Chapter 1

Introduction

1.0 INTRODUCTION

The reliable information about the prevalence of hypertension in different world regions is essential to the development of national and international health policies for prevention and control of this condition. The estimated total number of adults with hypertension in the year 2000 was 972 million (937-987 million) in economically developed countries and 639 million (625-654 million) in economically developing countries. The number of adults with hypertension in 2025 is predicted to increase by about 60% to a total of 1.56 billion (1.54-1.58 billion). Hypertension is an important public-health challenge worldwide. Prevention, detection, treatment, and control of this condition should receive high priority (Kearney et al. 2005).

In India, hypertension is the leading non communicable disease risk and estimated to be attributable for nearly 10 per cent of all deaths. Adult hypertension prevalence has risen dramatically over the past three decades from 5 per cent to between 20-40 per cent in urban areas and 12-17 per cent in rural areas. The number of hypertensive individuals is anticipated to nearly double from 118 million in 2000 to 213 million by 2025. It is estimated that 16 per cent of ischemic heart disease, 21 per cent of peripheral vascular disease, 24 per cent of strokes are attributable to hypertension underlining the huge impact effective hypertension prevention and control can have on reducing the rising burden of cardiovascular disease (CVD). (IJMR April 2013).

Olmesartan medoxomil is an orally administered pro-drug of olmesartan, a non-peptide Angiotensin Receptor Blocker (ARB) that has high selectivity for the AT1 receptor, to which it is highly bound, having a limited affinity to the AT2 receptor. Since activation of the AT1 receptor by angiotensin II induces arteriolar vasoconstriction, sympathetic nervous system activation, salt and water retention, and aldosterone secretion, olmesartan is presumed to reduce high blood pressure (BP) levels mostly by blocking the vasoconstrictor and aldosterone-secreting effects of angiotensin II (Giuliano et al. 2011).

Olmesartan is indicated for the treatment of stage 1 & stage 2 essential hypertension alone or in combination with diuretic, Calcium Channel Blocker (CCB), and Beta-blockers.

The safety and tolerability of olmesartan medoxomil have been evaluated in several clinical trials. Data were pooled from seven randomized trials involving a total of 3095
patients with hypertension who received olmesartan medoxomil (2.5 mg to 80 mg/Day) for 6 to 12 weeks. Overall, patient tolerated the drug well, and the incidence of adverse events was similar to that for placebo (42.2% and 42.7%, respectively) (SPC 2009).

Olmesartan medoxomil is a prodrug that is rapidly hydrolyzed into olmesartan in the gastrointestinal tract. Olmesartan is rapidly absorbed from the gastrointestinal tract into the body, with a maximum plasma concentration \( C_{\text{max}} \) of 0.22–2.1 mg/L and time to \( C_{\text{max}} \) of 1.4–2.8 h following administration of olmesartan medoxomil 10–160 mg. For the same doses, the mean area under the concentration-time curve (AUC) was 1.6–19.9 mg·h/L. Olmesartan is the only metabolite of olmesartan medoxomil, and is excreted in the feces (≈60%) and the urine. The terminal elimination half-life of olmesartan varied between 10 and 15 hours after multiple oral dosing. Steady state was reached after the first few doses and no further accumulation was evident after 14 days of repeated dosing. Renal clearance was approximately 0.5 – 0.7 L/h and was independent of dose (Schwocho et al. 2001, Lurbe et al. 2009).

The efficacy of olmesartan medoxomil alone or in combination have been evaluated in several clinical trials for example, Gomes et al. conducted a clinical trial in Brazil to evaluate the efficacy of olmesartan in 144 patients with primary stage 1 & stage 2 arterial hypertension. Patient treatment was divided into 4 phases with olmesartan as monotherapy and in combination with Hydrochlorothiazide & Amlodipine besylate. The result of the study shows that treatment with olmesartan medoxomil in monotherapy or in combination showed to be very effective and safe. In patients with stage 1 and 2 hypertension (mean of 158/97 mmHg), 86% of the individuals reached the goal of BP < 130/85 mmHg. Additionally, there were significant decreases of up to 44 mmHg in SBP and up to 22 mmHg in DBP without a significant increase in adverse events (Gomes et al. 2008).

Patients with hypertension frequently suffer from other conditions like diabetes and cardiovascular disease. Various Clinical trials investigated the efficacy of Olmesartan medoxomil in reducing cardiovascular disease beyond BP reduction involving patients who were at high risk due to atherosclerosis or type 2 diabetes. Type 2 diabetes is strongly associated with hypertension and kidney damage. The first clinically detectable sign of renal disease is microalbuminuria which is a predictor for nephropathy as well as cardiovascular disease. Studies have shown that angiotensin II receptor antagonists have renoprotective effects in diabetes and can slow the progression of microalbuminuria.
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(Brunner et al 2001, Lewis et al 2001). In addition to its BP-lowering and renoprotective effect, olmesartan may produce beneficial effects on atherosclerosis and thus on overall cardiovascular risk in patients with hypertension who have atherosclerosis, or are at risk of developing it. Chronic vascular inflammation is believed to play a major role in atherosclerosis and the European Trial on Olmesartan and Pravastatin in Inflammation and Atherosclerosis (EUTOPIA) set out to investigate the effects of olmesartan medoxomil 20 mg on markers of vascular inflammation. After treatment for 6 weeks, olmesartan medoxomil reduced serum levels of high-sensitivity C reactive protein (hsCRP), a strong predictor of cardiovascular events, by 15% from baseline (p<0.05). Olmesartan medoxomil also significantly reduced levels of high-sensitivity tumor necrosis factor-α (hsTNF-α) by 8.9% (p<0.02), interleukin-6 (IL-6) by 14.0% (p<0.05) and monocyte chemotactic protein-1 by 6.5% (p<0.01). These anti-inflammatory changes indicate that olmesartan medoxomil may produce beneficial effects on atherosclerosis and thus on overall cardiovascular risk beyond BP reduction (Hans Brunner, 2006).

The rising cost of health care has compelled health agencies and regulatory bodies to devise strategies to decrease costs without compromising the health care services. It is a fact that generic substitution results in considerable cost savings to patients and other payers. A pharmacoeconomic analysis, using efficacy data from the trial that compared olmesartan medoxomil with losartan, valsartan, and irbesartan has been performed from the perspective of the managed healthcare environment in the US. The results indicated that substantial cost savings were possible with olmesartan medoxomil. For example, when compared with valsartan, olmesartan medoxomil reduced estimated costs over 5 years in a hypothetical cohort of 100 000 patients by $16 231 000 for cardiovascular disease and $11 955 000 for coronary heart disease (Brunner et al 2001). However, switchability amongst the brand and generic is dubious and may require prior confirmation of bioequivalence (J. Bras. Nefrol. June 2010). Generic substitution may alter the toxicity and efficacy profile after switching from one brand to another. There are number of patients with a history of good results on brand name products observed difficulties when generics were substituted. For instance, lack of bioequivalence among different brands has been well documented with mefloquine (Weidekamm et al. 1998), clozapine (Kluznik et al. 2001), diclofenac sodium (Suleiman et al. 1989), diltiazem
(Joshi et al. 1990) and estrogens tablets (Adams et al. 1979) which may be due to poor quality or high inter-individual variability.

The rationality for conducting this study was that, the health care costs continue to increase, and one important component that can be reduced substantially is drug cost. For this purpose, substitution of the expensive originator drugs with cheaper generic copies is required. Generic drugs are less expensive than brands as generic manufacturers do not have to conduct costly clinical trials to test the safety and effectiveness. Hence, the present project was planned to compare bioavailability of Olmesartan medoxomil 40 mg with reference product in healthy, adult, human subjects under fasting condition to launch the generic version for same in the market.