6.0 SUMMARY AND CONCLUSION

The development of an improved pharmaceutical dosage form, such as an oral sustained release preparation, should be based upon the pharmacokinetic and pharmacodynamic properties of the drug. In addition, issues such as minimization of adverse drug reactions, patient compliance factors and overall treatment cost must be considered. The aim of present study involving extended release formulations was to reduce the dosing frequency of olopatadine from twice daily to once daily and thereby improving patient compliance and minimization of adverse drug reaction.

This was an open label, balanced, randomized three-treatment, three-period, three-sequence, single-dose, crossover bioavailability study in healthy, adult, human male subjects under fed condition comparing the two formulations of single dose of olopatadine hydrochloride 10 mg extended release tablet of Ranbaxy laboratories limited with two doses of Allelock® 5 mg tablets of Kyowa Hakko Kogyo Co. Ltd.

The clinical study was carried out in accordance with ICH Good Clinical Practices. The study protocol and the informed consent forms were approved by the Jamia Hamdard Institutional Review Board. Each of the subjects was required to understand and give his consent to participate in the study by signing the informed consent form. The signed original copy was retained and a copy was given to each study subject for record. The washout period maintained between the each period was of six days.

Blood samples were collected within 2 minutes of the specified time as per study design. Intravenous indwelling cannulae were kept in situ as long as possible, otherwise an alternative method of collecting by fresh clean vein punctures using standard disposable sterilized
syringe and a needle was used. After collection, blood samples were centrifuged as per the processing method to separate plasma. All plasma samples were stored in suitably labeled polypropylene tubes at -50°C or lower till analysis.

A high performance liquid chromatographic method was developed and validated in terms of selectivity, linearity, sensitivity, accuracy and precision, was used for the estimation of olopatadine in plasma. The standard curve was linear & coefficient of co-relation was found to be greater than 0.99 throughout the study.

In the present study bioavailability was assessed by measuring the pharmacokinetic parameters $AUC_{0-t}$, $AUC_{0-24}$, $AUC_{0-\infty}$, $C_{max}$, for olopatadine.

The ER formulations showed a similar area under the curve as compared to the reference IR formulation and there was no statistically significant difference ($p<0.0001$) in $AUC$ of test formulation A and B and reference R. The ratios of $AUC_{0-t}$, $AUC_{0-24}$ and $AUC_{0-\infty}$ for A/R were 91.08, 94.90 & 91.32 and for B/R were 89.63, 93.95 and 89.63 respectively. These were within the bioequivalence criteria of 80-125%.

The ER formulations reported a higher $C_{max}$ value as compared to the reference IR formulation and there was statistically significant difference ($p<0.0001$) in $C_{max}$ of test formulation A and B and reference R. The ratios of $C_{max}$ for A/R and B/R were 151.09 and 167.96 respectively. Therefore, none of the test formulation achieved bioequivalence criteria of 80-125%. But these higher $C_{max}$ did not pose any safety issue there were no serious adverse events reported throughout the study.
Finally on the basis of results, following conclusions can be drawn from the study:

- Test formulation A is not bioequivalent to reference product in terms of $C_{\text{max}}$
- Test formulation B is not bioequivalent to reference product in terms of $C_{\text{max}}$
- Both A and B formulation are bioequivalent to reference product in term of AUC
- 100% power was attained at AUC; however, for $C_{\text{max}}$ it was only 60%. But this does not have much impact on final result as Test/Reference ratio is very high.
- Intra-subject variability for AUC was very low (i.e. approx. 8%) and for $C_{\text{max}}$ it was 26%, suggesting that olopatadine is not highly variable.
- The test formulations were not able to achieve the comparable $C_{\text{max}}$ and longer $T_{\text{max}}$ as expected form an extended release formulation though the extent of absorption was similar in all the three formulations. So considering the result the test formulations need to be reformulated in order to prove bioequivalence against the 12 hourly administered reference formulation.

There are few points which can be explored in future research

- Research can be done to study the dose dumping effect which was suspected to cause higher $C_{\text{max}}$ values of the test formulations.
- Effect of smoking on the pharmacokinetic parameters of olopatadine can be investigated.