Chirality and the Blueprint of Life
In nature nearly all biological molecules must be homochiral to function.\(^1\) It is well known that all amino acids are left-handed and all sugars in DNA and RNA are right-handed\(^1\). Moreover, we eat optically active bread and meat, we wear optically active clothes, we read books made of optically active cellulose, our muscle proteins are optically active, glycogen is optically active, and the list goes on. Our body is chiroselective i.e. it gives different or varying responses to the different enantiomers\(^2\). The Anaesthesist. 1998 states… ‘Human body comprises a chiral environment due to optically active proteins. Thus enantiomeric drugs exhibit different pharmacological properties, when used as pure optical isomers.’\(^2\)

It is well known that drugs bind on specific receptor sites, and the enantiomers that best fit the receptor has the highest therapeutic activity\(^3\). Thus, separation of PURE enantiomers becomes extremely important. Most of the organic molecules that are available are chiral and very few are achiral. In fact the chiral market internationally was estimated to be of $133 billion in the year 2000.

Drawbacks of Racemates
In certain instances racemates of drugs have been proven to be extremely harmful. A classical example is that of Thalidomide. The Racemate of Thalidomide was marketed as a “morning sickness” drug. The drug when administered to pregnant patients produced teratogenic effects. Later on it was found that only the (S) isomer produced teratogenic effects and led to phocomelia, whereas later on it was found out that only the (R) isomer of Thalidomide possessed therapeutic activity and was devoid of the teratogenic effects. The R isomer is very useful for the treatment of cancer, AIDS and erythema nodosum leprosum.

Chirality – An Emerging Trend in Therapeutics
Stereochemical aspects of drug action have intrigued researchers ever since the introduction of the receptor concept.\(^3\) Today, enantioselectivity is increasingly understood in molecular and atomic detail. As a result, chirality has emerged as an important aspect in the Pharmaceutical Technology. The development of chiral technology has opened a new era in the pharmaceutical field, bringing to the
patients an array of drugs that stand a class apart in terms of therapeutic efficacy and safety.

As early as in 1980’s and more so since the FDA recognized the importance of single isomer drugs, the pharmaceutical research and development has started focusing on single isomer or chiral drugs. The need arose because of the fact that our body is chiroselective, i.e. the body shows different biological responses to different isomers. Moreover, 2/3rd of the molecules in nature are chiral, hence the best way to interact with nature for a positive outcome would be to use chiral molecules.

The most commonly used antihypertensives are now available as chirally pure molecules. Two major antihypertensive drug categories have been studied and explored are:

1. Calcium Channel Blockers (e.g. S-Amlodipine)
2. Beta Blockers (e.g. S-Atenolol)

Amlodipine is commonly used calcium channel blocker which is available as R- and S- forms. Studies show that only S-amlodipine (ASOMEX) has calcium channel blocking activity, and is responsible for all the therapeutic activity of amlodipine. The R-isomer has been shown to be inactive.

Randomised controlled trials in patients with hypertension conclusively states that S-amlodipine 2.5mg has a similar clinical efficacy as that of amlodipine 5mg patients.6,7

A post marketing surveillance study conducted in 1859 patients, makes an interesting revelation. According to the study,8 of the 314 patients who presented peripheral edema with conventional amlodipine when switched over to S-amlodipine, the edema subsides, i.e. a success rate of 98.72%. Thus S-amlodipine can prove to be an ideal switch-over therapy in patients on other calcium channel blockers.

Beta-blockers – A Historical Review

Since the discovery of Adrenaline by John Jacob Abel (1897), the stereochemical aspects of beta-blockers, one of the most commonly used class of cardiovascular drugs, came into picture. In the year 1948 Dr. Raymond P. Ahlquist hypothesized that effects of catecholamines were mediated by activation of α- & β- adrenergic receptors9. Ahlquist’s 1948 paper was noticed primarily because of the confirmation of his work by Powell & Slater. They postulated the idea of dual receptor mechanism. Powell & Slater described the first agent dichloro-isoproterenol. In 1962, Sir James Black with Stephenson and Prichard synthesized Pronethalol and Propranolol10. For his invaluable contribution, Sir James Black was awarded the Nobel Prize in the year 1988. Since then, Propranolol remains a prototype against which others agents are compared. In 1967 Lands postulated existence of β1- & β2- receptors. This formed the basis of development of selective beta-adrenergic blocking drugs. And soon followed atenolol.

Stereospecificity - An inherent property of Beta-blockade

β-blockers were introduced in clinical practice in the 1960’s as racemic mixtures consisting of two enantiomers in a fixed 1:1 ratio. Studies since then have shown that β-blockers possess an inherent high degree of enantioselectivity in binding to the β-adrenergic receptor10. For β-blockers with a single chiral center, the (-)enantiomer possesses much greater affinity for binding to the β-adrenergic receptors than the antipode. It has been clearly shown in vitro as well as in vivo human studies that only the S-enantiomers exert β-blockade when clinical doses of the racemic drugs are used. R-Atenolol does not contribute significantly to the negative chronotropic or inotropic effects of racemic atenolol11. A report published in the Chemical & Pharmaceutical bulletin 1998 states that a lowered heart rate is sometimes encountered after administration of racemic atenolol, but the use of (S)-Atenolol avoids this side effects12. Stoschitcky et al13 states that d- & l-enantiomers of all β-blockers have different pharmacodynamics and pharmacokinetic properties. Therefore, optically pure enantiomers should be recognized as
distinct drugs. And hence racemates can no longer be regarded as optimal for patients on beta-blocker therapy.

It further also states that the non β-blocking isomer may contribute to increased side effects. Thus it would make sense to perform the so-called ‘CHIRAL SWITCH’ i.e. to replace currently used racemic β-blockers by optically pure l-enantiomers. This can avoid potential harm to patients.

Amongst chiral drugs, the beta-adrenergic blocking drugs are one of the best-understood classes from the perspective of stereoselectivity in pharmacokinetics and pharmacodynamics. The enantiomers of β-blockers possess markedly different pharmacodynamics, and in some cases, pharmacokinetics.

Stereoselectivity in Pharmacologic Action
The available data regarding the pharmacologic action of beta-blockers indicate that the interaction of these agents with beta-adrenoceptors is highly stereoselective. Generally, the cardiac beta-blocking activity of the beta-blockers with two enantiomers resides in their S (-) enantiomers, the reported S:R activity ratio being in the range of 33 to 530. However, the R (+)-enantiomer has relatively strong activity in blocking β receptors in ciliary process.10

Stereoselectivity in Pharmacokinetics
Generally, beta-blockers are absorbed from the gastrointestinal tract via passive diffusion. Therefore, their absorption is not considered stereoselective. The dissociation rate constant of binding may be stereoselective. It has been shown that atenolol; a hydrophilic drug is stored into and released from the adrenergic nerve endings. Further, it has been reported that the uptake into and release of atenolol from the models of adrenergic cells are stereoselective, favoring the more active S(-)-enantiomer of atenolol by 2 to 5 fold. Additionally, a study in humans, chronically receiving racemic atenolol, indicated that the S(-)-enantiomer of atenolol is selectively released into the plasma after exercise. The exercise-induced stereoselective release of atenolol from adrenergic nerve ending significantly changed the (+): (-) plasma concentration ratio of atenolol from 1.18 (at rest) to 0.64 (after exercise). The elimination of most beta-blockers occurs via hepatic metabolism and/or renal excretion of the unchanged drug. The hydrophilic beta-blockers, such as atenolol are exclusively excreted unchanged in urine. It is seen that the elimination of beta-blockers is stereoselective. Only the S-enantiomers are excreted stereoselectively. The R-enantiomer on the other hand accumulates in the body.10

(S)-Atenolol [ATPURE]
(S)-Atenolol is a highly β₁-selective adrenergic receptor antagonist used in the management hypertension, angina pectoris and myocardial infarction. Studies have shown that atenolol exists as a racemic mixture of R- and S-enantiomers in a fixed 1:1 ratio, and human studies have unequivocally shown that the S-enantiomer of atenolol almost exclusively possesses the β₁-blocking activity. The R –enantiomer do not contribute to the cardiovascular effects. S-atenolol is indicated in patients with Hypertension, Angina pectoris and Myocardial infarction.

S-atenolol reduces the dose of atenolol by half. The normal dose of atenolol is Stage I Hypertension...
(As per JNC VII: SBP=140-159 mm Hg; DBP= 90-99 mm Hg) is 12.5 – 25 mg once daily. In Stage II Hypertension (As per JNC VII: SBP=≥160 mm Hg; DBP=≥100 mm Hg) a dose of 50mg once daily is recommended. In patients with Angina and Myocardial infarction a dose of 12.5 – 25 mg once daily recommended.

Clinical efficacy: Extensive International Data Supports the Clinical Efficacy of (S)-Atenolol
Clinical trials conducted internationally\(^\text{14}\) and in India conclusively prove the excellent clinical efficacy of (S)-Atenolol. Studies conclude that only (S)-atenolol, but not (R)-atenolol, contributes to the $\beta_1$-blocking effect of currently used racemic-atenolol and the same effect can be elicited with the (S)-enantiomer administered alone. In-vitro studies have shown that atenolol is stereoselectively taken up by and released from adrenergic nerve endings by membrane depolarisation\(^\text{15}\).

Indian clinical data confirms the International findings
A summary of the 5 Randomized Controlled trials\(^\text{16}\)
Five randomized, double-blind, double-dummy, parallel group, multicentric controlled trials were conducted in 250 patients to compare the efficacy and tolerability of (S)-Atenolol 25mg with racemic Atenolol 50mg in the treatment of stage 1 and 2 hypertension (As per JNC VI: Stage I Hypertension: Systolic blood pressure [SBP] =140-159mm Hg; Diastolic blood pressure [DBP]= 90-99mm Hg. Stage II Hypertension: SBP=160-179mm Hg; DBP=100-109mm Hg). Of the 250 patients, 232 (114 patients in the (S)-Atenolol & 118 patients in the Atenolol group) completed the study; 11 in the (S)-Atenolol and 7 in the atenolol treatment groups lost to follow up, and were dropped out. Patients were administered either Atenolol 50mg or (S)-Atenolol 25mg for a period of 6 weeks after a 2 week washout therapy. The investigations performed were blood pressure (standing, supine and sitting), heart rate, ECG, serum creatinine, SGPT, SGOT, routine urine analysis, and lipid profile. In these studies the observer bias was taken care of by the double blind, double dummy study design where the investigators and the patients were kept unaware of the study medication administered throughout the study period.

![Fig. 2: The graph shows a significant reduction in systolic and diastolic BP after treatment with (S)-Atenolol 25mg and Atenolol 50mg. The reduction in BP was similar between the two groups. This confirms the equivalent efficacy of (S)-Atenolol 25mg and atenolol 50mg.](image)

The clinical trial findings as shown in figure 2 demonstrates a significant reduction in blood
pressure by a daily dose of (S)-Atenolol 25mg, which was found to be similar to that of racemic Atenolol 50mg in patients with stage 1 and 2 hypertension (JNC VI). The diastolic and systolic blood pressure recorded in the standing, sitting and supine positions were found to be similar in both the treatment groups. There was no statistically significant change in the levels of Serum Creatinine, SGOT, SGPT, HDL, LDL, Triglyceride and Total Cholesterol in patients receiving Atenolol 50mg and (S)-Atenolol 25mg in the clinical trials.

Angina pectoris: (S)-Atenolol effectively reduces the frequency of anginal episodes in patients with angina. During symptom limited treadmill exercise testing, atenolol, and hence (S)-Atenolol reduces electrocardiographic indices of myocardial ischemia, whether painful or pain-free, and improves exercise time. Atenolol has been shown to be effective in reducing both angina and silent ischemic events in patients with mixed angina.

Myocardial infarction (MI): When given early in the course of MI (within 12 h of the onset of symptoms), Atenolol, and hence (S)-Atenolol significantly reduces the frequency of ventricular extrasystoles and more complex ventricular arrhythmias. In addition, atenolol has been shown to produce effective relief of ischemic pain in acute myocardial infarction; pain relief coincided with significant reduction in heart rate, systolic blood pressure, and double product.

Conclusion
Human body comprises a chiral environment due to optically active proteins. Thus enantiomeric drugs exhibit different pharmacological properties, when used as pure optical isomers. It is well known that drugs bind on specific receptor sites, and the enantiomers that best fit the receptor has the highest therapeutic activity. Thus separation of chirally pure drugs becomes very important.

ASOMEX (S-Amlodipine), which is the chirally pure form of amlodipine, has a proven clinical efficacy in the treatment of hypertension. It has been extensively studied in the clinical set-up. A trial in 1893 patients showed that when S-amlodipine is administered to patients who developed peripheral edema with amlodipine, the edema subsided in 98.72% patients (310/314).

ATPURE (S-Atenolol) is the chirally pure form of atenolol, used in the treatment of hypertension. Studies conducted internationally and in India concluded that only S-atenolol has β1-blocking activity and R-atenolol does not contribute towards the inotropic and chronotropic effects of atenolol. Since the dose of atenolol is reduced by half, there is less metabolic load on the body. Moreover, it may reduce the side effects of atenolol.

Thus, in situations where applicable, it makes a perfect sense to switch over the patients on racemic drugs to chirally pure drugs.

References
9. Goodman & Gillman’s: The Pharmacological basis of Therapeutics. 10th Ed. Page 249