1.0 INTRODUCTION & RATIONALE OF STUDY

Type-2 diabetes mellitus (T2DM), a progressive disease characterized by insulin resistance and eventual insulin deficiency, is caused by a gradual decrease of insulin secretion following loss of beta-cell function (Polonsky et al. 1988). Approximately 95% of diabetic patients have type-2 diabetes, whereas about 5% of patients have type-1 diabetes. World Health Organization (WHO 2005) reports show that 32 million people had diabetes in the year 2000 (Wild et al. 2004). The International Diabetes Federation (IDF) estimates the total number of diabetic subjects to be around 40.9 million in India and this is further set to rise to 69.9 million by the year 2025 (Sicree et al. 2006). Type-2 diabetes is associated with significant cardiovascular morbidity and mortality (UKPDS 1997; Cerveny et al. 1988).

Hyperglycemia increases the risk of microvascular complications (Stratton et al. 2000). Patients with type-2 diabetes are associated with a 2 to 4 fold increased risk of coronary heart disease (CHD) (Haffner 1998), while dyslipidemia is a major risk factor in patients with type-2 diabetes (Farmer et al. 2008; Turner et al. 1998). According to the National Cholesterol Education Program Adult Treatment Panel (NECP ATP) III, patients with type-2 diabetes should generally be considered to be at equivalent cardiovascular disease risk to patients with established CHD and should have low-density lipoprotein (LDL) cholesterol levels reduced to <100 mg/dL or by 30–40% (NCEP-3).

HMG-CoA reductase inhibitors (statins) are the drugs of choice for lowering LDL cholesterol levels (O’Brien et al. 1988). Atorvastatin 10–80 mg/day is more potent in reducing LDL cholesterol, has a longer half-life, and can be administered at any time of the day (Choi et al. 2006, Jones et al. 2003; Aguilar et al. 2000). Clinical trials have also shown that administration of Atorvastatin 10 mg/day in patients with type-2 diabetes reduced the risk of cardiovascular events by 35% (Colhoun et al. 2004).

Antihyperglycaemic agents are used for treatment of diabetes, Metformin is one of the oldest, most widely used and least expensive antihyperglycaemic drugs for the treatment of type-2 diabetes. Metformin is specified as the first-line oral antihyperglycemic drug of choice (Nathan et al. 2006, IDF 2006; LADA 2000).
Chapter 1

Introduction

Metformin is an oral antihyperglycaemic drug that decreases hepatic glucose production, decreases intestinal absorption of glucose and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. (Krentz et al. 2005). Metformin Benefits are observed at doses 500 mg to 2550 mg. (US FDA 2008; Garber et al. 1997). Additionally beneficial effects of Metformin on lipids are also reported (Ginsberg et al. 1999, Grant 1996, Fanghanel et al. 1996, Giugliano et al. 1993, DeFronzo et al. 1995; Dunn et al. 1995).

To control the concomitant diseases rationale drug combination are being marketed. More than one-third of all the new drug products introduced worldwide during the last decade were fixed dose combination (FDC) preparations. Fixed dose combinations (FDCs) are available for the treatment of various ailments range from nutritional deficiency to cardiovascular diseases. The development of anti-hyperglycemic and anti-hyperlipidemic fixed dose combinations is to improve patient compliance and to benefit from the added effects of the two active drugs given together.

Multiple drug therapy is very common in patients with diabetes. A combined therapy of an antihyperglycaemic agent and a statin is indicated for the treatment of diabetes patients with a risk of CHD. However, poor patient compliance with treatment is a recognized problem in the treatment of chronic diseases that require multiple drug therapy. A meta-analysis of nine studies in patients with diabetes, hypertension, HIV and tuberculosis demonstrated that FDCs reduced the relative risk of non-compliance by 26% compared with single-component regimens. (Bangalore et al. 2007). Additionally, FDCs offer a strategy to reduce the pill burden for patients and a simple, more convenient way of managing their medicines. FDCs yield better clinical outcomes compared with combinations of the same drugs given separately (WHO 2011). Therefore, a fixed dose combination (FDC) of an antihyperglycaemic agent and a statin (given once daily) is an attractive option for patients with type-2 diabetes with hyperlipidemia (Bolen et al. 2007) or without hyperlipidaemia (Ridker et al. 2009, Brugts et al. 2009; Ridker et al. 2008).

Data from various clinical trials has indicated that there is no significant pharmacokinetic and/or pharmacodynamic interaction between Atorvastatin and Metformin (Krentz et al. 2005). Based on such findings, an FDC tablet of Atorvastatin 10 mg and Metformin 500 mg extended release (ER) was developed for patients with
type-2 diabetes with or without hyperlipidaemia. For FDC tablet regulatory authorities (FDA, EMEA; DCGI) insist that generic products should compulsorily be "essential similar" with that of reference product in order to exclude any clinically significant difference. The notion of essential similarity has three fundamental aspects. Comparing brand-name drug, the generic drug must have: similar composition (same quantity and type of active principle), route of administration and therapeutically equivalent (bioequivalent).

The aim of this study was to assess the single oral dose bioequivalence of the test formulation i.e. Fixed dose combination tablet of Atorvastatin 10 mg (as Atorvastatin Calcium) and Metformin HCl 500 mg ER of Ranbaxy Laboratories Limited, with Lipitor® tablets (containing Atorvastatin 10 mg as Atorvastatin calcium) of Pfizer and Glucophage® XR tablets (containing Metformin HCl 500 mg) of Bristol-Myers Squibb company, administered concurrently in healthy, adult, human male subjects under fed condition.