: Degree of freedom

Table 8: Analysis of variable on recovery day

	Analysis variable					
Treatment	Number of observation	Mean	Standard deviation	Minimum	Maximum	Coefficient of variation
Treatment (Clevira tablet along with standard treatment) day 10	20	8.00	1.30	6.00	10.00	16.22

DISCUSSION

In the current study totally 20 patients were to determine the safety and efficacy of Clevira with standard treatment in patients with influenza. All haematology parameters were found to be normal at the end of the study period of day 10. During the course of study at day 01 and 10, blood pressure, radial pulse rate and temperature was found to be normal.

The safety features regarding blood pressure and pulse rate were eloquently demonstrated by patients receiving treatment with Clevira tablets. There is no statistically significant ($p = 0.6006$) difference was observed between Clevira tablet (39.60 ± 16.82) of age. Patients in treatment with Clevira tablets clearly illustrated the safety aspects with respect to blood pressure and pulse rate.

Also, statistically significant ($p<0.0001$) improvement showed in temperature from baseline (102.03 ± 0.64) to end of the study treatment (98.14 ± 0.70). Additionally, Mean recovery day (Mean±SD) of Treatment (Clevira tablet were found to be 8.00 ± 1.30). Twenty patients had a healthy recovery rate, according to the overall clinical efficacy.

When compared to the baseline and control groups, the Clevira group's patients' quality of life significantly improved in relation to fatigue, a sense of being week, dizziness and depression. The Clevira group's overall reaction shown a notable improvement; they were totally free of viral symptoms and excellent subject compliance was also noted. Over the course of the study, there were no adverse events that were considered clinically significant[1].

The study findings demonstrate that, in contrast to the control group, which saw normalization of body temperature after days six and seven, the Clevira-treated group experienced normalization of body temperature starting on day 5. Clevira has good antipyretic efficacy as a result. Additionally, it is clear that Clevira is significantly improving ($*p<0.001$) in the arthralgia and myalgia scores on days 3-5, indicating that the medication has good analgesic and antipyretic properties. With a considerable decrease in the WBC count and haematocrit, all haematological and biochemical parameters were within the normal range, indicating that Clevira has antiviral properties and the ability to modulate the immune system against viral infectious fever diseases like dengue. Tests for liver and kidney function that remain unchanged indicate that Clevira pills are safe when taken as prescribed by Ramesh *et al.*[1].

In order to battle the catastrophic effects of influenza and contagious respiratory illnesses, different countries are currently concentrating their efforts on finding a treatment for the sickness as well as quick diagnosis and patient isolation. Studying the positive effects of the numerous licensed antivirals already on the market for SARS-CoV-2, such as Clevira, which has been recommended as a safe and effective treatment for respiratory infections, is crucial. The *C. papaya*[5], *M. azedarach*, *A. paniculata*, *V. zizanioides*, *C. rotundus*, *Z. officinale*, *P. nigrum*, *M. cerviana* and *T. cordifolia* plants have pharmacological qualities that offer a practical method for creating safe treatment alternatives against respiratory virus infections brought on by influenza A and influenza B as well as contagious respiratory illnesses[2].

Following a gross pathological examination at the conclusion of the study, no alterations were observed in any of the groups. Accordingly, it was clear from the results that the CSPHF was safe up to a single, high oral dose of 2000 mg/kg body weight without causing any death. There haven't been many previous acute toxicity studies in Wistar albino rats that demonstrate toxicity symptoms and mortality for a Polyherbal formulation. This study continued with the CSPHF repeated dose toxicity investigation based on the data[3].

Increased platelet synthesis is said to be caused by enhanced expression of the platelet activating factor receptor gene and arachidonate 12-lipoxygenase. Due to the presence of several flavonoids and phenolic components, it also reduces peripheral platelet destruction by membrane stabilizing activity, which may have contributed to the notable increase in platelet counts in patients receiving Clevira[11].

Tinospora cordifolia is recognized for its anti-pyretic, antiviral and hepatoprotective properties. It also has the ability to boost the host immune system by stimulating macrophages, NF-kappa beta translocation and cytokine production[12].

It has been demonstrated that *P. nigrum* increases the bioavailability of medications, shields the liver, neutralizes endotoxins and cleanses the blood and liver of harmful residues have antibacterial[14,15], antifungal, analgesic and anti-inflammatory properties. Possesses an immune-suppressive impact that delays the onset of the disease, this could have made a major difference in the clinical signs and symptoms of dengue fever associated with thrombocytopenia and in patients with pathogenic other viral fevers[16,17].

The medicinal plant *A. paniculata* has been shown to have anti-HIV, anti-bacteria and immune-modulator properties. It also has blood purification properties, which help to get rid of harmful metabolites and analgesic, anti-inflammatory and antipyretic properties[18].

CONCLUSION

From the results of the present study, it was showed that Clevira is clinically effective in normalizing haematology parameters, vitals, temperature and relieving clinical signs and symptoms of influenza. The overall clinical efficacy shows high recovery percentage. Henceforth, Clevira can be used in infected patients with flu to relieve the signs and symptoms of it and for a rapid recovery without any adverse events.

SIGNIFICANCE STATEMENT

The use of numerous herbal remedies for a range of ailments has grown recently. Among these is Clevira, a polyherbal combination of many substances with antipyretic, analgesic, antiviral and immuno-regulatory effects. Purpose of this study was to compare the efficacy of Clevira tablets. Total 20 patients were enrolled for the study and received Clevira tablet along with standard treatment for influenza. All hematology parameters were found to be normal and within limits and at the end of the study period of day 10. Patients in Treatment with Clevira tablets clearly illustrated the safety aspects with respect to blood pressure and pulse rate, also improvement showed in temperature. Overall clinical efficacy demonstrates a high rate of recovery. Hence, Clevira can be used in treatment of flu and viral infections.

ACKNOWLEDGMENTS

The authors are thankful to the management of Apex Laboratories Private Limited and Mr. S.S. Vanagamudi, Chairman and Managing Director, Mr. Vishagan Sulur Vanagamudi, Director and President and also Ms. Subashini Vanagamudi, Executive Director, Apex Laboratories Private Limited, Chennai, for their continuous encouragement and support in carrying out the study.

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