THE HYPOLIPEMIC EFFECT OF UNILIPID

STUDY REPORT

UNINATR/001/HYLIP

Title An open study to establish the hypolipemic effect of a herbal preparation .

This study was carried out in accordance with the Good Clinical Practice Guidelines of WHO and the current version of the Declaration of Helsinki (copy attached as Annexure A)

A. The Investigators of the study were :
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CO - INVESTIGATORS :

1. Dr. B.D.Samant, Assoc. Prof., Dept. OfPharmacology , Seth GSMC & KEM Hospital, Parel, Mumbai – 400012
2. Dr. K.C.Patel, Assoc. Prof., Dept. Of Medicine,Seth GSMC & KEM Hospital, Parel,Mumbai – 400012
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4. Dr. Shirish Joshi, Lecturer, Dept. OfPharmacology, Seth GSMC & KEM Hospital, Parel, Mumbai – 400012

B. Study monitoring was undertaken by Mr. Dipen Khanna, Deputy Manager - Medical Services and Ms. Bharati Gawade - Asst. Manager, Medical Services of M/s.ULL

C. Data entry was undertaken by Ms. Bharati Gawade of M/s. ULL.The Study Report is complied by Dr. (Mrs) D. A. Gadgil, Vice President - Medical Services and Ms. Bharati Gawade , Assistant Manager - Medical Services of M/s. ULL. Ethics Committee Clearance was obtained from K. E. M. Hospital, Parel, Mumbai .

- Informed consent was obtained from all patients.

Study period : 29.5.98 to 23.12.98

I **Introduction**

Cholesterol and triglycerides form the major lipids in the body. The transportation of these lipids between various body tissues and fluids is possible because of the formation of complex called lipoproteins. These lipoproteins help in the transportation of lipids through the vascular and extravascular fluid compartments. These lipoproteins have varing quantities of cholesterol and triglycerides. They are referred to as very low density lipoproteins (VLDL), low density lipoproteins(LDL) and high density l ipoproteins (HDL). The lipoprotein densities depend upon the amount of triglyceride content and the higher the triglyceride lower is the lipoprotein density.

The concentration of total plasma cholesterol and triglycerides depends on the diet, exercise, body weight, sex and alcohol consumption etc. Hyperlipidemia is a biochemical diagnosis and it refers to a raised level of fasting plasma cholesterol or triglycerides and HDL, LDL , VLDL helps in the diagnosis of hyperlipidaemia.

Epidemiological studies have established a definite relationship between the incidence of atherosclerosis and total plasma cholesterol, especially the cholesterol fraction in LDL. There is an increased entry of LDL and deposition of cholesteryl ester into established atherosclerotic plaques. The level of HDL has an inverse relation with coronary artery disease, as it has the ability to transport cholesterol from the peripheral tissues to the liver.

It is known that lowering of plasma lipid levels is associated with a decrease in incidence of coronary artery disease. Needless to say, other risk factors like smoking ceasation, maintaining normal body weight etc are also essential. Besides drug theapy, various lipid lowering agents are available today like Bile Acid Sequestrants, Fibric Acid Derivatives, Statins etc.

Many traditional herbal agents including some mentioned in ayurveda are known/reported to have lipid lowering properties. The product known as Product C1(code name) has been developed by Dr. Vikram Naharwar, Director, **Amsar P Ltd, Indore**. All the ingredients of the product are also mentioned in the Ayurvedic Pharmacopoeia and this product with the above mentioned composition has already been granted manufacturing license to **M/s Amsar P.Ltd..**

We were keen to evaluate this herbal product for its lipid lowering effect in hyperlipedemia and to undertake clinical and laboratory evaluation using modern techniques.

II Study Objective

To evaluate clinically efficacy and tolerability of a herbal hypolipemic agent, containing known herbal extracts, in patients with uncomplicated hyperlipidemia. The efficacy was established if there is atleast a 20% fall in S.cholesterol and/or S.triglyceride levels or a rise of 20% in HDL levels within 1-3 months.

III Patients and Methods

III 1. Study Design

This was an open study in patients with uncomplicated hyperlipedemia. A total of 30 patients were studied . Patients were screened from the hypertension clinic of the K.E.M. hospital. Each patient was observed for 1 - 3 months.

III 2. Inclusion Criteria

- Patients of either sex, above 18 years of age, having the following :

- Raised Serum cholesterol levels (greater than 240 mg %)
  and / or
- Raised triglyceride levels(greater than 250 mg %)
- Willing to come for regular follow-up visits.
- Willing to adhere to recommended dietary control.
- Willing to take medications as directed by the investigator.
- Patients willing to sign informed consent.

III 3. Exclusion criteria

- Pregnant women, nursing mothers and women of child bearing potential, not following adequate contraception measures.
- Patients with significant atherosclerotic disease, including patients with significant coronary artery disease (CAD). History of acute MI in preceding 6 months.
- Uncontrolled/poorly controlled Diabetes Mellitus or Juvenile Diabetes Mellitus, or any endocrine disorder.
- When patient has multiple risk factors for CAD.
- Prior therapy with any lipid lower agents within preceding 4 weeks.
- Any secondary cause of hyperlipidemia
- Smokers
- History of alcohol and/or drug abuse.
- Severe hepatic, renal or cardiac dysfunction , or uncontrolled hypertension.
- Treatment with any investigational drug in preceding 4 weeks.
- Familial hyper cholesterolaemia and hyperlipoproteinaemia(type III) as there is an increased risk of CAD.
- Patient unwilling to take regular medication and or come for follow-up.

III 4. **Patient Withdrawal / Replacement**

Patients were withdrawn from the study at their own request or at the discretion of the Investigator. In all cases, the reasons why the patient is withdrawn were entered in the CRF. These patients were not replaced and the next patient enrolled was allotted the next consecutive number available.

III 5. **Dosage Regimen**

All patients found eligible for the study were screened. They were then advised dietary restrictions and given placebos for 2 weeks. At end of 2 weeks, patients were assessed for compliance and then dispensed the study drug.

Each patient received :
Tablet Placebo 2 BD with meals i.e. lunch and dinner x 14 days.
Then
Tablet Unilipid 2 BD with meals x 1 - 3 months.

The duration of active drug treatment should be at least 1 month and ideally for 3 months.

Concomitant medications received by the patients were recorded in the CRF. All pre-existing medications were permitted during the study period, as far as possible unchanged dosage.

III 6. **Compliance**
All medications were dispensed by the Investigator to all eligible patients, during all visits. At each visit, patients were instructed to bring back the empty packs and all unused medications, with a view to check compliance.

III 7. **Observations**
At baseline, when patients were enrolled, the background demographic data was collected, like patients' age, sex, weight, relevant history etc.

All patients underwent a detailed medical history and clinical examination schedule.

SCHEDULE OF OBSERVATIONS

Background observations

Demographic data such as patients age, sex, weight was documented. A detailed medical history had to be taken and a detailed physical examination had to be conducted.
The following examinations/investigations were carried out :

Clinical Exam

General Physical Exam	
Systemic Exam	On Days 15, 46,76 & 106
Body weight records	

Lab investigations

- Hemogram at start and end of study
- Liver function tests at start and end of study.
- S. creatinine and BUN at start and end of study
- Blood Sugar Fasting and Post prandial at start and end of study
- Complete Lipid Profile, including S. triglycerides, S. cholesterol, HDL, LDL & VLDL levels and cholesterol / HDL ratio on Days 1,15,46,76,106
- ECG on Days 1, 46 and 106

III 8. **ADE Monitoring**

Adverse events were monitored up to Day 106. Special attention was given to Blood sugar levels & ECG changes. Serious adverse events were monitored throughout the study , upto atleast 1 week after the dose of study drug, or longer, if indicated.
All observed or volunteered events, which was any reaction, side-effect, intercurrent disease or untoward event that occurred during the course of clinical trial, regardless of treatment group or suspected causal relationship to study drug, were labeled as ‘Adverse Event’ and recorded on the Adverse Event page of the Case Report Form. The Investigator pursued and obtained information adequate both to determine the outcome of the adverse event

and to assess whether it meets the criteria for classification as a Serious Adverse Event requiring immediate notification to the Company. Followup of the adverse event, even after the date of therapy discontinuation, was done if the adverse event or its sequelae persisted.

Serious Adverse events

All **serious** adverse events which occurred during the study until the last follow-up visit required by the protocol, regardless of treatment group or suspected relationship to drug, were reported **immediately** by telephone/fax to the Company appointed monitor.

Serious Adverse Events include those that suggest a significant hazard, such as events which:

- are fatal
- are life-threatening
- result in permanent disability
- require in-patient hospitalisation or prolongation of a hospital stay
- involve cancer, a congenital anomaly or drug overdose

It was also emphasised that, regardless of the above criteria, any additional adverse experiences which the Investigator considered serious should be immediately reported.

For all serious adverse events, the Investigator was obligated to pursue and provide information as requested by the Company in addition to that on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. In the case of a patient’s death, a summary to be provided, if available . Autopsy findings must be submitted if possible to the Company appointed monitor at the earliest. The Investigator was to ensure that information on such cases is reported by telephone or other means and information entered in the case report form is accurate and consistent.

III 9. **Assessments**

- All patients were assessed for response of all the various parameters as mentioned in the section on Observations.

PARAMETER	DAY 1	DAY 15	DAY 46	DAY **76**	DAY 106
Informed Consent	✔				
Inclusion / Exclusion criteria	✔				
Laboratory investigations	✔				✔
ECG	✔		✔		✔
S. triglycerides, S.cholesterol, HDL, LDL & VLDL levels and cholesterol / HDL ratio	✔	✔	✔	✔	✔
Concomitant medication / Illness	✔	✔	✔	✔	✔
Compliance and tolerability		✔	✔	✔	✔
Investigator's overall assessment of efficacy			✔	✔	✔
Patient's overall assessment of tolerability					✔
Adverse Events		✔	✔	✔	✔

NOTE : A window of 3-5 days was permitted for each follow-up visit. However, Investigator was to ensure that, as far as possible, the patients returned for evaluation on their 'scheduled' day of visit.

Assessment of Response
The fall in serum lipid values was assessed on Day 30, 60 & 90 or at the time of discontinuation from study due to lack of efficacy or adverse event.

- Clinical response, including changes in body weight was assessed
- Any changes in lab. investigations was assessed.
- Overall assessment in terms of efficacy and tolerability was assessed by investigator and patient.

Overall assessment in terms of efficacy By Investigator was done as :

- ➔ Less than 10% fall in lipid values = Poor response
- ➔ 10% - 20% fall in lipid values = Moderately good response.
- ➔ Above 20% fall in lipid values = Good response.

In case patient has low HDL values(below 35 mg %), the rise in HDL levels was also considered in assessment of response.

Tolerability was assessed by patient as :
- ➔ Well tolerated
- ➔ Satisfactory tolerability
- ➔ Poorly tolerated

IV. **RESULTS**

1. **Patient Demographics**
A total number of 30 **patients** were recruited in the study from 1 centre. Therefore the "Intention To Treat" (ITT) population is 30 patients, who will also be considered for safety evaluation.

Out of 30 patients , 6 were lost to follow-up and therefore 24 patients were finally included in the "per protocol" analysis".

Table No.1a and 1b shows the summary disposition of the patients, for efficacy and safety, on ITT and PP basis. Thus, a total of 24 patients were analysable for efficacy and a total of 27 patients were analysable for safety.

All conclusions and inferences are drawn on “per protocol” patient groups i.e. all 24 patients who completed study as per the protocol requirements of 1-3 months of study period.

Table 1a. Enrollment Status

	Included	Dropouts
	30	**10**
Total	**20**	

Table 1b. Summary Disposition of patients

Total Enrolled	30
Major Protocol Violations	10
Total	20
Total	20
Analysable	
Efficacy	
• Lost to followup after washout period	3
• Safety*	27

Out of 30 patients, 3 patients lost the follow up after washout period. Therefore, total number of patients analysable for safety evaluation become 27.

Major protocol violations were noted in 8 patients. (***Table No. 2***)

Table 2.	Major Protocol Violations
1	Lost to Follow-up after washout period
2	Patient Discontinued on her own due to AE after 2nd visit. The AE was skin rash restricted to both legs which may not be due to study drug as per investigator's opinion. Also,patient developed constipation the causality of which could not be judged.
7	Patient came 13 days late for visit 3. Still was continued because response was moderately good. Patient missed 10 doses between visit 3 and visit 4. Patient Discontinued the study drug on her own after 4th visit due to AE . The AE was eczematous allergic skin rash all over the body , the likely cause of which is the study medication as per the investigator's opinion.
11	Came 26 days late for visit 3. Lost to Followup after 3rd visit.
14	Lost to Follow-up after washout period.
15	Lost to Follow-up after washout period.
20	Missed 8 days medication intermittently between visit 2 and visit 3. Also, came 6 days late for visit 5.
22	Came late for 22 days for visit 3.
23	Lost to follow up after visit 2.
29	Missed 5 days medication between visit 3 and visit 4

Thus, it is seen that, a total of 10/30 patients were considered as drop-outs of the study.

Table No. 3 gives the patient numbers who completed 1 month, 3 month of study period

Patient numbers who completed 1 month of study period.	Patient numbers who completed 3 months of study period.
12, 13	3,4,5,6,8,9,10,16, 17,18,19,21,24,25,26,27,28,30
Total = 2	Total = 18

Table 4 gives the distribution of patients enrolled as per the sex .

Table 4. Sex Distribution

Female	**20**
%	**66.7**
Male	**10**
%	**33.3**
Grand Total	**30**
%	**100.0**

Table 5 lists the concomitant illness at baseline and the concomitant medications used during the study period

Patient No.	Concomitant Disease	Concomitant Medication
3	Hypertension	Nifedipine
4	Hypertension, Diabetes, Myocardial Ischaemia	Atenolol, nifedipine, enalapril, alprazolam
5	Hypertension, Myocardial Ischaemia	Aspirin, isosorbide dinitrate, atenolol, amlodipine,glipizide
6	Hypertension	Enalapril, amlodipine, aspirin, isosorbide dinitrate
8	Hypertension	Nifedipine, triamterene, benzthiazide
9	Myocardial Ischaemia, Hypertension	Enalapril, nifedipine, triamterene, benzthiazide, aspirin
10	Hypertension	Aspirin, isosorbide - 5 - mononitrate, felodepine, nifedipine
12	Hypertension	Nifedipine, enalapril
13	Hypertension	Triamterene, benzthiazide
16	Hypertension	Nifedipine, enalapril, aspirin
17	Hypertension	Atenolol, amlodepine, frusemide
18	Hypertension	Atenolol, aspirin
19	Hypertension	Nifedipine, enalapril, aspirin
21	Hypertension	Enalapril, aspirin, isosorbide dinitrate
24	Hypertension	Nifedipine
25	Hypertension	Propranalol
26	Hypertension, Diabetes	enalapril, glipizide
27	Hypertension	Nifedipine, atenolol
28	Hypertension	Amlodepine
30	Hypertension	Enalapril, amlodepine

2. **Efficacy variables**

a. Comparison of pre-treatment and post-treatment total cholesterol value of patients who had completed 3 months of study period :

Table 6 : lists pre-treatment and post-treatment total cholesterol value and percentage decrease in total cholesterol value of patients who had completed 3 months of study period :

Patient Number	Pre-treatment (Day 15) Total Cholesterol	Post-treatment (Day 106) Total Cholesterol	Percentage decrease in Total Cholesterol
3	**325**	**210**	**35.38**
4	**330**	**210**	**36.36**
5	**245**	**230**	**6.12**
6	**240**	**190**	**20.83**
8	**300**	**210**	**30**
9	**255**	**200**	**21.57**
10	**330**	**170**	**48.48**
16	**350**	**240**	**31.43**
17	**300**	**220**	**26.66**
18	**350**	**245**	**30**
19	**280**	**265**	**5.36**
21	**250**	**210**	**16**
24*	**230**	**250**	**8.7▲**
25	**385**	**265**	**31.17**
26	**295**	**250**	**15.25**
27	**265**	**190**	**28.3**
28	**285**	**180**	**36.84**
30	**325**	**205**	**36.92**

- In patient number 24, post treatment cholesterol value was more than pre treatment cholesterol value. Therefore, % increase in total cholesterol has been mentioned as 8.7 ❑
As per the inclusion criteria, the patients who are recruited as per the baseline total cholesterol value are patient numbers 3,4, 6,8,9,10,16,17,18,19, 21, 25, 2627,28,30. Overall assessment of efficacy was good for all these patients except patient numbers 5,19,21, 26.

Table 7:

Parameter	Total number of patients	Percentage of patients
➢ 20 % decrease in Total Cholesterol	**4**	**22.22**
20% - 30 % decrease in Total Cholesterol	**4**	**22.22**
➢30% - 40 % decrease in Total Cholesterol	**8**	**44.44**
➢ 40% decrease in Total Cholesterol	**1**	**5.55**

b. Comparison of pre-treatment and post-treatment total triglyceride value of patients who had completed 3 months of study period :

Table 8 : lists pre-treatment and post-treatment total triglyceride value and percentage decrease in total triglyceride value of patients who had completed 3 months of study period :

Patient Number	Pre- treatment Serum Triglyceride	Post-treatment Serum Triglyceride	Percentage decrease in Serum Triglyceride
3	**180**	**145**	**19.44**
4	**230**	**145**	**36.96**
5	**310**	**215**	**30.65**
6	**245**	**155**	**36.73**
8	**220**	**110**	**50**
9	**200**	**165**	**17.5**
10	**225**	**125**	**44.44**
16	**275**	**150**	**45.45**
17	**320**	**70**	**78.13**
18	**270**	**195**	**27.77**
19	**290**	**85**	**70.69**
21	**220**	**95**	**56.82**
24	**295**	**110**	**62.71**
25	**245**	**100**	**59.18**
26	**350**	**120**	**65.71**
27	**245**	**45**	**81.63**
28	**310**	**50**	**83.87**
30	**345**	**70**	**79.71**

As per the inclusion criteria, the patients who are recruited as per the baseline serum triglyceride value are patient numbers 5,16, 17,18,19,21,24,26,28,30. Overall assessment of efficacy was good for all these patients.

Table 9 :

Parameter	Total number of patients	Percentage of patients
➢ 20 % decrease in Total Cholesterol	**2**	**11.11**
220% - 30 % decrease in Serum Triglyceride	**1**	**5.55**
➢30% - 40 % decrease in Serum Triglyceride	**3**	**16.66**
➢ 40% decrease in Serum Triglyceride	**12**	**66.66**

c. Comparison of pre-treatment and post-treatment HDL value of patients who had completed 3 months of study period :

Table 10 : lists pre-treatment and post-treatment total HDL value and percentage increase in total HDL value of patients who had completed 3 months of study period :

Patient Number	Pre- treatment Serum Triglyceride	Post-treatment Serum Triglyceride	Percentage decrease in Serum Triglyceride
3	**40**	**50**	**25**
4	**45**	**55**	**22.22**
5	**55**	**60**	**9.09**
6	**50**	**55**	**10**
8	**50**	**70**	**40**
9*	**45**	**40**	**11.11↓**
10	**45**	**50**	**11.11**
16	**45**	**45**	**44.44**
17	**40**	**75**	**87.5**
18	**45**	**50**	**11.11**
19	**50**	**60**	**20**
21	**55**	**60**	**9.09**
24	**40**	**50**	**25**
25	**45**	**50**	**11.11**
26*	**50**	**40**	**20↓**
27*	**45**	**30**	**33.33↓**
28	**45**	**60**	**33.33**
30	**45**	**50**	**11.11**

* In patient numbers 9,26,27 decrease in HDL was observed post-treatment, which is indicated as percentage decrease **↓.**

Table 11 :

Parameter	Total number of patients	Percentage of patients
➢ 20 % rise in HDL	**7**	**38.88**
20% - 30 % rise in HDL	**4**	**22.22**
➢30% - 40 % rise in HDL	**2**	**11.11**
➢ 40% rise in HDL	**2**	**11.11**

d. Comparison of pre-treatment and post-treatment LDL value of patients who had completed 3 months of study period :

Patient Number	Pre- treatment LDL	Post-treatment LDL	Percentage decrease in LDL
3	**249**	**131**	**47.39**
4	**239**	**126**	**47.28**
5	**128**	**127**	**0.78**
6	**141**	**104**	**26.24**
8	**206**	**118**	**42.72**
9	**170**	**127**	**25.29**
10	**240**	**95**	**60.42**
16	**250**	**175**	**30**
17	**196**	**131**	**33.16**
18	**251**	**156**	**37.85**
19*	**162**	**188**	**16.05▲**
21	**151**	**131**	**13.25**
24*	**131**	**178**	**35.88▲**
25	**291**	**195**	**32.99**
26*	**175**	**186**	**6.29▲**
27	**171**	**151**	**11.7**
28	**178**	**110**	**38.2**
30	**211**	**141**	**33.18**

* In patient numbers 19,24,26 increase in HDL was observed post-treatment, which is indicated as percentage increase▲.

Table 13 :

Parameter	Total number of patients	Percentage of patients
➢ 20 % decrease in LDL	**3**	**16.66**
20% - 30 % decrease in LDL	**2**	**11.11**
➢30% - 40 % decrease in LDL	**6**	**33.33**
➢ 40% decrease in LDL	**4**	**22.22**

3. **Safety variables**

No abnormality was detected during general and systemic examination. Haematological and biochemical investigations did not reveal any abnormality following the study drug administration. The weight of patients remained stable. There were no changes in the ECG during or after the drug therapy in any of the patients.

Two patients complained of epigastric fullness and one patient complained of constipation of mild intensity. Two patients developed skin rash, one during the wash-out phase and one during the therapy period. Both of them discontinued from the study.

CONCLUSIONS

The study drug is effective in causing appreciable reduction in the serum cholesterol and triglyceride levels. And moderately good in raising the serum HDL-C levels.