LINAGLIPTIN PRESCRIPTION FREQUENCY AS ANTIDIABETIC DRUG

SUBMITTED TO

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EAST WEST UNIVERSITY

DECLARATION BY THE CANDIDATE

I, Farhana Azad, hereby declare that, **"LINAGLIPTIN PRESCRIPTION FREQUENCY AS ANTIDIABETIC DRUG** "submitted by me to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the Degree of Masters of Pharmacy (M.Pharm) is a confide record of original research work carried out by me under the supervision and guidance of Md. Anisur Rahman, Senior Lecturer, Department of Pharmacy, East West University, Bangladesh. I also declare that no part of this report has been or is being submitted elsewhere for the award of any Degree.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitle "**LINAGLIPTIN PRESCRIPTION FREQUENCY AS ANTIDIABETIC DRUG** "submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the Degree of Masters of Pharmacy , was carried out by Farhana Azad, ID No. 2014-1-79-008 under my supervision and no part of this dissertation has been or is being submitted elsewhere for the award of any Degree.

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ENDORSMENT BY THE CHAIRPERSON

This is to certify that the entitled **"LINAGLIPTIN PRESCRIPTION FREQUENCY AS ANTIDIABETIC DRUG"** is a genuine research work carried out by Farhana Azad, ID No.2014-1-79-008 under the supervision of Md. Anisur Rahman (Senior Lecturer, East West University, Dhaka). I Father certify that no part of the thesis has been submitted for any other degree and all the resources of the information in this connection are duly acknowledged.

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Farhana Azad

DEDICATED TO

MY BELOVED PARENTS

AND TEACHERS

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Abbreviation

1. ACEIs - Angiotensin Converting Enzyme Inhibitors.
2. ALT - Alanin Amino Transferase
3. ARBs - Angiotensin Receptor Blockers
4. AST - Aspartate Amino Transferase
5. AUC - Alter the Overall Exposure
6. CHF - Congestive Heart Failure
7. CPK - Creatine Phosphokinase
8. CRP - C-Reactive Protine
9. CYP - Cyptochrome P
10. DM - Diabetes Mellitus
11. DPP-4 - Dipeptidyle Peptidase-4
12. ED - Energy Dependent
13. EMEA - European Medicines Energy
14. ESRD - End-stage Renal Disease
15. FDA - Food and Drug Administration
16. GDM - Gestational Diabetes Mellitus
17. GIP - Glucose-Dependent Insulinotropic Peptide
18. GLP - Glucagone-like Peptide

19. GLP-1 - Glucagone-like Peptide-1

20. IDDM - Insulin-Dependent Diabetes Mellitus

21. IDF - International Diabetic Federation

22. LADA - Latent Autoimmune Diabetes of Adult

23. MRDR Malnutrition-related Diabetes Mellitus

24. NPH - Neutral Protamine Hagedorn

25. NIDDM – Non insulin-Dependent Diabetes Mellitus

26. NYHA - New York Heart Association

27. PEP - Prolyl Oligopeptidase

28. PPARs - Peroxizome Proliferated Activated Receptors

29. PPRE- Peroxizome Proliferator Responsive Elements

30. RBCs - Red Blood Cells

Abstract

This retrospective study was designed to observe the adherence of the new antidiabetic drugs prescribing practice in diabetic hospital of our country. During two months study period, 500 prescription (Diabetic Books prescription and new patients initial form prescription) suffering from diabetes mellitus were enrolled from the BIRDEM, Shahabag, Dhaka. This research revealed that insulin alone or in combination with metformin or alone metformin or alone vildagliptin, sitagliptin, linagliptin or metformin in combination with vildagliptin, sitagliptin, linagliptin and other types of drugs which were prescribed for the treatment of patient suffering from diabetes. Our study found only 19 prescriptions with linagliptin among 500 prescriptions which was only 3.8%. So it can be calculated that linagliptin still seems to be not well accepted by most of the physicians. Another outcome of this study indicated that in 42% prescription there is a practice of old antidiabetic drugs. Furthermore, county wide multicenter research with a large sample is still needed to consolidate the observation of this study.

Keywords: Diabetes, Antidiabetic drugs, Insulin, Metformin, Vildagliptin, Sitagliptin, Linagliptin.

CHAPTER: ONE

INTRODUCTION

1.1 INTRODUCTION

The aim of the study was to find out how much in frequency Linagliptin is prescribed to the diabetic patients. In addition this study was performed to identify the adherence of the given treatment with the new antidiabetic drugs in our country. Furthermore this study was also focus on how many old antidiabetic drugs is prescribed by physician. If the old antidiabetic drugs is suficient and very effective than new antidiabetic drugs. So, why we take new antidiabetic drugs? Where previous antidibetic drugs is given enough support to the diabetic patient.

Significance of the study

This research will bring the list of old antidiabetic drugs which are commonly prescribed in hospital of Bangladesh to the patient. If the outcome of the study is not sufficient for new ant diabetic drugs this will be indicated that old antidiabetic drugs are sufficient for diabetic patient. And the old antidiabetic drugs are better than new antidiabetic drugs. In future, we have need to develop the new antidiabetic drugs for the patient. Therefore, it will bring a radical change in treatment of diabetic patients.

1.2 Diabetes mellitus:

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugarlevels over a prolonged period.(WHO, 2014).Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. More commonly referred to as "diabetes" a chronic disease associated with abnormally high levels of the sugar glucose in the blood. Diabetes is due to one of two mechanisms:

1. Inadequate production of insulin (which is made by the pancreas and lowers blood glucose), or

2. Inadequate sensitivity of cells to the action of insulin.

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left

untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, stroke, chronic, foot ulcers, and damage to the eyes. (International Diabetes Federation. 2006)

1.3 Types of Diabetes:

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced (Dornal, 1977).

There are three main types of diabetes mellitus:

- Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown. (WHO, 2013)
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly. As the disease progresses a lack of insulin may also develop.This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise. (WHO, 2013)
- Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood-sugar level.(WHO, 2013)

Table 1. Classification and observations on types of diabetes mellitus

Type	Characteristic	Clinical comment
Type 1	Autoimmune, previously called juvenile or insulin-dependent diabetes mellitus	Potential association with other autoimmune diseases
Type 2	Polygenic and influenced by environment	Increasing incidence associated with higher life span and western cultural habits
Gestational	Aggressive clinical progress	May persist after pregnancy
Secondary	Side effect of medications or pancreas dysfunction (e.g.; steroids, chronic alcoholism)	Causative disease or medication may also influence ocular and lacrimal function
Genetic	Genetic defects in insulin secretion or action	Potential ocular associated malformations

Figure: 1 Classification of Diabetes mellitus

(Source: http://www.scielo.br/img/revistas/abo/v71n6s0/18t1.gif)

Type 1 Diabetes:

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhansin the pancreas, leading to insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T-cell-mediatedautoimmune attack leads to the loss of beta cells and thus insulin.(Rother,2007) It causes approximately 10% of diabetes mellitus cases in North America and Europe. Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children.(Rother *et al.,* 2007).

"Brittle" diabetes, also known as unstable diabetes or labile diabetes, is a term that was traditionally used to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This term, however, has no biologic basis and should not be used.(WHO,1990) Still, type 1 diabetes can be accompanied by irregular and unpredictable high blood sugar levels, frequently with ketosis, and sometimes with serious low blood sugar levels. Other complications include an impaired counterregulatory response to low blood sugar, infection, gastroparesis (which leads to erratic absorption of dietary carbohydrates), and endocrinopathies. (Merck Publishing, 2010)These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes. (Dornal *et al*., 1977).

Type 2 diabetes:

Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion.The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 DM is the most common type of diabetes mellitus.In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, high blood sugar can be reversed by a variety of measures and medicationsthat improve insulin sensitivity or reduce the liver's glucose production.Type 2 DM is due primarily to lifestyle factors and genetics.A number of lifestyle factors are known to be important to the development of type 2 DM, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization.(Williams textbook of endocrinology 12th ed) Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders.Even those who are not obese often have a high waist–hip ratio.(Shoback *et al*.,2011).

Dietary factors also influence the risk of developing type 2 DM. Consumption of sugar-sweetened drinks in excess is associated with an increased risk.(American Diabetes Association,2014) The type of fats in the diet is also important, with saturated fats and trans fatty acids increasing the risk and polyunsaturated and monounsaturated

fat decreasing the risk.Eating lots of white ricealso may increase the risk of diabetes.A lack of exercise is believed to cause 7% of cases. (Davis, 2004).

Gestational diabetes

Gestational diabetes is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood sugar level. (WHO, 2013)Prevention and treatment involve a healthy diet, physical exercise, not using tobacco and being abnormal. Blood pressure control and proper foot care are also important for people with the disease. Type 1 DM must be managed with insulin injections. Type 2 DM may be treated with medications with or without insulin. Insulin and some oral medications can cause low blood sugar. Weight loss surgery in those with obesity is sometimes an effective measure in those with type 2 DM. Gestational diabetes usually resolves after the birth of the baby.Gestational diabetes (or gestational diabetes mellitus, GDM) is a condition in which women without previously diagnoseddiabetes exhibit high blood glucose (blood sugar) levels during pregnancy (especially during their third trimester).Gestational diabetes is caused when insulin receptors do not function properly. This is likely due to pregnancy-related factors such as the presence of human placental lactogen that interferes with susceptible insulin receptors. This in turn causes inappropriately elevated blood sugar levels.(International Diabetes Federation.2006).Gestational diabetes generally has few symptoms and it is most commonly diagnosed by screening during pregnancy. Diagnostic tests detect inappropriately high levels of glucose in blood samples. Gestational diabetes affects 3-10% of pregnancies, depending on the population studied. (Kitabchi *et al*.,2009).As with diabetes mellitus in pregnancy in general, babies born to mothers with untreated gestational diabetes are typically at increased risk of problems such as being large for gestational age (which may lead to delivery complications), low blood sugar, andjaundice. If untreated, it can also cause seizures or stillbirth. Gestational diabetes is a treatable condition and women who have adequate control of glucose levels can effectively decrease these risks. The food plan is often the first recommended target for strategic management of GDM.Women with unmanaged gestational diabetes are at increased risk of developing type 2 diabetes mellitus (or, very rarely, latent autoimmune diabetes or Type 1) after pregnancy, as well as having a higher incidence of pre-eclampsia and Caesarean section; their offspring are prone to developing childhood

obesity, with type 2 diabetes later in life. Most women are able to manage their blood glucose levels with a modified diet and the introduction of moderate exercise, but some require antidiabetic drugs, includinginsulin. (Kitabchi *et al*., 2009).

Other types

Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes. Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology. Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cellfunction. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to thepancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization when the current taxonomy was introduced in 1999. (Cooke *et al.*, 2008).

Type 1	Type 2	Gestational
Usually young	Usually older	First detected in pregnancy
Short history- acute onset	Insidious onset	Routine testing
Not overweight	Often overweight	Often overweight
Insulin deficiency	Insulin resistance	Usually insulin resistance - placental hormones
Rare	Common	Becoming more common
Requires insulin from diagnosis	Diet and lifestyle change can reverse it Then add oral medications May require insulin	Diet and lifestyle plus medications to limit effects on the growing baby
Often random	Strong family history	Family history of T2DM

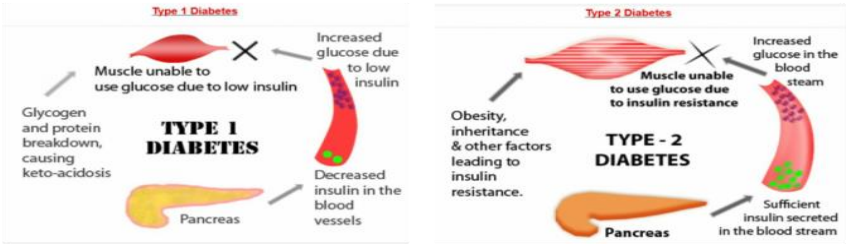


Figure2: Describe of Diabetes (weebly.com)

(Source: http://describediabetes.weebly.com/types-of-diabetes.htm)

1.4 Pathophysiology

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, muscle, and adipose tissue. Therefore, deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. The body obtains glucose from three main places: the intestinal absorption of food, the breakdown of glycogen, the storage form of glucose found in the liver, andgluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. (American Diabetes Association, 2014)

Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhansin the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to

glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin. If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis. When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine(glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia). (Shoback *et al.*, 2011)

1.5 Epidemiology

As of 2013, 382 million people have diabetes worldwide. Type 2 makes up about 90% of the cases. This is equal to 8.3% of the adult population with equal rates in both women and men. In 2014, the International Diabetes Federation (IDF) estimated that diabetes resulted in 4.9 million deaths. The World Health Organization (WHO) estimated that diabetes resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death. The discrepancy between the two estimates is due to the fact that cardiovascular diseases are often the cause of death for individuals with diabetes.More than 80% of diabetic deaths occur in low and middle-income countries. (International Diabetes Federation, 2014).

1.6 Sign and Symptoms

The classic symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia (increased thirst), and polyphagia (increased hunger). Symptoms may develop rapidly (weeks or months) in type 1 DM, while they usually develop much more slowly and may be subtle or absent in type 2 DM. Several other signs and symptoms can mark the onset of diabetes, although they are not specific to the disease. In addition to the known ones above, they include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye,

which leads to changes in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes. (Cooke *et al.*, 2008).

1.7 History

Diabetes was one of the first diseases described, with an Egyptian manuscript from c.1500 BCE mentioning "too great emptying of the urine".The first described cases are believed to be of type 1 diabetes. Indian physicians around the same time identified the disease and classified it as madhumeha or "honey urine", noting the urine would attract ants. The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Appollonius of Memphis. The disease was considered rare during the time of the Roman empire, with Galencommenting he had only seen two cases during his career. This is possibly due the diet and life-style of the ancient people, or because the clinical symptoms were observed during the advanced stage of the disease. Galen named the disease "diarrhea of the urine" (diarrhea urinosa). (Leonid, 2009)

The earliest surviving work with a detailed reference to diabetes is that of Aretaeus of Cappadocia (2nd or early 3rd century CE). He described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School". He hypothesized a correlation of diabetes with other diseases and he discussed differential diagnosis from the snakebite which also provokes excessive thirst.Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400-500 CE with type 1 associated with youth and type 2 with being overweight. The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes insipidus, which is also associated with frequent urination. Effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Herbert Best isolated and purified insulin in 1921 and 1922. This was followed by the development of the long-acting insulin NPH in the 1940s.(Leonid, 2009).

1.8. Classification and Causes

Diabetes mellitus is classified into four broad categories: type 1, type 2, gestational diabetes, and "other specific types". The "other specific types" are a collection of a few dozen individual causes. The term "diabetes", without qualification, usually refers to diabetes mellitus(Leonid,2009).

1.9 Treatment

For type 2 diabetic patients, several treatment options are available (Shoback *et al.*, 2011). While the major focus of diabetes treatment is glycaemic control, other strategies target coincident features of the disease such as insulin resistance or obesity. The current consensus treatment of type 2 diabetes follows a stepwise manner, starting with lifestyle interventions (e.g. diet and exercise) and pharmacotherapy with metformin. Eventually, combination therapy with lifestyle interventions, oral agents, and/or insulin is generally indicated for many type 2 diabetic patients.The success of the antidiabetic therapy is controlled by measuring blood glucose, as an index of acute glycaemia and HbA1c, i.e. glycosylated haemoglobin, as an index of chronic glycaemia. Lifestyle interventions to promote weight loss and increase exercise should, if possible, always be included in the treatment of diabetes.While weight loss can effectively ameliorate hyperglycaemia the long-term success of incorporating such intervention programs into the usual lifestyle and maintaining them is limited. For pharmacotherapy, several classes of antidiabetic medications are currently available, targeting different angles of the disease. Hepatic glucose production is decreased by metformin, resulting in decreased fasting glycaemia. Sulfonylureas and glinides act by enhancing insulin secretion. α-Glucosidase inhibitors reduce the rate of digestion of polysaccharides, thereby lowering postprandial glucose levels.Glitazones increase the sensitivity of muscle, fat, and liver to insulin Finally, insulin is the oldest and most effective treatment for lowering glycaemia, and over time, as β-cell function decreases, many diabetics require intensive insulin therapy. Metformin, sulfonylureas and glinides lower HbA1c by ~1.5%, more than the other oral antidiabetics, but not as much as insulin. Metformin is indicated at every stage of the disease .In the United Kingdom Prospective Diabetes Study it was shown not to affect body weight (Schulman *et al.*,2009).

These currently available therapies for type 2 diabetes have several disadvantages including increased risk of hypoglycaemia (sulphonylureas,insulin), gastrointestinal side effects (metformin, α-glucosidase inhibitors, amylin agonists), weight gain (sulphonylureas, glitazones, glinides, insulin), fluid retention and congestive heart failure (glitazones) (Diabetes Mellitus, Alvin C 18th ed), as well as myocardial infarction (rosiglitazone).One new approach yielding.Type 2 DM is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 DM is the most common type of diabetes mellitus. In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity. At this stage, high blood sugar can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce the liver's glucose production.Type 2 DM is due primarily to lifestyle factors and genetics. A number of lifestyle factors are known to be important to the development of type 2 DM, including obesity (defined by a body mass index of greater than 30), lack of physical activity, poor diet, stress, and urbanization. Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders. Even those who are not obese often have a high waist–hip ratio. Dietary factors also influence the risk of developing type 2 DM. Consumption of sugar-sweetened drinks in excess is associated with an increased risk. The type of fats in the diet is also important, with saturated fats and trans fatty acids increasing the risk andpolyunsaturated and monounsaturated fat decreasing the risk. Eating lots of white rice appears to also play a role in increasing risk. A lack of exercise is believed to cause 7% of cases. (Schulman *et al.*, 2009).

1.10 Diagnosis

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:

 Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)

 Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test

 Symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

 Glycated hemoglobin(HbA1C) ≥ 48 mmol/mol (≥ 6.5 DCCT %). A positive result, in the absence of unequivocal high blood sugar, should be confirmed by a repeat of any of the above methods on a different day. It is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test. According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) is considered diagnostic for diabetes mellitus. Per the World Health Organization people with fasting glucose levels from 6.1 to 6.9 mmol/l(110 to 125 mg/dl) are considered to have impaired fasting glucose. people with plasma glucose at or above 7.8 mmol/l (140 mg/dl), but not over 11.1 mmol/l (200 mg/dl), two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two prediabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as cardiovascular disease. The American Diabetes Association since 2003 uses a slightly different range for impaired fasting glucose of 5.6 to 6.9 mmol/l (100 to 125 mg/dl). The rare disease diabetes insipidus has similar symptoms to diabetes mellitus, but without disturbances in the sugar metabolism (insipidusmeans "without taste" in Latin) and does not involve the same disease mechanisms. Diabetes is a part of the wider condition known asmetabolic syndrome.(Schulman *et al*.,2009).

1.11 Prevention

There is no known preventive measure for type 1 diabetes. Type 2 diabetes can often be prevented by a person being a normal body weight, physical exercise, and following a healthful diet. Dietary changes known to be effective in helping to prevent diabetes include a diet rich inwhole grains and fiber, and choosing good fats, such as polyunsaturated fats found in nuts, vegetable oils, and fish. Limiting sugary beverages and eating less red meat and other sources of saturated fat can also help in the prevention of diabetes. Active smoking is also associated with an increased risk of diabetes, so smoking cessation can be an important preventive measure as well. (Harvard School of Public Health,2014)

1.12 Management

Diabetes mellitus is a chronic disease, for which there is no known cure except in very specific situations. Management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with a healthy diet, exercise, weight loss, and use of appropriate medications (insulin in the case of type 1 diabetes; oral medications, as well as possibly insulin, in type 2 diabetes). Learning about the disease and actively participating in the treatment is important, since complications are far less common and less severe in people who have well-managed blood sugar levels. The goal of treatment is an HbA1C level of 6.5%, but should not be lower than that, and may be set higher. Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These includesmoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise. Specialized footwear is widely used to reduce the risk of ulceration, or re-ulceration, in at-risk diabetic feet. Evidence for the efficacy of this remains equivocal *(*Nathan *et al., 2005).*

Lifestyle

People with diabetes can benefit from education about the disease and treatment, good nutrition to achieve a normal body weight, and exercise, with the goal of keeping both short-term and long-term blood glucose levels within acceptable bounds. In addition, given the associated higher risks of cardiovascular disease, lifestyle modifications are recommended to control blood pressure.(Adler , 2000).

Medications

Medications used to treat diabetes do so by lowering blood sugar levels. There are a number of different classes of anti-diabetic medications. Some are available by mouth, such as metformin, while others are only available by injection such as GLP-1 agonists. Type 1 diabetes can only be treated with insulin, typically with a combination of regular and NPH insulin, or synthetic insulin analogs. Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality. It works by decreasing the liver's production of glucose. Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in type II DM. These include agents that increase insulin release, agents that decrease absorption of sugar from the

intestines, and agents that make the body more sensitive to insulin. When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications. Doses of insulin are then increased to effect.Since cardiovascular disease is a serious complication associated with diabetes, some recommend blood pressure levels below 120/80 mmHg; however, evidence only supports less than or equal to somewhere between 140/90 mmHg to 160/100 mmHg. Amongst medications that lower blood pressure, angiotensin converting enzyme inhibitors (ACEIs) improve outcomes in those with DM while the similar medications angiotensin receptor blockers (ARBs) do not. Aspirin is also recommended for patient with cardiovascular problems, however routine use of aspirin has not been found to improve outcomes in uncomplicated diabetes. (Cheng *et al.*, 2014).

Surgery

A pancreas transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including end stage kidney disease requiring kidney transplantation. Weight loss surgery in those with obesity and type two diabetes is often an effective measure. Many are able to maintain normal blood sugar levels with little or no medications following surgery and long-term mortality is decreased. There however is some short-term mortality risk of less than 1% from the surgery. The body mass index cutoffs for when surgery is appropriate are not yet clear. It is recommended that this option be considered in those who are unable to get both their weight and blood sugar under control. Support.In countries using a general practitioner system, such as the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects. In other circumstances, general practitioners and specialists share care in a team approach. Home telehealth support can be an effective management technique. (Polisena *et al.*, 2009)

1.13 Anti-Diabetic Drug

Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide andpramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. There are different classes of anti-diabetic drugs, and their selection depends on the nature of the

diabetes, age and situation of the person, as well as other factors. Diabetes mellitus type 1 is a disease caused by the lack of insulin. Insulin must be used in Type I, which must be injected. Diabetes mellitus type 2 is a disease of insulin resistance by cells. Type 2 diabetes mellitus is the most common type of diabetes. (Polisena *et al.*,2009)

Treatments include:

(1) agents that increase the amount of insulin secreted by the pancreas,

(2) Agents that increase the sensitivity of target organs to insulin, and

(3) Agents that decrease the rate at which glucose is absorbed from the gastrointestinal tract.

Several groups of drugs, mostly given by mouth, are effective in Type II, often in combination.The therapeutic combination in Type II may include insulin, not necessarily because oral agents have failed completely, but in search of a desired combination of effects. The great advantage of injected insulin in Type II is that a well-educated patient can adjust the dose, or even take additional doses, when blood glucose levels measured by the patient, usually with a simple meter, as needed by the measured amount of sugar in the blood. (Polisena *et al*., 2009)

1.13.1 Type of anti-diabetic medication

A. Insulin

B. Sensitizers

C. Secretagogues

D. Alpha-glucosidase inhibitor

E. Peptide analogs

F. Glycosurics

A. Insulin

Insulin is usually given subcutaneously, either by injections or by an insulin pump. Research of other routes of administration is underway. In acute-care settings, insulin may also be given intravenously. In general, there are three types of insulin, characterized by the rate which they are metabolized by the body. They are rapid acting insulins,

intermediate acting insulins and long acting insulins. (Powers in Harrison's Principles of Internal Medicine)

Examples of rapid acting insulins include

- Regular insulin (Humulin R, Novolin R)
- Insulin lispro (Humalog)
- Insulin aspart (Novolog)
- Insulin glulisine (Apidra)
- Prompt insulin zinc (Semilente, Slightly slower acting)

Examples of intermediate acting insulins include

- Isophane insulin, neutral protamine Hagedorn(NPH)(Humulin N, NovolinN)
- Insulin zinc (Lente)

Examples of long acting insulins include

- Extended insulin zinc insulin (Ultralente)
- Insulin glargine (Lantus)
- Insulin detemir (Levemir)

Most anti-diabetic agents are contraindicated in pregnancy, in which insulin is preferred.

B. Sensitizers

Insulin sensitizers address the core problem in Type II diabetes—insulin resistance.

Biguanides

Biguanides reduce hepatic glucose output and increase uptake of glucose by the periphery,including skeletal muscle. Although it must be used with caution in patients with impaired liver or kidney function, metformin, a biguanide, has become the most commonly used agent for type 2 diabetes in children and teenagers. Among common diabetic drugs, metformin is the only widely used oral drug that does not cause weight gain.

Typical reduction in glycated hemoglobin (A1C) values for metformin is 1.5–2.0%

 Metformin (Glucophage) may be the best choice for patients who also have heart failure, but it should be temporarily discontinued before any radiographic procedure involving intravenous iodinated contrast, as patients are at an increased risk of lactic acidosis.

 Phenformin (DBI) was used from 1960s through 1980s, but was withdrawn due to lactic acidosis risk.

 Buformin also was withdrawn due to lactic acidosis risk.

Metformin is usually the first-line medication used for treatment of type 2 diabetes. In general, it is prescribed at initial diagnosis in conjunction with exercise and weight loss, as opposed to in the past, where it was prescribed after diet and exercise had failed. There is an immediate release as well as an extended-release formulation, typically reserved for patients experiencing GI side-effects. It is also available in combination with other oral diabetic medications.

Thiazolidinediones

Thiazolidinediones (TZDs), also known as "glitazones," bind to PPARγ, a type of nuclear regulatory protein involved in transcription of genes regulating glucose and fat metabolism. These PPARs act on peroxysome proliferator responsive elements (PPRE). The PPREs influence insulin-sensitive genes, which enhance production of mRNAs of insulin-dependent enzymes. The final result is better use of glucose by the cells.

Typical reductions in glycated hemoglobin (A1C) values are 1.5–2.0%. Some examples are:

 rosiglitazone (Avandia): the European Medicines Agency recommended in September 2010,that it be suspended from the EU market due to elevated cardiovascular risks.

 pioglitazone (Actos)

troglitazone(Rezulin): used in 1990s,withdrawn due to hepatitis and liver damage risk

Multiple retrospective studies have resulted in a concern about rosiglitazone's safety, although it is established that the group, as a whole, has beneficial effects on diabetes. The greatest concern is an increase in the number of severe cardiac events in patients taking it. The ADOPT study showed that initial therapy with drugs of this type may prevent the progression of disease, as did the DREAM trial. (Wood *et al.*, 2007)

Concerns about the safety of rosiglitazone arose when a retrospective meta-analysis was published in the New England Journal of Medicine. There have been a significant number of publications since then, and a Food and Drug Administration panel voted, with some controversy, 20:3 that available studies "supported a signal of harm," but voted 22:1 to keep the drug on the market. The meta-analysis was not supported by an interim analysis of the trial designed to evaluate the issue, and several other reports have failed to conclude the controversy. This weak evidence for adverse effects has reduced the use of rosiglitazone, despite its important and sustained effects on glycemic control. Safety studies are continuing. In contrast, at least one large prospective study, PROactive 05, has shown that pioglitazone may decrease the overall incidence of cardiac events in people with type 2 diabetes who have already had a heart attack. (Ajjan *et al.*, 2008).

C. Secretagogues

Secretagogues are drugs that increase insulin output from the pancreas. Sulfonylureas Sulfonylureas were the first widely used oral anti-hyperglycaemic medications. They are insulin secretagogues, triggering insulin release by inhibiting the KATP channel of the pancreatic beta cells. Eight types of these pills have been marketed in North America, but not all remain available. The "second-generation" drugs are now more commonly used. They are more effective than first-generation drugs and have fewer side-effects. All may cause weight gain. Sulfonylureas bind strongly to plasma proteins. Sulfonylureas are useful only in Type II diabetes, as they work by stimulating endogenous release of insulin. They work best with patients over 40 years old who have had diabetes mellitus for under ten years. They cannot be used with type I diabetes, or diabetes of pregnancy. They can be safely used with metformin or glitazones. The primary side-effect is hypoglycemia. Typical reductions in glycated hemoglobin (A1C) values for second-generation sulfonylureas are 1.0–2.0%. (Ajjan *et al.*, 2008).

- First-generation agents
- tolbutamide (Orinase, Rastinon brand name)
- acetohexamide (Dymelor)
- tolazamide (Tolinase)

 chlorpropamide (Diabinese)

 Second-generation agents

 glipizide (Glucotrol, Minidiab, Glibenese)

 glyburide or glibenclamide (Diabeta, Micronase, Glynase, Daonil, Euglycon)

 glimepiride (Amaryl)

 gliclazide (Uni Diamicron)

 glycopyramide

 gliquidone (Glurenorm)

Nonsulfonylurea secretagogues

Meglitinides

Meglitinides help the pancreas produce insulin and are often called "short-acting secretagogues." They act on the same potassium channels as sulfonylureas, but at a different binding site. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, thereby enhancing insulin secretion. They are taken with or shortly before meals to boost the insulin response to each meal. If a meal is skipped, the medication is also skipped.

Typical reductions in glycated hemoglobin (A1C) values are 0.5–1.0%.

 repaglinide (Prandin, NovoNorm)

 nateglinide (Starlix).Adverse reactions include weight gain and hypoglycemia. (Ajjan *et al.*, 2008).

D. Alpha-glucosidase inhibitor

Alpha-glucosidase inhibitors are "diabetes pills" but not technically hypoglycemic agents because they do not have a direct effect on insulin secretion or sensitivity. These agents slow the digestion of starch in the small intestine, so that glucose from the starch of a meal enters the bloodstream more slowly, and can be matched more effectively by an impaired insulin response or sensitivity. These agents are effective by themselves only in the earliest stages of impaired glucose tolerance, but can be helpful in combination with other agents in type 2 diabetes.

Typical reductions in glycated hemoglobin (A1C) values are 0.5–1.0%.

 miglitol (Glyset)

 acarbose (Precose/Glucobay)

 Voglibose

These medications are rarely used in the United States because of the severity of their side-effects (flatulence and bloating). They are more commonly prescribed in Europe. (National Prescribing Service, 2010)

E. Peptide analogs

Injectable Incretin mimetics

Incretins are insulin secretagogues. The two main candidate molecules that fulfill criteria for being an incretin are glucagon-like peptide-1 (GLP-1) and gastric inhibitory peptide(glucose dependent insulinotropic peptide, GIP). Both GLP-1 and GIP are rapidly inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Injectable Glucagon-like peptide analogs and agonists Glucagon-like peptide (GLP) agonists bind to a membrane GLP receptor. As a consequence, insulin release from the pancreatic beta cells is increased. Endogenous GLP has a half-life of only a few minutes, thus an analogue of GLP would not be practical.

 Exenatide (also Exendin-4, marketed as Byetta) is the first GLP-1 agonist approved for the treatment of type 2 diabetes. Exenatide is not an analogue of GLP but rather a GLP agonist. Exenatide has only 53% homology with GLP, which increases its resistance to degradation by DPP-4 and extends its half-life. Typical reductions inA1C values are 0.5–1.0%.

 Liraglutide, a once-daily human analogue (97% homology), has been developed by Novo Nordisk under the brand name Victoza. The product was approved by the European Medicines Agency (EMEA) on July 3, 2009, and by the U.S. Food and Drug Administration (FDA) on January 25, 2010.

 Taspoglutide is presently in Phase III clinical trials with Hoffman-La Roche.

 Lixisenatide (Lyxumia) Sanofi Aventis These agents may also cause a decrease in gastric motility, responsible for the common side-effect of nausea, and is probably the mechanism by which weight loss occurs. Dipeptidyl Peptidase-4 Inhibitors GLP-1 analogs resulted in weight loss and had more gastrointestinal side-effects, while in general DPP-4 inhibitors were weight-neutral and increased risk for infection and headache, but both classes appear to present an alternative to other antidiabetic drugs..(National Prescribing Service, 2010) Dipeptidyl peptidase-4 (DPP-4) inhibitors increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4. Examples are:

 vildagliptin (Galvus) EU Approved 2008

 sitagliptin (Januvia) FDA approved Oct 2006

 saxagliptin (Onglyza) FDA Approved July 2009

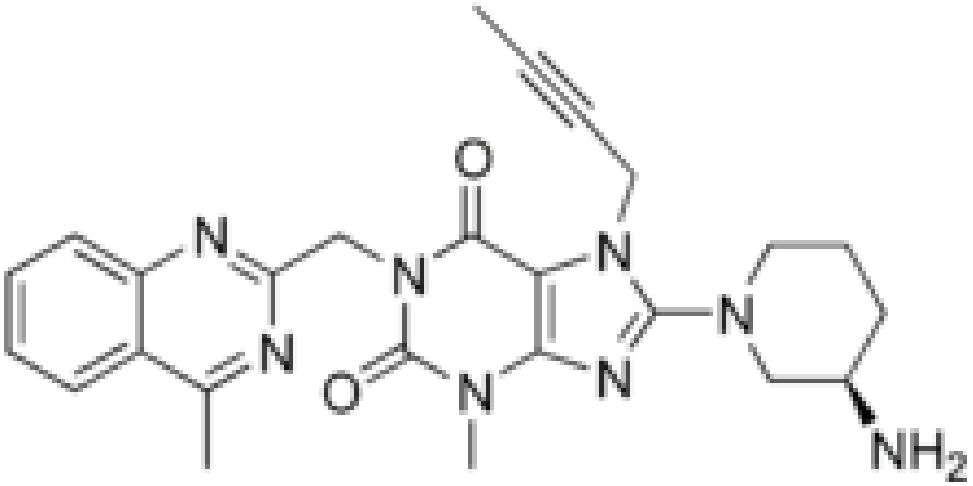
 linagliptin (Tradjenta) FDA Approved May 2, 2011

 alogliptin

 septagliptin

1.14 Linagliptin

In this work pharmacometric analyses were performed to investigate the pharmacokinetics and the pharmacokinetic/pharmacodynamic relationship of the novel dipeptidyl-peptidase 4 (DPP-4) inhibitor linagliptin, which is undergoing clinical development for the treatment of type 2 diabetes.Type 2 diabetes mellitus (T2DM) is a progressive disease, and it occurs with increasing prevalence in the elderly and those with other comorbidities. Blood glucose control presents a challenge that is magnified by these co-existing problems. To achieve glycemic targets, many patients need more than one antidiabetic drug, and additional medications are often required as glucose control deteriorates.Consequently, the development of new antidiabetic drugs that can help meet this challenge has been an area of intensive research.The dipeptidyl peptidase-4 (DPP-4) inhibitors are one of the recently developed therapeutic classes for treatment of hyperglycemia in T2DM. The various agents in the class have differing chemical structures, but all act by inhibiting the DPP-4 enzyme, thus prolonging the life of incretin hormones, which in turn raise insulin levels and suppress glucagon secretion in a glucose-depend- ent manner. As a class, DPP-4 inhibitors have been shown to provide significant improvements in glycosylated hemoglobin (HbA1c), and to have a good safety profile. In addition, their glucose- dependent mechanism of action is associated with a low rate of hypoglycemic events High-throughput screening using an assay to detect inhibition of DPP-4 led to the discovery of linagliptin, a xanthine-based molecule with a high selectivity for DPP-4. The pharmacokinetics and pharmacodynamics of linagliptin have been reviewed in detail elsewhere . Of note, unlike other DPP-4 inhibitors, which are predominantly excreted via the kidneys, linagliptin is mainly excreted unchanged via the enterohepatic system. Based on pharmacokinetic studies, no dose adjustment is needed for patients with renal or hepatic impairment (Boehringer Ingelheim Pharmaceuticals Inc,2011). Early studies showed linagliptin is suitable for once-daily dosing, with similar reductions in HbA1c to those seen with other DPP-4 inhibitors and without clinically significant pharmacokinetic interactions when co-administered with other medications (Richter *et al.*,2008).



8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4- methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6dione

Figure 3: chemical structure of Linagliptin (wikipedia.org)

(Source: https://en.wikipedia.org/wiki/Linagliptin#Mechanism_of_action)

On the basis of the early studies, an extensive clin- ical trial program was undertaken to assess the efficacy and safety of linagliptin. Of these, four pivotal trials, trials designed to meet US Food and Drug Administration (FDA) criteria for assessing efficacy and safety of a drug before it is approved for use in patients in the US, have been reported over the past year or so. The positive results of these trials led to FDA approval of lina- gliptin to improve glycemic control in patients with T2DM in May 2011.Linagliptin is a novel competitive DPP-4 inhibitor under clinical development for the treatment of type II diabetes.It binds to the active site of the DPP-4 enzyme, as shown by the crystal structure of human DPP-4 in complex with linagliptin (Thomas *et al.,* 2008).

1.15 Mechanism of action

Linagliptin is an inhibitor of DPP-4, an enzyme that degrades the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Both GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in

hepatic glucose output. Thus, linagliptin stimulates the release of insulin in a glucose-dependent manner and decreases the levels of glucagon in the circulation. (Stoffers *et al*., 2008)

1.16 New treatment options based on incretins

1.16.1. Incretins

An oral glucose load leads to a greater insulin secretion compared to an intravenous (i.v.) glucose load matched to produce a similar glycaemic profile. This phenomenon is called 'incretin effect'. The incretin hormones mainly responsible for this effect are glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).Incretin hormones are secreted from intestinal endocrine cells in response to oral but not intravenous glucose administration. GLP-1 is secreted from L-cells, GIP from K-cells.Secretion occurs in response to oral intake of carbohydrates, lipids and, in the case of GLP-1, also proteins GLP-1 and GIP both enhance the insulin secretion in pancreatic ß-cells In addition, GLP-1 acts on glucose homeostasis by inhibiting the glucagon secretion of pancreatic α-cells, thereby further decreasing the hepatic glucose production.Both mechanisms directly lower the plasma glucose levels in a glucose-dependent manner. For rodents, GLP-1 and GIP have been shown to have protective effects on pancreatic ß-cells by enhancing their proliferation and increasing their resistance to apoptosis Moreover, the survival of isolated human islets of Langer-hans was prolonged in the presence of GLP-1.Other beneficial aspects of GLP-1 are the prolongation of gastric emptying and the induction of satiety, both supporting dietary goals in diabetes treatment. In type 2 diabetic patients, incretin levels (mainly GLP-1) are reduced the incretin effect is markedly decreased compared to healthy volunteers . In line with these studies, patients with impaired glucose tolerance show a reduced suppression of glucagon following an oral glucose load compared to healthy volunteers In type 2 diabetic patients, the insulinotropic activity of GLP-1, in contrast to GIP, remains relatively intact.Pharmacotherapy therefore mainly focuses on GLP-1. Continuous subcutaneous infusion of GLP-1 over six weeks normalised blood glucose levels, decreased HbA1c and body weight and greatly improved the first-phase insulin response in type 2 diabetic patients (Zander *et al.*,2002).

1.16.2. Dipeptidyl-peptidase 4

DPP-4 rapidly inactivates the incretins, making the long-term diabetes treatment with GLP-1 itself difficult. The hydrolytic activity of DPP-4 results in half-lives of 1–2 min for GLP-1 and 7 min for GIP (Deacon,2005). In fact, more than 50% of secreted GLP-1 is degraded by DPP-4 immediately following release into intestinal capillaries, i.e. before reaching the general circulation (Hansen, 1999). DPP-4 (EC 3.4.14.5) is an ubiquitous serine-type peptidase that cleaves dipeptide frag-ments from the N-terminus of polypeptides with either proline or alanine as their second residue most effectively .Furthermore, DPP-4 acts as regulatory peptidase on a large number of bioactive peptides. Substrates that have been identified for DPP-4 include, besides gastrointestinal hormones like GLP-1 and GIP the neuropeptides) endomorphin, neuropeptide Y substance P and bradykinin, as well as growth hormone-releasing hormone and several chemokines (Wolf, 2008). Apart from its catalytic activity, it interacts with a number of other proteins, e.g. collagen ,the chemokine receptor CXCR4 ,adenosine deaminase, and the human immunodeficiency virus gp120 surface protein .In the immune system, DPP-4, also known as CD26, acts as a co-stimulatory molecule in T cell activation. It also plays a role in malignant transformation, cancer progression, and possibly human immunodeficiencyvirus entry .DPP-4 is expressed in a variety of tissues, primarily on the apical membrane of epithelial and endothelial cells The distribution of DPP-4 when determined with a polyclonal antibody corresponds to the distribution of DPP-4 activity determined histo-chemically).In blood vessels, lung, myocardium and striated muscles, almost the total DPP-4 activity is located endothelially. In kidney, intestine, and liver however, where DPP-4 is abundantly expressed endothelial DPP-4 activity accounts for only a small part of the total DPP-4 activity .The membrane-bound form of DPP-4 is also found on fibroblasts T-cells and other cell types . In addition to the mem-brane-bound form, DPP-4 exists as a soluble form lacking the intracellular part and the transmembrane region Soluble DPP-4 is present in low nanomolar concentrations in plasma and other body fluids. The origin of soluble DPP-4 in human plasma is not completely understood, but several lines of evidence suggest that soluble DPP-4 may originate from endothelial or epithelial cells or from circulating leukocytes.A substrain of Fischer rats (F344/DuCrlCrlJ) bred by Charles

River, Japan exhibits a mutation resulting in the complete loss of DPP-4 activity (Watanabe *et al.*, 1987).

1.16.3. GLP-1 agonists and DPP-4 inhibitors

With the aim of obtaining clinical benefit from the positive effects of incretins despite their short half-life, GLP-1 analogues resistant to DPP-4 degradation and compounds inhibiting DPP-4 have been developed. GLP-1 agonists such as exenatide or liraglutide bind to the GLP-1 receptor on pancreatic ß-cells and augment glucose-mediated insulin secretion.They also suppress glucagon secretion, resulting in a decreased hepatic glucose production, and they slow down gastric emptying.GLP-1 agonists mainly reduce post-prandial glucose levels and do not cause hypoglycaemia. Clinical studies have indicated that the administration of GLP-1 agonists lowers body weight by ~2–3 kg over 30 weeks and by ~4 kg after 80 weeks.The main adverse effects are nausea, vomiting, and diarrhoea, but these apparently abate over time.Some patients were shown to develop antibodies against GLP-1 agonists, albeit with weak binding affinity and low titres .Being peptide molecules, GLP-1 agonists require subcutaneous injection. In April 2005, the U.S. Food and Drug Administration (FDA) approved the first GLP-1 agonist, synthetic exendin-4, exenatide. Exenatide needs to be administered twice daily due to its short half-life. Liraglutide is a new GLP-1 agonist with a longer half-life, submitted to the FDA in 2008, that can be given once daily.While GLP-1 agonists mimic the biologic function of GLP-1, DPP-4 inhibitors prevent the degradation of incretins by DPP-4, prolonging the beneficial effects of these regulatory peptides for type 2 diabetic patients. They stimulate insulin secretion and inhibit glucagon secretion, but unlike GLP-1 agonists they are not associated with the prolongation of gastric emptying and clinical studies demonstrated that DPP-4 inhibitors do not affect body weight .In general, they are well tolerated and, like GLP-1 agonists, do not cause hypoglycaemia. As DPP-4 is involved in the immune system,DPP-4 inhibitors carry the potential risk of interfering with immune function. In fact, an increase in infections, e.g. of the upper respiratory tract was reported for sitagliptin, but not for vildagliptin In October 2006, the FDA approved the first DPP-4 inhibitor sitagliptin.The second DPP-4 inhibitor vildagliptin is so far only approved in Europe, since February 2008. Alogliptin and saxagliptin were submitted to the FDA in 2007 and 2008, respec-

tively. In general, GLP-1 agonists and DPP-4 inhibitors are well tolerated and lower HbA1c by 0.5–1%, comparable to α-glucosidase inhibitors. Both classes have the potential advantage of preserving the ß-cell mass through stimulation of cell proliferation and inhibition of apoptosis, as demonstrated in animal models ((Drucker, 2006-2008).

1.17 Pharmacodynamic properties

1.17.1 In Vitro investigations and preclinical pharmacodynamics

In vitro studies revealed linagliptin to be a highly potent, competitive DPP-4 inhibitor. The concentration leading to half-maximal inhibition (IC 50) of DPP-4 in vitro was approximately 1 nM, and thus linagliptin was more potent compared to sitagliptin (IC 50 : 19 nM), alogliptin (IC 50 : 24 nM), saxagliptin (IC 50 : 50 nM), and vildagliptin (IC 50 : 62 nM). Linagliptin binding to DPP-4 exhibits a slow off-rate ($3.0 \cdot 10^{-5}\ s^{-1}$) (Thomas *et al.*,2008).

The potent DPP-4 inhibition of linagliptin was confirmed in vivo in various species including male Wistar rats, Beagle dogs, and Rhesus monkeys. In all three species, linagliptin was highly efficacious and resulted in long-lasting and potent DPP-4 inhibition of >70% for >7 h after oral administration of 1 mg/kg . After a single oral dose of 3 mg/kg, linagliptin increased active GLP-1 and insulin levels, and reduced the glucose levels compared to the control group after an oral glucose tolerance test (OGTT) in Zucker fatty rats. The effect on glucose tolerance was long-lasting. Glucose excursion was significantly reduced 16 h after a single administration in C57/BL6 mice, or 24 h in Zucker fatty (fa/fa) rats. Glucose excursion was measured by an OGTT, as the increment of the area under the plasma concentration-time curve (AUC) of glucose. In addition, basal active GLP-1,but not basal insulin levels, were elevated in Zucker fatty rats and in the postprandial phase, plasma glucagon values tended to be lower (Thomas *et al,* 2008). The effects of linagliptin after a single dose were confirmed for multiple dosing in two animal models for diabetes, high-fat diet/streptozotocin-induced diabetic mice and Zucker diabetic fatty rats In addition, HbA1c was decreased after 4–5 weeks of treatment. In both animal models, body weight was unaffected compared to placebo treatment. (Thomas *et al.*,2008).

1.17.2 Clinical pharmacodynamics

Linagliptin treatment resulted in a rapid, potent and long-lasting inhibition of plasma DPP-4 in clinical studies. Already after a single dose of linagliptin, DPP-4 was effectively inhibited as shown by maximum DPP-4 inhibitions of 72.7 and 86.1% for 2.5 and 5 mg, and >95% for doses ≥25 mg.At steady-state, plasma DPP-4 activity was inhibited over 24 h by >80% in most patients receiving 5 or 10 mg linagliptin once daily.Generally, DPP-4 inhibition ≥80% over 24 h is aimed for, as this was shown to be related to maximum effects in incretin response and glucose reduction The effects of linagliptin on the incretins and the glucose levels in type 2 diabetic patients were investigated during an OGTT after twelve days of treatment. Treatment with 2.5, 5, and 10 mg, but not 1 mg linagliptin, considerably elevated the increase of GLP-1 levels during the OGTT on day 13 compared with baseline. In line with this, 2.5, 5, and 10 mg linagliptin, but not 1 mg, significantly reduced glucose excursion during the OGTT on days 1 and 13 compared to placebo (Hansen *et al*.,2009).

1.18 Pharmacokinetic properties

Preclinical pharmacokinetics and in vitro investigationsThe pharmacokinetics of linagliptin was mainly investigated in rats and cynomolgus monkeys. The pharmacokinetics of linagliptin was nonlinear in both species (Boehringer Ingelheim 2008) accompanied by a dose-dependency of pharmacokinetic parameters like clearance and volume of distribution. After intravenous administration of 5 mg/kg linagliptin to rats and 1.5 mg/kg to cynomolgus monkeys, an apparent clearance (CL) of 37.3 mL/min/kg in rats and 15.8 mL/min/kg in monkeys was determined. The volumes of distribution at steady-state were 5.4 L/kg in rats and 15.8 L/kg in cynomolgus monkeys both exceeding the total body volume indicating that linagliptin is extensively distributed in the tissues. The gastrointestinal absorption of linagliptin was moderate with an oral bioavail-ability (F) of ~50% in rats and cynomolgus monkeys. This absolute bioavailability estimate was determined by a comparison of the area under the plasma concentration-time curve of oral 5 mg/kg linagliptin to intravenous 5 mg/kg (rats) and 1.5 mg/kg (monkey). Despite the moderate bioavailability, only a minor first-pass metabolism was observed (Boehringer Ingelheim 2007). The mean residence times after oral administration of 5 mg/kg linagliptin

were 14.3 h and 17.4 h in rats and cynomolgus monkeys, respectively. The terminal half-lives (t 1/2) of linagliptin after oral administration were long in both species (35.9 h in rats and 41.4 h in cynomolgus monkeys) Plasma protein binding of linagliptin was investigated for various species including rats, cynomolgus monkeys and humans, by equilibrium dialysis. At plasma concentrations >30 nM, the fraction bound ranged from 75–89% .At lower concentrations, the fraction bound increased to 99%. In human liver microsomes linagliptin only weakly inhibited cytochrome P450 (CYP) 3A4 and no other CYP isoforms. These findings were confirmed in rats, mice, rabbits, and cynomolgus monkeys. In these animals, metabolism was only a minor elimination pathway. Excretion mainly occurred via faeces with a prominent biliary fraction, whereas renal excretion was only of minor importance. (Eckhardt *et al.*,2007).

1.18.1. Clinical pharmacokinetics

The pharmacokinetics of linagliptin after oral administration was investigated in healthy volunteers and type 2 diabetic patients.Basic pharmacokinetics was compara-ble between both groups. Linagliptin was rapidly absorbed, with a median time of maximum plasma concentration (t max) of ~1.5 h (range: 0.5–6.0 h) after single and multiple dosing (Heise,2009). Linagliptin exhibited nonlinear pharmacokinetics after single and multiple dosing, in contrast to other DPP-4 inhibitors including sitagliptin,vildagliptin, saxagliptin and alogliptin.At supratherapeutic doses (25–600 mg), the exposure after a single dose of linagliptin increased more than dose-proportionally .In contrast, in the therapeutic dose range (1–10 mg linagliptin once daily), the nonlinearity was characterised by a less than dose-proportional increase in the maximum linagliptin plasma concentration (C max) and the AUC. Both the time to reach steady-state and the accumulation ratio decreased withincreasing dose. Steady-state was achieved after 4–6 days for dose groups 1–5 mg and after two days in case of the 10 mg dose. The accumulation ratio was 2.0-fold for the 1 mg dose group and 1.2-fold for the 10 mg dose group. The accumulation half-life 1 decreased accordingly with dose from 24 h for the 1 mg dose group to 8.6 h for the 10 mg dose group. The contribution of renal clearance to overall clearance was small. In the therapeu-tic dose range of 1–10 mg, the cumulative amount of linagliptin excreted in urine was below 1% of the administered dose on day 1 and 3–6% on day 12. With higher single

doses, the fraction of dose excreted increased up to 33% in the 600 mg dose group (Heise *et al.*,2008).

1.19. Safety

Binding of linagliptin to DPP-4 is highly selective. The in vitro selectivity of binding to DPP-4 is ≥10,000-fold higher compared to dipeptidyl-peptidase 8 (DPP-8) and dipeptidyl-peptidase 9 (DPP-9), and a number of other proteases tested . A low inhibition of DPP-8 and DPP-9 is of great importance, as inhibition of these enzymes is assumed to be associated with severe immunotoxic side effects.In addition, linagliptin has a low affinity for the hERG channel indicating that the risk for a prolongation of the QT interval is small. In preclinical toxicity studies linagliptin exhibited a very low toxicity with a high safety margin to clinical use (Boehringer Ingelheim). No genotoxic or teratogenic effects were observed.In healthy volunteers, single oral doses of linagliptin up to 600 mg were well tolerated. The incidence of adverse events was not dose-dependent and was not different between subjects treated with linagliptin or placebo This positive safety and tolerability profile after single doses in healthy volunteers was confirmed by a multiple dose study in type 2 diabetic patients. In this study, 1–10 mg oral doses of linagliptin were administered once daily over twelve days. Again linagliptin was well tolerated in all dose groups, and no patient discontinued the treatment due to adverse events. In addition, there were noclinically relevant changes in laboratory or electrocardiogram (ECG) parameters and no signs of hypoglycaemia were reported during the study (Huttner *et al.*,2008).

1.20 Pharmacometrics in drug development

Pharmacometrics:

Pharmacometrics is the development and application of mathematical and statistical methods in order to characterise, understand, and predict the pharmacokinetic and pharmacodynamic properties of a given drug. It allows the differentiation of variability into interindividual, intraindividual, and residual variability (η, κ, and ε, respectively), as well as their quantification, aiding rational drug development and pharmacotherapy.Pharmacometric analyses involve the development of a pharmacokinetic and/or pharmaco-dynamic model. A pharmacokinetic model describes the relationship

between the administered drug and the concentration of the drug in plasma or other body fluids. This relationship is often described using compartmental models. A pharmacodynamic model describes the relationship between the observed exposure of the drug and the observed pharmacody- namic response (e.g. biomarker). A commonly used pharmacodynamic model is for example the Emax model.Depending on the availability of data, the knowledge about the drug and the objective of the analysis, pharmacometric models can be empirical, i.e. purely descriptive, or mechanism-based, i.e. reflecting the underlying physiological system as much as possible. In pharmacometric analyses, semi-mechanistic models are often used incorporating only the key elements of a physiological system. Pharmacometric models not only provide estimates for pharmacokinetic and/or pharmaco-dynamic parameters, but they can also be used for simulations.By illustrating the implications of a pharmacometric model, e.g. the amount of drug in the peripheral compartment, simulations can help to understand the pharmacokinetics or pharmacodynamics. (Huttner *et al*.,2008).

1.21 Population approach

The models applied in pharmacometrics are often population models using the nonlinear mixed-effect modelling technique.Population analysis is the characterisation of the typical pharmacokinetic and/or pharmacodynamic behaviour of a drug together with the study of sources and correlates of the variability in the drug concentration and/or the pharmacologi-cal effect.This includes explorations on the impact of certain patient characteristics like age or weight (called covariates) on the pharmacokinetic and/or pharmacodynamic behaviour of a drug. A population analysis typically investigates the pharmacokinetics and/or pharmacodynamics of clinically relevant doses of a drug in the patient population.The population approach using the nonlinear mixed-effect modelling technique has several advantages compared to the two-stage approach that has traditionally been used for population analyses .In the two-stage approach, the individual parameters are estimated first and then their distribution statistics are calculated. In contrast, in the population approach based on nonlinear mixed-effect modelling the data of all individuals are analysed together, and different kinds of variabilities are directly taken into account.Thereby, the individuality of each subject is maintained and accounted for. In

consequence, the population approach based on nonlinear mixed-effect modelling is the more versatile approach .(Samara *et al.*,1997)

It can be applied to different types of data and can be used to analyse extensively as well as sparsely sampled data. The analysis of sparse data is important in situations in which dense sampling is not possible for ethical reasons, e.g. studies in children or severely ill patients. A balanced study design is not required, thus irregular sampling or the combination of data from different studies is possible.As the data are analysed together, information can be 'borrowed' between individuals, this is also important for the investigation of nonlinear processes in which every dose group contains different kinds of information Furthermore, the population approach based on nonlinear mixed-effect modelling provides considerably more accurate estimates of the variability compared to the two-stage approach.(U.S. Food and Drug Administration,1907,2000,2009)

1.20.1 Regulatory perspective on pharmacometrics

Pharmacometrics is widely accepted and recommended by authorities to contribute to a better understanding of the pharmacokinetic and pharmacodynamic behaviour of a drug in order to allow a safe and efficacious therapy. The FDA and the European Medicines Agency (EMEA) have both issued guidances on population analysis. The FDA's Guidance for industry: Population Pharmacokinetics elaborates when and how to perform a population analysis while the EMEA guidance focuses on documentation and reporting.

In their white paper Challenge and Opportunity on the Critical Path to New Medical Products,the FDA urges, amongst other approaches, the use of computer-based predictive models to optimise the time-consuming and expensive development of new products. Furthermore, the FDA has published two summaries illustrating the impact of pharmacometrics on new drug approval or labelling (Bhattaram, 2005, 2007)

1.20.2. Impact of pharmacometrics in different phases of clinical drug development

Pharmacometrics can be applied throughout different phases of drug development.Early clinical development includes phase I studies, typically conducted in healthy volunteers as well as phase IIa studies, typically performed in the patient population. The objectives of phase I and IIa studies are to investigate safety and tolerability of a compound, as well as pharmacokinetics and pharmacodynamics. In these studies proof-of-mechanism

biomarkers are usually determined to provide evidence of target engagement. Due to the short study period or when the study population is composed of healthy volunteers, disease-related biomarkers are often not meaningful. Usually, in phase I and IIa studies many pharmacokinetic and pharmacodynamic observations are available per subject, but the number of subjects is lower compared to phase IIb and III studies. In pharmacometric analyses, the dense data of phase I and IIa studies can be used to characterise and understand the pharmacokinetics and the relationship between pharmacokinetics and pharmacodynamics of the compound. Due to strict inclusion and exclusion criteria, the variability in the subject-specific characteristics is usually small, and thus the data will only provide limited information about the impact of subject-specific characteristics on the pharmacokinetic or pharmacodynamic model parameters.In contrast, phase IIb and phase III trials include a larger and more diverse patient population, but the number of pharmacokinetic and pharmacodynamic observations per patient is lower than in early clinical development. The objective of phase IIb trials is to investigate safety and provide the 'proof of concept', i.e. demonstrating positive effects on disease related biomarkers/surrogate endpoints. The objective of phase III studies is to assess safety and efficacy in a large patient population. The sparse data of phase IIb and III trials can be analysed by nonlinear mixed-effect modelling techniques to understand and confirm the dose-exposure-response relationship in the target population. Investigations about the relationship between patient characteristics and model parameters may partially explain the variability observed in the drug concentration or effect. By this approach, one may identifysubgroups of patients exhibiting a deviant exposure or pharmacological effect. For these patients, safety or efficacy may be compromised, necessitating a dose adjustment.Throughout all phases of drug development, pharmacometrics is a valuable tool to predict untested scenarios, support dosing recommendations and design future clinical trials Simulations are of special interest for compounds with nonlinear pharmacokinetics, as for these the pharmacokinetic and pharmacodynamic drug behaviour is difficult to predict. (Bhattaram, 2005,2007).

1.21. FDA NEWS RELEASE: **For Immediate Release:** May 2, 2011, **Media Inquiries:** Morgan Liscinsky, 301-796-0397, **Consumer Inquiries:** 888-INFO-FDA

FDA approves new treatment for Type 2 diabetes

The U.S. Food and Drug Administration today approved Tradjenta (linagliptin) tablets, used with diet and exercise, to improve blood glucose control in adults with Type 2 diabetes.People with Type 2 diabetes do not produce or respond normally to insulin, a hormone that regulates the amount of glucose in the blood. Over time, high blood glucose levels can increase the risk for serious complications, including heart disease, blindness, and nerve and kidney damage."This approval provides another treatment option for the millions of Americans with Type 2 diabetes," said Mary Parks, M.D., director of the Division of Metabolism and Endocrinology Products in the FDA's Center for Drug Evaluation and Research. "It is effective when used alone or when added to existing treatment regimens."Type 2 diabetes is the most common form of the disease, affecting between 90 percent and 95 percent of the 24 million people in the United States with diabetes. Tradjenta increases the level of hormones that stimulate the release of insulin after a meal by blocking the enzyme dipeptidyl peptidase-4 or DPP-4, which leads to better blood glucose control.Tradjenta was demonstrated to be safe and effective in eight double-blind, placebo-controlled clinical studies involving about 3,800 patients with Type 2 diabetes. The studies showed improvement in blood glucose control compared with placebo.Tradjenta has been studied as a stand-alone therapy and in combination with other Type 2 diabetes therapies including metformin, glimepiride, and pioglitazone. Tradjenta has not been studied in combination with insulin, and should not be used to treat people with Type 1 diabetes or in those who have increased ketones in their blood or urine (diabetic ketoacidosis).Tradjenta will be dispensed with an FDA-approved Patient Package Insert that explains the drug's uses and risks. The most common side effects of Tradjenta are upper respiratory infection, stuffy or runny nose, sore throat, muscle pain, and headache.Tradjenta is marketed by Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Conn., and Indianapolis-based Eli Lilly Co.(Morgan Liscinsky,2011).

FDA approves updated prescribing information for Tradjenta (linagliptin)tablets for add-on therapy to insulin in adults with type 2 diabetes.RIDGEFIELD, Conn. and

INDIANAPOLIS, August 17, 2012, 2012 /PRNewswire/ -- Boehringer Ingelheim Pharmaceuticals, Inc. and Eli Lilly and Company today announced the U.S. Food and Drug Administration (FDA) has approved a supplemental new drug application (sNDA) for Tradjenta (linagliptin) tablets for use as add-on therapy to insulin. Tradjenta is a prescription medication used along with diet and exercise to lower blood sugar in adults with type 2 diabetes, and can be used as monotherapy or in combination with other commonly prescribed medications for type 2 diabetes, such as metformin, sulfonylurea, pioglitazone or insulin. Tradjenta should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis **(**increased ketones in the blood or urine).The FDA's decision is based on data from a 52-week, phase 3 trial demonstrating the efficacy of Tradjenta in combination with insulin (with or without metformin and/or pioglitazone). The trial results showed adding Tradjenta to insulin produced better glucose control than insulin alone, with similar incidence of hypoglycemia (low blood sugar) in both treatment groups.Tradjenta belongs to a class of prescription medications called dipeptidyl peptidase-4 (DPP-4) inhibitors and is the first member of its class to be approved at one dosage strength (5 mg, once-daily).Additionally, the FDA-approved label includes a clinical study in people with severe chronic renal impairment. Data from a 52-week, double-blind, randomized, placebo-controlled trial showed that use of Tradjenta 5 mg plus other glucose-lowering therapies in this patient population provided a statistically significant improvement in glycated hemoglobin (HbA1c or A1C) compared to placebo (placebo-adjusted reduction of 0.7 percent).

"Many people with type 2 diabetes taking insulin also require additional medication. With today's FDA decision, Tradjenta can be an effective add-on therapy with a demonstrated safety profile to help adult patients on insulin to improve their blood sugar control," said John Smith, M.D., Ph.D., senior vice president for clinical development and medical affairs, Boehringer Ingelheim Pharmaceuticals, Inc. "Tradjenta is the only once-daily, one-dose drug in its class without the need for dose adjustment regardless of declining renal function or hepatic impairment."Tradjenta lowers blood sugar in a glucose-dependent manner by increasing incretin levels, which increase insulin levels after meals and throughout the day. Among many considerations when treating patients with type 2 diabetes, approximately 40 percent of individuals have some degree of renal

impairment.With Tradjenta, no dose adjustment is required regardless of declining renal function or hepatic impairment.The primary endpoint of this trial was change in A1C after 24 weeks of treatment. At 24 weeks, Tradjenta plus basal insulin demonstrated a placebo-adjusted reduction in hemoglobin A1C of 0.65 percent from a baseline A1C of 8.3 percent. The mean change in basal insulin dose after 24 weeks was +0.6 IU/day for Tradjenta versus +1.3 IU/day for placebo. The differences in A1C seen between Tradjenta and placebo were comparable for patients with or without renal impairment, and regardless of the severity of impairment. Overall the mean change in body weight from baseline to week 24 was similar in both treatment groups. The rate of hypoglycemia also was similar in both groups (21.4 percent, Tradjenta and 22.9 percent, placebo) in the first 24 weeks of the study. The use of Tradjenta in combination with insulin in patients with severe renal impairment was associated with a higher rate of hypoglycemia.The 52-week trial evaluated the efficacy and safety of Tradjenta in patients (n=133) who had both type 2 diabetes and severe chronic renal impairment, defined as eGFR of less than 30 ml/min. In addition to the study medication, patients also received background antihyperglycemic therapy, which included insulin or any combination with insulin; sulfonylurea or glinides as monotherapy; and pioglitazone or any other glucose lowering medications excluding any other DPP-4 inhibitors. For the initial 12 weeks of the study, doses of background antihyperglycemic were kept stable. During the subsequent 40-week period, the doses of background antihyperglycemic therapy could be adjusted if certain blood sugar targets were not met.The primary endpoint of this study was the change from baseline in A1C after 12 weeks of treatment. After 12 weeks of treatment, Tradjenta 5 mg provided statistically significant improvements in A1C with an adjusted mean change of -0.6 percent, compared to placebo. Efficacy was maintained for 52 weeks with an adjusted mean change from baseline in A1C of -0.7 percent, compared to placebo.

Symptoms of a serious allergic reaction to Tradjenta are rash, raised red patches on your skin (hives), swelling of your face, lips, and throat that may cause difficulty breathing or swallowing. If you have any symptoms of a serious allergic reaction, stop taking Tradjenta and call your doctor right away.Tell your doctor if you take other medicines that can lower your blood sugar, such as a sulfonylurea or insulin.Tradjenta may cause serious side effects, including low blood sugar (hypoglycemia). If you take Tradjenta with another

medicine that can cause low blood sugar, such as sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered while you take Tradjenta.

Signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, or feeling jittery.Also tell your doctor if you take rifampin (Rifadin(R), Rimactane(R), Rifater(R), Rifamate(R)), an antibiotic that is used to treat tuberculosis.Tradjenta may affect the way other medicines work, and other medicines may affect how Tradjenta works.Tell your doctor if you are pregnant or planning to become pregnant or are breastfeeding or plan to breastfeed.The most common side effects of Tradjenta include stuffy or runny nose and sore throat.You are encouraged to report negative side effects of prescription drugs to the FDA.(Conn,2012)

August 14 2012 Approximately 25.8 million Americans and an estimated 366 million people worldwide have type 1 or type 2 diabetes. Type 2 diabetes is the most common type, accounting for an estimated 90 to 95 percent of all diabetes cases. Diabetes is a chronic disease that occurs when the body either does not properly produce, or use, the hormone insulin.

In January 2011, Boehringer Ingelheim and Eli Lilly and Companyannounced an alliance in the field of diabetes that centers on four pipeline compounds representing several of the largest treatment classes. This alliance leverages the companies' strengths as two of the world's leading pharmaceutical companies, combining Boehringer Ingelheim's solid track record of research-driven innovation and Lilly's innovative research, experience, and pioneering history in diabetes. By joining forces, the companies demonstrate commitment in the care of patients with diabetes and stand together to focus on patient needs.

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 145 affiliates and more than 44,000 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel medications of high therapeutic value for human and veterinary medicine.As a central element of its culture, Boehringer Ingelheim pledges to act socially responsible.

Involvement in social projects, caring for employees and their families, and providing equal opportunities for all employees form the foundation of the global operations. Mutual cooperation and respect, as well as environmental protection and sustainability are intrinsic factors in all of Boehringer Ingelheim's endeavors.In 2011, Boehringer Ingelheim achieved net sales of about $17.1 billion (13.2 billion euro). R&D expenditure in the business area Prescription Medicines corresponds to 23.5% of its net sale.

Lilly, a leading innovation-driven corporation is developing a growing portfolio of pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, IN, Lilly provides answers - through medicines and information - for some of the world's most urgent medical needs. Lilly has been a global leader in diabetes care since 1923, when we introduced the world's first commercial insulin. Today we work to meet the diverse needs of people with diabetes through research and collaboration, a broad and growing product portfolio and a continued commitment to providing real solutions -- from medicines to support programs and more -- to make lives better.

(1) Tradjenta(R) (linagliptin) tablets. Highlights of Prescribing Information. Initial US Approval: 2011.

(2) Plantinga LC, Crews DC, Coresh J, et al; for the CDC CKD Surveillance Team. Prevalence of chronic kidney disease in US adults with undiagnosed diabetes or prediabetes. Clin J Am Soc Nephrol. 2010;5:673-682

(3) Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Center for Disease Control and Prevention, 2011

(4) International Diabetes Federation. Diabetes Atlas, 5th Edition: Fact Sheet. 2011

(5) International Diabetes Federation. IDF Diabetes Atlas, 5th Edition: Accessed on: July 27, 2012.

1.22 AVAILABLE BRANDS IN BANGLADESH

LINAGO (Medicon Pharmaceuticals Ltd.)

LIJENTA 5(NIPRO JMI Pharma Limited)

LIGATIN(Eskayef Bangladesh Ltd., Tongi)

LINAROL (Drug International Ltd.)

LINATIN (Delta Pharma Limited)

LINTIN (Kemiko Pharmaceuticals Ltd.)

TRANETA (Beximco Pharmaceuticals Ltd.)

LINADI (Pacific Pharmaceuticals Ltd.)

LINITA (Square Pharmaceuticals Ltd. Pabna)

LINAPTIN 5 (General Pharmaceuticals Ltd.)

LINATAB (Incepta Pharmaceuticals Ltd.)

LINAJEN (Popular Pharmaceuticals Ltd.)

Chapter: Two

Literature Review

Eckhardt *et al.*, 2007, Linagliptin binds tightly to the core of the DPP-4 enzyme forming three hydrogen bonds between the amino function on the piperidine ring and acceptor groups on residues Glu205, Glu206, Tyr662. A fourth hydrogen bond is formed between the C-6 carbonyl of the xanthine scaffold and the backbone amide of residue Tyr631. Finally, aromatic stacking interactions are established between the xanthine ring and Tyr547 as well as between the quinazoline ring and Trp629.(Eckhardt *et al*., 2007)

Thomas *et al*., 2008; Deacon, 2011, Linagliptin exhibits a 10,000-fold higher selectivity for DPP-4 than for other dipeptidyl peptidases such as DPP-2, DPP-8, and DPP-9, a property that makes this molecule, together with alogliptin, the highest selective compound vs. DPP-4. Similarly, the selectivity of linagliptin vs. peptidases N and P, prolyl oligopeptidases, and proteases such as trypsin, plasmin, and thrombin is much more than 10,000-fold. Linagliptin also inhibits fibroblast activating protein (FAP) with an IC50 of 89 nM (about 90-fold higher selectivity vs. DPP-4. (Thomas et *al.*, 2007)

Thomas *et al*., 2008 ,Linagliptin inhibits DPP-4 activity *in vitro* with an IC50 value of 1 nM, exhibiting a potency higher than all other DDP-4 inhibitors which yield IC50 values of 19 (sitagliptin), 24 (alogliptin), 50 (saxagliptin), and 62 (vildagliptin) nM, respectively (Maximal efficacy for DPP-4 inhibition is similar for linagliptin and other compounds of the same class. The kinetics of linagliptin interaction with DPP-4 reveals a slow dissociation from the enzyme with a calculated k_{off} rate (3×10^{-5}/s) that is approximately 10-fold slower than the off-rate for vildagliptin (Thomas *et al*., 2008).

Thomas *et al*., 2008, if inhibition of plasma DPP-4 activity is compared with that achieved using the same dosage of other DPP-4 inhibitors, linagliptin exhibits a similar efficacy vs. other compounds, at the 7 h time point. An exception is sitagliptin that appears less effective at both time points examined, 7 and 24 h. In contrast, at 24 h, linagliptin exhibits a sustained and maximal inhibition of DPP-4 activity, not observed with the other drugs. (Thomas *et al*, 2008)

In a phase I study carried out by Hüttner (2008), linagliptin was shown to be well tolerated in healthy male volunteers when administered in doses ranging from 2.5 to 600 mg per day. The overall incidence of adverse effect was similar in placebo- and linagliptin-treated subjects and there were no serious adverse effects (Hüttner et al., 2008). Hypoglycemia was never present and no changes of electrocardiographic or other cardiac function parameters could be detected (Hüttner ,2008).

Janet B. McGill in 2009,Type 2 diabetes mellitus (T2DM) is a progressive disease, and it occurs with increasing prevalence in the elderly and those with other comorbidities. Blood glucose control presents a challenge that is magnified by these co-existing problems. To achieve glycemic targets, many patients need more than one antidiabetic drug, and additional medications are often required as glucose control deteriorates Consequently, the development of new antidiabetic drugs that can help meet this challenge has been an area of intensive research.The dipeptidyl peptidase-4 (DPP-4) inhibitors are one of the recently developed therapeutic classes for treatment of hyperglycemia in T2DM. The various agents in the class have differing chemical structures, but all act by inhibiting the DPP-4 enzyme, thus prolonging the life of incretin hormones, which in turn raise insulin levels and suppress glucagon secretion in a glucose-dependent manner. As a class, DPP-4 inhibitors have been shown to provide significant improvements in glycosylated hemoglobin (HbA_{1c}), and to have a good safety profile. In addition, their glucose-dependent mechanism of action is associated with a low rate of hypoglycemic events. (Nathan *et al*., 2009).

Graefe-Mody *et al*., 2009, No reciprocal interaction was evident when linagliptin and metformin were administered together Metformin *per se* did not modify DPP-4 activity and did not affect inhibition of the enzyme induced by linagliptin in healthy subjects. No clinically relevant pharmacokinetic interactions at steady state between the two drugs were observed. Metformin increased AUC by 20% and t_{max} of linagliptin by about 50%, but these effects are unlikely to have clinical relevance. Conversely, linagliptin co-administration only slightly reduced metformin C_{max} and delayed its t_{max}.(Graefe-Mody , 2009)

Fuchs *et al*., 2009,a,Absorption of linagliptin is modified by intestinal P-glycoprotein. In Wistar rats receiving a single oral dose of linagliptin, administration of a P-glycoprotein inhibitor produced an increased bioavailability of the drug (suggesting that P-glycoprotein activity limits absorption of linagliptin.(Fuchs *et al.*, 2009)

Greischel *et al*., 2010, Pharmacokinetics of linagliptin is characterized by its binding to the DPP-4 target, not only in plasma, but mainly in tissues, where the enzyme is bound to membranes After single or repeated oral administration in male Fischer rats, linagliptin is highly present in kidney, liver, and lung, coincident with the distribution of DPP-4 (Fuchs *et al*., 2009 b).

Graefe-Mody *et al*., 2010, b Linagliptin did not either affect pharmacokinetics of pioglitazone when the two drugs were administered together. This may appear particularly significant since pioglitazone is a substrate for CYP2C8. Hence, pioglitazone (45 mg/day) did not modify linagliptin (10 mg/day) AUC and C_{max}, whereas linagliptin only slightly reduced pioglitazone C_{max} (The two drugs appear fully administrable in combination with no relevant pharmacokinetic interaction. (Graefe-Mody *et al.*, 2010)

Graefe-Mody *et al*., in 2010a An open-label, multiple-dose study examined, in healthy subjects, the pharmacokinetic interaction of linagliptin (10 mg/day) and simvastatin (40 mg/day), that is classified as a sensitive substrate of CYP3A4. Changes in CYP3A4 activity may significantly modify simvastatin metabolism, leading even to the occurrence of severe adverse effects. Co-administration of linagliptin increased (by 10–30%) both exposure and C_{max} of simvastatin and its active analog simvastatin acid without however achieving clinical relevance in terms not only of pharmacokinetic parameters, but also of safety and appearance of adverse effects during co-administration.(Graefe-Mody *et al.*, 2010, b)

Friedrich *et al*.,in 2011b, To test the interaction of linagliptin with drugs that act as substrate for P-glycoprotein, an open-label cross over study enrolling 20 healthy subjects was carried out to evaluate co-administration of linagliptin and digoxin .(Friedrich *et al*., 2011b)

Graefe-Mody *et al*.,in 2011d .A randomized open-label, two-way crossover study exami ned the effects of co-administration of multiple oral doses of linagliptin (5 mg/day × 6 days) and a single dose of glyburide (1.75 mg/day administered for 1 day) on the reciprocal pharmacokinetic parameters of the two drugs. Glyburide did not affect any pharmacokinetic feature of linagliptin and conversely, linagliptin slightly reduced glyburide AUC and C_{max}without achieving a clinically relevant effect). As glyburide is a recognized substrate of CYP2C9 and CYP3A4, this lack of interaction confirms that linagliptin does not modify the activity of these metabolic enzymes.(Graefe-Mody *et al*., 2011).

Scheen and Toth, in 2011. High-throughput screening using an assay to detect inhibition of DPP-4 led to the discovery of linagliptin, a xanthine-based molecule with a high selectivity for DPP-4. The pharmacokinetics and pharmacodynamics of linagliptin have been reviewed in detail elsewhere Of note, unlike other DPP-4 inhibitors, which are predominantly excreted via the kidneys, linagliptin is mainly excreted unchanged via the enterohepatic system (Blech et al. 2010; Heise *et al*., 2009).

Ring in 2011,a randomized, double-blind, placebo-controlled study was carried out in healthy subjects to evaluate the potential effect of linagliptin on QT interval. At the therapeutic dose (5 mg/day) and the 20-fold therapeutic dose (100 mg/day) administered, linagliptin did not cause any prolongation of the QT interval.(Ring , 2011)

Boehringer Ingelheim Pharmaceuticals Inc., 2011 Based on pharmacokinetic studies, no dose adjustment is needed for patients with renal or hepatic impairment. Early studies showed linagliptin is suitable for once-daily dosing, with similar reductions in HbA_{1c} to those seen with other DPP-4 inhibitors and without clinically significant pharmacokinetic interactions when co-administered with other medications Excretion of linagliptin. Approximately 90% of linagliptin is excreted unchanged, indicating that metabolism is a minor elimination pathway. (Forst *et al*., 2010)

Graefe-Mody In May 2011, On the basis of the early studies, an extensive clinical trial program was undertaken to assess the efficacy and safety of linagliptin. Of these, four pivotal trials, trials designed to meet US Food and Drug Administration (FDA) criteria for assessing efficacy and safety of a drug before it is approved for use in patients in the US, have been reported over the past year or so. The positive results of these trials led to FDA approval of linagliptin to improve glycemic control in patients with T2DM in (Graefe-Mody 2011).

Taskinen in 2011 Since patients in clinical practice may well be receiving more than one antidiabetic medication, the efficacy of linagliptin was assessed alone (as monotherapy) and in combination with other commonly used antidiabetic agents (metformin, a sulfonylurea or a thiazolidinedione).summarizes the design of the studies . All four were multicenter trials with a randomized, double-blind, placebo-controlled design, and a treatment phase of 6 months (24 weeks), considered the optimum balance between robust assessment of efficacy and the risk for patients exposed to placebo [All of the study designs incorporated a rescue therapy option for any patient whose glucose control was poor. (Taskinen,2011)

Gomis and Taskinen ,2011.The nature of clinical trials can alter patients' behavior, such as diet, exercise or compliance with medication, which may in turn impact blood glucose control. To counteract this, all trials included a 2-week open-label placebo run-in to allow patients to acclimatize to trial conditions. All patients were provided with standard diet and exercise counseling as well as equipment for home blood glucose monitoring at the start of the run-in.All four trials recruited adults with T2DM and a body mass index $\leq$40 kg/m^2, and the primary outcome measure was mean change in HbA_{1c} level from baseline at 24 weeks, which is a standard measure of efficacy in the testing of investigational agents for T2DM.The number of patients achieving target reductions in HbA_{1c} and fasting plasma glucose (FPG) levels were assessed as secondary endpoints in all trials, while postprandial glucose (PPG) was assessed in a subgroup of patients in two of the trials. (Gomis and Taskinen 2011)

Gomis in 2011,Treatment-naïve patients were eligible if screening HbA_{1c} levels were between 7.5% and 11.0%; patients receiving treatment with any other OAD were eligible if HbA_{1c} levels were between 7.0% and 9.5% at screening, and between 7.5% and 11.0% after a 4-week washout of all OADs. After the washout, all patients underwent a 2-week open-label placebo run-in, and were then randomized in a 2:1 ratio to either an initial combination of pioglitazone 30 mg/day and linagliptin 5 mg/day or pioglitazone 30 mg/day and placebo for 24 weeks (Gomis, 2011)

Owens in 2011, As with all well-designed studies for T2DM, rescue medication was used as a safety net for any patient who had inadequate blood glucose control. All patients were trained in home blood glucose monitoring and provided with equipment at the beginning of the study. During the washout and open-label placebo run-in periods, patients were asked to monitor blood glucose daily before breakfast and at any time they felt symptoms of hyperglycemia or hypoglycemia. During the randomized, double-blind period of the trials, daily testing was no longer required, but patients could perform tests if they had symptoms. If the patient did measure high blood glucose levels, they were confirmed with a second measurement on a different day, with at least one measurement at the study site, before rescue therapy was started. During the trials, a significantly higher proportion of patients in the placebo group received rescue medication than in the linagliptin group. Patients receiving rescue medication were included in the primary efficacy analysis, using their HbA_{1c} measurement prior to the start of rescue therapy. When analyses were repeated, including only patients who received treatment per protocol, results were consistent with the primary analysis, with significantly greater reductions in HbA_{1c} in the linagliptin groups; Rescue medication. (Owens, 2011)

Willemen *et al*. in 2011,Nasopharyngitis, which has been associated with other DPP-4 inhibitors was reported in 5.8% of linagliptin patients *versus* 5.5% of placebo patients in a pooled analysis of placebo-controlled trials that included the four pivotal trials (Boehringer Ingelheim Pharmaceuticals Inc., 2011).

Boehringer Ingelheim Pharmaceuticals Inc., 2011.Cough, hyperlipidemia and weight increase were the only adverse events reported in at least 2% of patients treated with linagliptin and at a rate at least twofold greater than with placebo. Cough was reported in 2.4% of patients in the linagliptin group and 1.1% of patients in the placebo group when linagliptin was used as add-on to metformin and sulfonylurea.When linagliptin was used in combination with pioglitazone, hyperlipidemia was reported in 2.7% and 0.8%, and weight increase in 2.3% and 0.8% of the linagliptin and placebo groups, respectively.(Boehringer Ingelheim Pharmaceuticals Inc., 2011)

Gomis *et al*., 2011 For lipid profiles, more detailed information has been reported for only two studies, and the publications do not report the patients' use of lipid-lowering medication, leaving the results difficult to interpret from a clinical perspective. When linagliptin was added to a stable regimen of metformin and sulfonylurea, mean changes from baseline to 24 weeks were similar for the linagliptin and placebo groups for total cholesterol, high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C).At baseline, both groups had mean triglyceride values above the normal reference range. Mean values for the two groups remained above the reference range at 24 weeks, with the mean triglyceride level in the linagliptin group remaining stable, and the triglyceride level in the placebo group decreasing by 12 mg/dl. (Gomis *et al*., 2011)

Jelsing *et al*., 2012 In NOD mice that spontaneously develop a form of insulin-dependent diabetes caused by an autoimmune T cell-dependent destruction of islets, thus resembling human type 1 diabetes, linagliptin affects all the above described parameters. Specifically, exposure to linagliptin, given with food at doses of 3–10 mg/kg for 8 weeks, delays the onset and reduces the incidence of diabetes; it in fact induces reduction of basal blood glucose levels, decreases water intake and enhances GLP-1 levels. In addition, it significantly increases beta-cell mass in the pancreas without modifying the non-beta-cell component.
(Jelsing, *et al.*,2012).

Chen *et al.*, 2012 interestingly, recent evidence suggests a positive interaction of linagliptin with an inhibitor of sodium-glucose co-transporter 2 (SGLT2) that is emerging as a novel target for treatment of T2DM. In genetically diabetic mice, linagliptin improves in fact the effects induced by the SGLT2 inhibitor, not only in terms of glycemic control and islet function, but also with regards to the expression of genes associated with the inflammatory response.(Chen *et al.*, 2012)

Jelsing *et al.*, 2012 the effects of linagliptin are not restricted to direct control of glycemic levels. As already mentioned, linagliptin in fact increases beta-cell mass component in the pancreas .In human cell islets in vitro, linagliptin (100 nM for 48 h) protects from apoptosis induced by exposure to insults such as palmitic acid, interleukin-1/interferon-γ, or hydrogen peroxide (Shah et al., 2010), restores beta-cell function and reverts oxidative stress responsible for islet dysfunction.

(Jelsing *et al.*, 2012)

Kern and Klein *et al.*, 2012 When administered, in a period comprised from 4 weeks to 3 months (3 or 30 mg/kg), to diet-induced obese rats and HFD-fed mice, linagliptin significantly reduces plasma leptin levels, as well as hepatic steatosis, measured as hepatic red oil staining and/or by magnetic resonance spectroscopy.

(Kern *et al.*, 2012)

Kröller-Schön, *et al*., in 2012. Linagliptin also seems to be endowed with vascular protective properties as it induces vasodilation in isolated aortic rings under basal conditions, in a concentration-dependent manner. This effect is mimicked by vildagliptin, but not by other DPP-4 inhibitors. It also affects vascular dysfunction-related reactive oxygen species and inflammation, thus exhibiting anti-oxidative and anti-inflammatory properties.(Kröller-Schön *et al.*, 2012).

Alter *et al*.,2012 linagliptin exhibits a protective effect against diabetes-dependent renal impairment. In diabetic endothelial nitric oxide synthase (eNOS) knockout mice, an established model of diabetic nephropathy, linagliptin, given as add-on therapy to the standard treatment telmisartan, improves albuminuria, a predictor of diabetic nephropathy, and reduces plasmatic levels of osteopontin, a marker of vascular calcification. These

effects are accompanied by reduction of glomerulosclerosis and renal oxidative stress, as measured by accumulation of malondialdehyde, as well as reduction of tumor necrosis factor α (TNF-α) levels, a marker of systemic inflammation. (Alter *et al*., 2012)

Darsalia *et al.,* 2012, Finally, very recent data have shown that treatment with linagliptin produces a neuroprotective effect, independent of its glucose lowering action. Specifically, in a model of stroke induced by middle cerebral artery occlusion in normal and diabetic mice, linagliptin is effective in reducing stroke volume (with a greater effect in normal mice) and in increasing the number of viable neurons in the peri-infarct area. (Darsalia *et al.*, 2012)

Jamonline in 2012,Linagliptin is an inhibitor of DPP-4 (Dipeptidyl peptidase 4) an enzyme thatdegrades the incretion hormones, Glucagon-like peptide-1 (GLP-1) and Glucose-dependent Insulinotropic polypeptide (GIP).Both GLP-1 and GIP increase insulinbiosynthesis and secretion from pancreaticbeta cells in the presence of normal andelevated blood glucose levels. GLP-1 alsoreduces glucagon secretion from pancreaticalpha cells, resulting in a reduction in hepaticglucose output. Thus, Linagliptin stimulatesthe release of insulin in a glucose-dependentmanner and decreases the levels of glucagonin the circulation. Linagliptin showed that thedrug can effectively reduce blood sugar.(Jamonline,2012)

Schernthaner *et al.,* 2012,Safety and tolerability data obtained with linagliptin in eight phase III clinical trials have been collected in a recent review article and data obtained from about 3,500 patients were analyzed altogether .The overall incidence of adverse events and serious adverse events was similar in placebo- and linagliptin-treated patients (55 vs. 55.8 and 2.7 vs. 2.8%, respectively). (Schernthaner *et al*., 2012)

In 2012 Brown DX, Choudhury M, Evans M found that pathogenesis of type 2 diabetes (T2D) can result in decreased levels of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which under normal circumstances increase insulin secretion and suppress glucagon release. A new form of drug therapy known as

dipeptidyl peptidase 4 (DPP IV) inhibitors has focused on increasing the circulating levels of these "incretin" hormones in order to improve glycemic control in patients with T2D. The DPP IV inhibitors saxagliptin, vildagliptin, linagliptin, alogliptin and sitagliptin function by inhibiting the enzyme DPP IV, which breaks down GLP-1 and GIP, and have had significant success. However, with most DPP IV inhibitors being extensively excreted renally, this is a significant issue, as a large proportion of diabetic patients suffer from renal complications. Linagliptin is a novel DPP IV inhibitor that is excreted primarily by the hepatic route, with little need for dose adjustment in patients with renal impairment. It therefore represents a major advancement in the pharmacotherapy of patients with T2D.**(**Brown ,2012).

Agrawal *et al*., 2012.Bentham Science Publishers. Chemically, methylxanthine nucleus based Linagliptin (BI-1356, BI-1356-BS) is a dipeptidyl peptidase-IV inhibitor, which has been developed by Boehringer Ingelheim in association with Lilly for the treatment of Type-II Diabetes. Linagliptin was marketed by Lilly under the trade name Tradjenta and Trajenta. Linagliptin was approved as the once-daily dose by USFDA on 2 May 2011, for the treatment of Type-II Diabetes. Linagliptin 5mg once daily dose was approved based on a clinical trial program, which was conducted on approximately 4,000 adults with Type-II Diabetes. Linagliptin demonstrated statistically significant mean difference in HbA1c from placebo of up to 0.72 percent, when it was used monotherapically. In patients, who were not adequately controlled on metformin or metformin plus sulphonylurea, the addition of Linagliptin resulted in a statistically significant mean difference in HbA1c from placebo of -0.6 percent. Linagliptin was observed to produce significant reduction in fasting plasma glucose (FPG) compared to placebo, when used as a monotherapy in combination with metformin, sulfonylurea and/or pioglitazone. Linagliptin demonstrated significant reduction post-prandial glucose (PPG) levels in two hours as compared with placebo in monotherapy as well as in combination with metformin. In vitro assays also anticipated that Linagliptin is a potent DPPIV inhibitor as well as it exhibits good selectivity for DPP-IV as compared with other DPPs.(Agrawal, Ritesh; Jain,2012)

MEDLINE (1966–January 12, 2012), PubMed (1950–January 12, 2012), Science Direct (1994–January 12, 2012), Web of Science (1980–January 12, 2012), and the American

Diabetes Association Scientific Abstracts (2008–2011) were searched using the term linagliptin. Articles and abstracts published in English, both original research and review articles, were identified for review. Reference lists from identified articles were also searched for additional references of interest. Manufacturers' prescribing information was additionally examined.Results:Data from clinical trials of linagliptin suggest clinical efficacy in terms of reductions in hemoglobin A_{1c} (A_{1c}), fasting plasma glucose, and postprandial glucose when linagliptin was administered as monotherapy or in combination with other oral antidiabetic agents, with placebo-subtracted A_{1c} changes ranging from −0.47% to −0.69% in placebo-controlled trials. Adverse events that occurred in ≥2% of patients treated with linagliptin and at a prevalence of ≥2-fold greater compared with placebo were nasopharyngitis, hyperlipidemia, cough, hypertriglyceridemia, and weight increase (when used in combination with a thiazolidinedione [TZD]). Although linagliptin administered as monotherapy or in combination with metformin or a TZD may convey a low risk for hypoglycemia (0%–1.2%), caution is warranted when linagliptin is administered in combination with insulin secretagogues due to an increased risk for hypoglycemic events. Dosage adjustments based on renal or hepatic function are not required. Additionally, according to the currently approved prescribing information, the efficacy of linagliptin may be limited in patients receiving concurrent inducers of the cytochrome P450 3A4 isozyme or P-glycoprotein (eg, rifampin).

Erratum in Drugs. 2013 Jan;73(1):99.Linagliptin (Trajenta®, Tradjenta™, Trazenta™, Trayenta™) is an oral, highly selective inhibitor of dipeptidyl peptidase-4 and is the first agent of its class to be eliminated predominantly via a nonrenal route. Linagliptin is indicated for once-daily use for the treatment of adults with type 2 diabetes mellitus, and a twice-daily fixed-dose combination of linagliptin/metformin (Jentadueto®) is also available. In this article, the pharmacological, clinical efficacy and tolerability data relevant to the use of linagliptin in patients with type 2 diabetes are reviewed. The efficacy of oral linagliptin in the treatment of adults with type 2 diabetes has been investigated in several double-blind, multicentre trials. Following 12-24 weeks of treatment, improvements in glycaemic control parameters, including glycosylated haemoglobin (HbA(1c); primary endpoint in all trials), were seen with linagliptin relative to placebo

when used as monotherapy, initial combination therapy (with metformin or pioglitazone) or add-on therapy to other oral antihyperglycaemia agents (metformin and/or a sulfonylurea) or basal insulin (with or without metformin and/or pioglitazone). In terms of lowering HbA(1c), linagliptin was more effective than voglibose in a 26-week monotherapy trial and noninferior to glimepiride when used as add-on therapy to metformin in a 104-week study. Additional trials and subgroup analyses of pooled data suggest that linagliptin improves glycaemic control regardless of factors such as age, duration of type 2 diabetes, ethnicity and renal function, and as linagliptin is eliminated primarily via a nonrenal route, it can be used without dosage adjustment in patients with renal impairment of any degree. Oral linagliptin was generally well tolerated and was associated with a low likelihood of hypoglycaemia (except when used in combination with a sulfonylurea) and had little effect on bodyweight. Further long-term and comparative efficacy and tolerability data are required to help position linagliptin more definitively with respect to other antihyperglycaemia agents. However, clinical data currently available indicate that linagliptin is an effective and generally well tolerated treatment option for use in patients with type 2 diabetes, including those with renal impairment for whom other antihyperglycaemia agents require dosage adjustment or are not suitable.(Erratum in Drugs. 2013)

In 2013 April Kožnarová R, studied that Dipeptidyl peptidase 4 inhibitors (DPP4) are used as an oral hypoglycaemic agent in Type-2 diabetic patients. From a clinical point of view the most important advantages of this preparation are improved diabetes compensation, significant reduction of hypoglycaemia risk compared with sulfonylurea derivatives, neutral weight profile and good GIT tolerance. Vildagliptin is a molecule from the group of DPP4 inhibitors which is recently used in internal outpatient care.(Kožnarová ,2013)

In 2013 June Khan S, Khan S, Imran M, Pillai KK, Akhtar M, Najmi AK identified that type 2 diabetes mellitus (T2DM) is intricately allied with an increased risk of atherothrombotic disease. Thrombosis is the cause of mortality in 80% of patients with diabetes mellitus. Endothelial abnormalities lead to elevated inflammatory and coagulation biomarkers as seen in diabetes. Progression of atherothrombotic disease in diabetes has

been linked with elevated levels of various coagulation factors including fibrinogen, plasminogen activator inhibitor-1, and von Willebrand factor.(June,2013)

In 2013 Nov 7 Araki S, studied the number of elderly diabetic patients who require chronic hemodialysis is progressively increasing in Japan. Thus, halting the progression of diabetic nephropathy in elderly diabetic patients is a clinically important issue. However, there is little information or evidence of this complication. Understanding the change of the kidney function with aging, theclinical characteristics and factors associated with the progression of diabetic nephropathy in this population should be useful for establishing effective therapeutic strategies to prevent this life threatening complication. (Araki S, 2013)

IN 2013 Araki S, Identified the number of elderly diabetic patients who require chronic hemodialysis is progressively increasing in Japan. Thus, halting the progression of diabetic nephropathy in elderly diabetic patients is a clinically important issue. However, there is little information or evidence of this complication. Understanding the change of the kidney function with aging, the clinical characteristics and factors associated with the progression of diabetic nephropathy in this population should be useful for establishing effective therapeutic strategies to prevent this life threatening complication. (Araki ,2013)

In 2014 Kim J, Samson SL Diabetes patients are at high risk for development of cardiovascular disease. The cardiovascular safety of antidiabetic medications is a concern. Incretin therapies, including glucagon-like peptide 1 receptor (GLP-1) receptor agonists and dipeptidyl peptidase 4 (DPP-4) inhibitors, have recently been introduced to clinical practice and are widely used. Data from phase 2 and 3 trials and retrospective analyses of clinical databases have shown favorable changes in cardiovascular risk factors and outcomes. However, only a few prospective trials have been designed with cardiovascular outcomes as a primary end point. From current data, alogliptin and saxagliptin do not change cardiovascular risk in type 2 diabetes mellitus (T2DM) patients. Vildagliptin does not alter myocardial function in T2DM patients with systolic dysfunction. However, the possibility of an increase in clinical heart failure and worsened outcomes in patients with existing heart failure is suggested by current data. Clinicians need to follow patients on

DPP-4 inhibitors carefully for this possibility until more prospective randomized controlled data are available. (Kim, 2014)

In 2014 september Ceriello A, Sportiello L, Rafaniello C, Rossi F was introduced incretin-based therapy for the treatment of type 2 diabetes (T2D). In particular, dipeptidyl peptidase-4 inhibitors (DPP-4i) (sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin)play an increasing role in the management of T2D.(Ceriello *et al*., 2014).

In 2014 June Janardhan S, Sastry GN showed Dipeptidyl peptidase IV (DPP4) is a promising target for the treatment of chronic metabolic type 2 diabetes mellitus (T2D). DPP4 is a highly specific serine protease involved in the regulation and cleavage of two incretin hormones, glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These incretin hormones are released by the gastrointestinal tract in response to ingestion of food and stimulate insulin secretion and thereby regulate glucose homeostasis with a low risk of hypoglycemia and glucagon secretion. Currently different chemical classes of DPP4 inhibitors are in last-stage of clinical trials and few of them such as sitagliptin, vildagliptin, saxagliptin alogliptin and linagliptin have already been successfully released into market. These drugs have been approved as either monotherapy or combination therapy with other oral hypoglycemic agents such as metformin, pioglitazone, sulfonylurea, glyburide and glibenclamide for the treatment of T2D. Though several clinical trial compounds were discontinued because of severe adverse toxic effects that are associated with other prolyldipeptidases include DPP8 and DPP9. The current review provides an overview of DPP4 and its inhibitors with emphasis on the structure, expression, activity, selectivity and pharmacokinetics information. This review further dwells upon the issues relating to the rational design and development of selective DPP4 inhibitors for the treatment of T2D. (Janardhan *et al*., 2014)

In 2014 april Stein SA, Lamos EM, Davis SN showed that Vildagliptin is a dipeptidyl peptidase-4 inhibitor targeting the incretin system to improve glycemic control in type 2 diabetes. It focuses on the pharmacokinetics, drug interactions and use of oral vildagliptin in special populations. Clinical efficacy and vildagliptin's role in the spectrum of therapeutics available are briefly addressed.(Stein *et al* ., 2014)

In 2015 Nov 24 Deacon CF, Lebovitz HE provide durable glycaemic control over the long-term. Sulphonylurea (SU) drugs have a history stretching back over 60 years, and have traditionally been the mainstay choice as second-line agents to be added to metformin once glycaemic control with metformin monotherapy deteriorates. However, they are associated with undesirable side effects, including increased hypoglycaemia risk and weight gain. Dipeptidyl peptidase-4 inhibitors (DPP-4i) are, by comparison, more recent, with the first compound being launched in 2006, but the class now globally encompasses at least eleven different compounds. DPP-4i improve glycaemic control with similar efficacy to SU, but do not usually provoke hypoglycaemia or weight gain, are relatively free from adverse side effects, and have recently been shown not to increase cardiovascular risk in large prospective safety trials. Because of these factors, DPP-4i have become an established therapy of type 2 diabetes and are increasingly being positioned earlier in treatment algorithms. This article reviews these two classes of oral antidiabetic drugs (DPP-4i and SU), highlighting differences and similarities between members of the same class, as well as discussing the potential advantages and disadvantages of the two drug classes. While both classes have their merits, the choice of which to use depends on the characteristics of each individual patient, but for the majority of patients, DPP-4i are now the preferred choice. (Deacon *et al.*,2015)

In 2015 June 25 Nakamura Y, Hasegawa H, Tsuji M, Udaka Y, Mihara M, Shimizu T, Inoue M, Goto Y, Gotoh H, Inagaki M, Oguchi K studies on the effects of dipeptidase-4 (DPP-4) inhibitors in diabetic hemodialysis (HD) patients . Eyesight failure caused by diabetic retinopathy and aging-related dementia make multiple daily insulin injections difficult for HD patients. Therefore, the effects of DPP-4 inhibitors with a focus on oral antidiabetic drugs as a new treatment strategy in HD patients with diabetes. The following 7 DPP-4 inhibitors are available worldwide: sitagliptin, vildagliptin, alogliptin, linagliptin, teneligliptin, anagliptin, and saxagliptin. All of these are administered once daily with dose adjustments in HD patients. Four types of oral antidiabetic drugs can be administered for combination oral therapy with DPP-4 inhibitors, including sulfonylureas, meglitinide, thiazolidinediones, and alpha-glucosidase inhibitor. Nine studies examined the antidiabetic effects in HD patients. Treatments decreased hemoglobin A1c and glycated albumin levels by 0.3% to 1.3% and 1.7% to 4.9%, respectively. The efficacy of DPP-4 inhibitor

treatment is high among HD patients, and no patients exhibited significant severe adverse effects such as hypoglycemia and liver dysfunction. DPP-4 inhibitors are key drugs in new treatment strategies for HD patients with diabetes and with limited choices for diabetes treatment.(Nakamura ,2015)

In 2015 April 16 Aziz KM studied diabetes management during Ramadan fasting is challenging to the physician in terms of minimizing the risk of hypoglycemia. As compared to oral hypoglycemic agents (OHAs) and sulfonylureas (SUs), which carry a higher and significant risk of hypoglycemia, newer antidiabetic agents such as dipeptidyl peptidase-4 (DPP-4) inhibitors have demonstrated lower risk of hypoglycemia during Ramadan fasting, with better patient compliance. In addition to diabetes education and pre-Ramadan assessments, the physician should also consider use of DPP-4 inhibitors (such as vildagliptin) during Ramadan fasting to minimize the risk of hypoglycemia in type 2 diabetic subjects. Severe episodes of hypoglycemia have been demonstrated in recent research and clinical trials with OHAs/SUs. Conversely, these research observations have also demonstrated comparative safety and efficacy with lower risk of hypoglycemia associated with vildagliptin. Current research review has collected evidence-based clinical trials and observations for the drug vildagliptin to minimize the risk of hypoglycemia during Ramadan fasting, while at the same time focusing the role of diabetes self-management education (DSME), pre-Ramadan assessments, and patients.(Aziz ,2015)

In 2015 April Scheen AJ showed that Dipeptidyl peptidase-4 (DPP-4) inhibitors (gliptins) occupy a growing place in the armamentarium of drugs used for the management of hyperglycemia in type 2 diabetes, although some safety concerns have been raised in recent years. After that providing an analysis of available safety data (meta-analyses, randomized controlled trials, observational cohort and case-control studies and pharmacovigilance reports) with five commercialized DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin). A special focus is given to overall safety profile; pancreatic adverse events (AEs) (acute pancreatitis, pancreatic cancer); overall cardiovascular safety (myocardial infarction and stroke); congestive heart failure concern and finally, safety in special populations (elderly, renal impairment).(Scheen *et al*.,2015)

In 2015 Jan Tella SH, Rendell MS studied Dipeptidyl peptidase inhibitors (DPP-4-i) are highly selective inhibitors of the enzyme DPP-4. They act by increasing levels of incretin hormones, which have potent effects on insulin and glucagon release, gastric emptying, and satiety. Our goal is to review the safety issues related to DPP-4-i. (Tella *et al.,* 2015)

In 2015 Jun Karagiannis T, Boura P, Tsapas A Dipeptidyl peptidase 4 (DPP-4) inhibitors are a relatively new class of oral antihyperglycemic agent that enhance insulin secretion by reducing degradation of endogenous glucagon-like peptide 1. Currently, sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin have been approved by the US Food and Drug Administration or the European Medicines Agency for use in patients with type 2 diabetes. Their glycemic efficacy has been well documented; however, data regarding their long-term safety are as yet inconclusive. While preclinical studies have indicated a potential cardioprotective effect of DPP-4 inhibitors, current clinical data from cardiovascular safety trials suggest a neutral effect on cardiovascular outcomes. Moreover, postmarketing experience has given rise to concerns about specific adverse events, including pancreatitis and hypersensitivity reactions. This review summarizes available evidence regarding safety of DPP-4 inhibitors. Overall, DPP-4 inhibitors appear to be a safe option for patients with type 2 diabetes. However, close pharmacovigilance is necessary to address the uncertainty regarding pancreas-related adverse events, while their potential impact on cardiovascular outcomes will be further elucidated after completion of more long-term studies. (Karagiannis *et al*., 2015)

Esther S. Kim in September 2015 with 2 Reads 1st and 2nd Emma D. Deeks Empagliflozin/linagliptin inhibitor and dipeptidyl peptidase (DPP)-4 inhibitor fixed-dose combination product that is approved in the USA as an adjunct to diet and exercise in adults with type 2 diabetes (T2D) when treatment with both empagliflozin and linagliptin is appropriate. This article reviews the clinical efficacy and tolerability of oral empagliflozin/linagliptin in patients with T2D and summarizes the pharmacological properties of the agents. Results of two randomized controlled trials of 52 weeks' duration in adults with T2D demonstrated that empagliflozin/linagliptin improved glycaemic control significantly more than linagliptin when administered as initial therapy (whereas results vs. empagliflozin were mixed in this setting) and significantly more than linagliptin

or empagliflozin when administered as an add-on therapy to metformin. In addition to glycaemic control, empagliflozin/linagliptin provided significant weight loss compared with linagliptin in both trials. Empagliflozin/linagliptin was generally well tolerated in patients with T2D, with a low risk of hypoglycaemia and no reports of exacerbations of, or hospitalizations for, heart failure during the trials. As the first SGLT2 inhibitor/DPP-4 inhibitor fixed-dose combination available, empagliflozin/linagliptin is a useful new option for patients with T2D.(Esther *et al.*,2015).

In 2015 Deacon CF, Lebovitz HE provide durable glycaemic control over the long-term. Sulphonylurea (SU) drugs have traditionally been the mainstay choice as second-line agents to be added to metformin once glycaemic control with metformin monotherapy deteriorates. However, they are associated with undesirable side effects, including increased hypoglycaemia risk and weight gain. Dipeptidyl peptidase-4 inhibitors (DPP-4i) improve glycaemic control with similar efficacy to SU, but do not usually provoke hypoglycaemia or weight gain, are relatively free from adverse side effects, and have recently been shown not to increase cardiovascular risk in large prospective safety trials. Because of these factors, DPP-4i have become an established therapy of type 2 diabetes and are increasingly being positioned earlier in treatment algorithms. He mentioned these two classes of oral antidiabetic drugs (DPP-4i and SU), highlighting differences and similarities between members of the same class, as well as discussing the potential advantages and disadvantages of the two drug classes. While both classes have their merits, the choice of which to use depends on the characteristics of each individual patient, but for the majority of patients, DPP-4i are now the preferred choice. (Deacon *et al*., 2015)

CHAPTER: THREE

METHODS AND MATERIALS

3.1 Methods and studies

Diabetic Books prescription and new patients initial form prescription of Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM.)

Camera or Mobile phone camera Windows 2010(Microsoft Excel)

3.2 Sample characteristic's

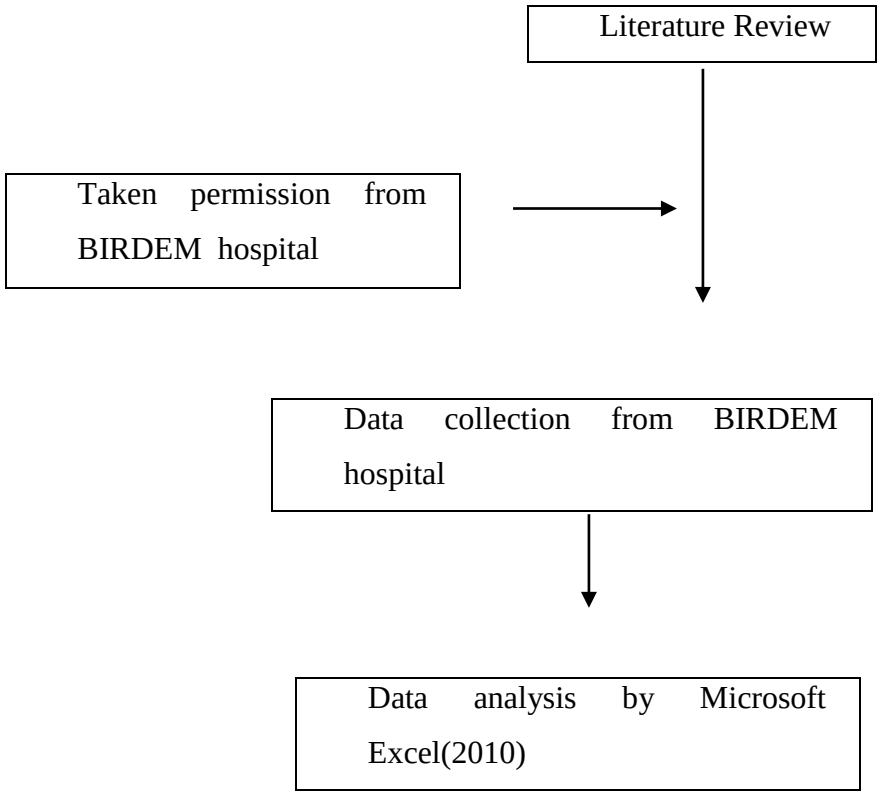
The sample was collected from the BIRDEM hospital Shahabag, Dhaka from 15th March 2015 to 15th December 2015. All the prescription were collected retrospectively from the outcome patients prescription.

3.2.1 Exclusion criteria

500 outcome diabetic patients age between 17 to 84 years was excluded for the study.

3.3 Procedure

The study was performed by completing 3 stages of the procedure. In the beginning literature review was done from 30 online literatures regarding diabetic treatment on prescription basis. The aim of the literature review was to observe the situations of the prescription of outcome diabetic patients. Followed by the literature review data collection step was executed by collecting data with the help of diabetic treatment on prescription basis. Data regarding treatment given to the outcome diabetic patients were collected by survey retrospectively from outcome patients diabetic prescriptions of BIRDEM hospital Shahabag, Dhaka. Data collection periods were March 2015 to December 2015. In the final stage data analysis was made with the help of analytical software Windows 2010(Microsoft Excel).


Literature Review
Taken permission from BIRDEM hospital
Data collection from BIRDEM hospital
Data analysis by Microsoft Excel(2010)

3.5 Data acquisition

In this thesis pharmacokinetic and/or pharmacodynamic observations of the DPP-4 inhibitor linagliptin from one nonclinical and six clinical studies were analysed.The analytical methods used to quantify the linagliptin plasma concentration and DPP-4 activity are described in the following sections.Before start of the actual population pharmacokinetic or pharmacodynamic analysis, the data were extensively explored graphically to further assure the data quality and to allow a comprehensive overview of the investigated data. In general, the distribution of subjects and observations per dose group, visit and time after dose was investigated.Pharmacokinetic and pharmacodynamic observations were plotted versus time and versus each other. Furthermore, frequency distributions of covariates and correlations between covariates were examined. The main results of the dataset description are presented in the respective section of each project.

CHAPTER: FOUR

RESULT

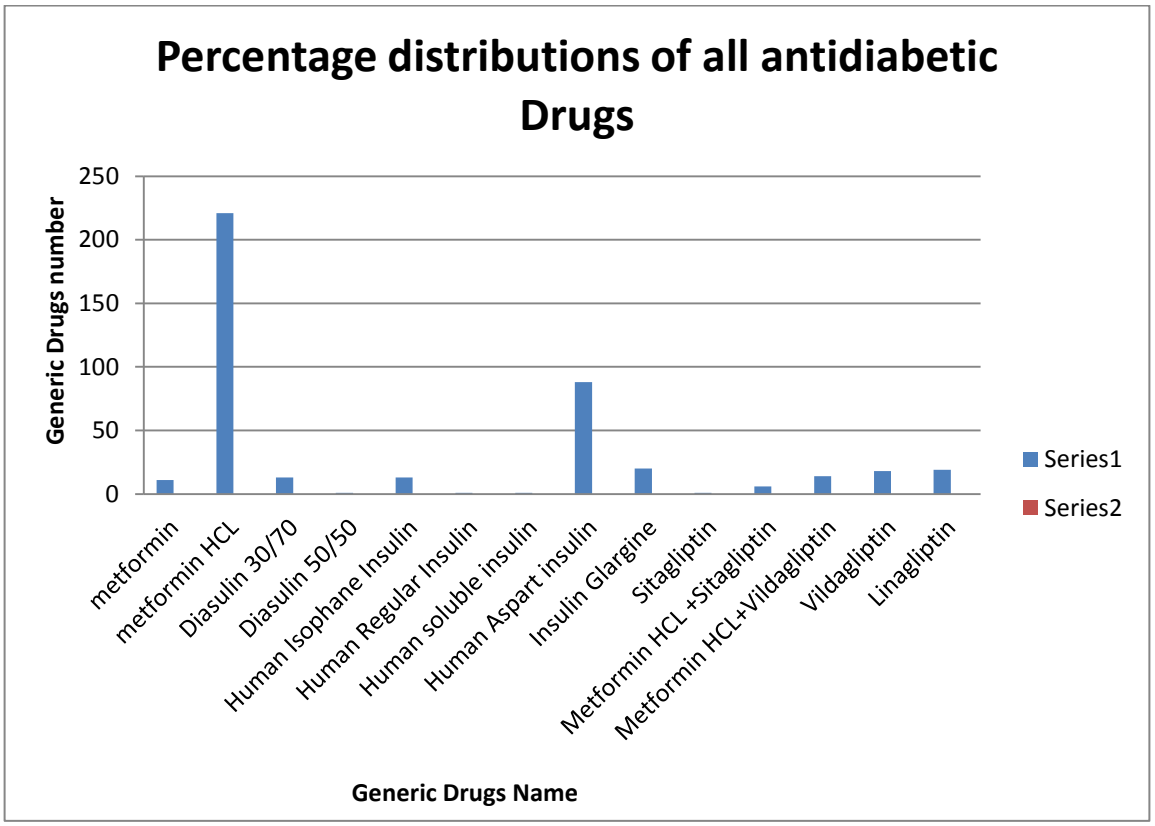


Figure 4: Percent distribution of Anti Diabetic Drug who is suffering by Diabetes

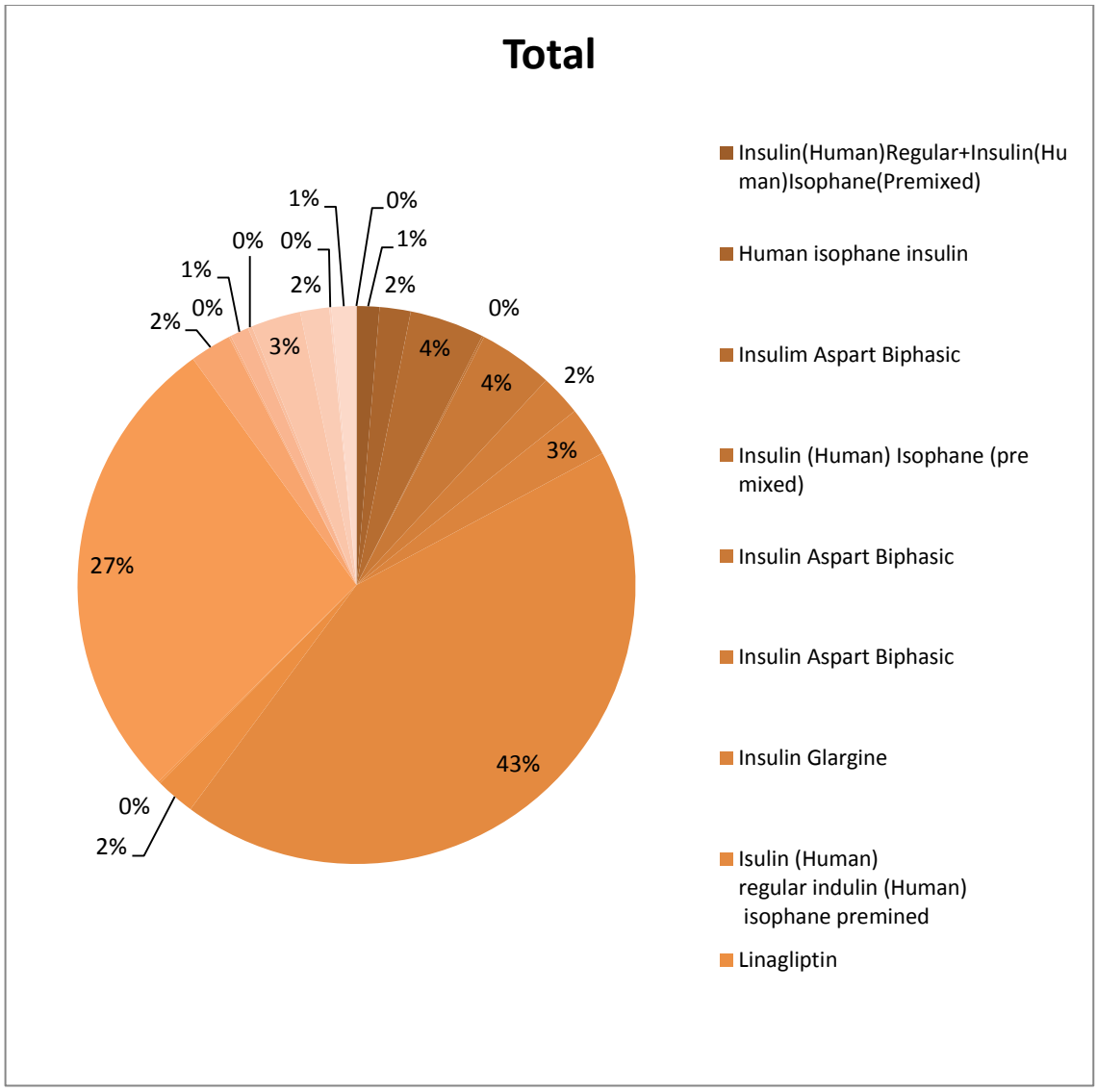


Figure 5: Percent distribution of Anti Diabetic Drug who is suffering by Diabetes

This Figure shows that 43% Insulin(Human)Regular +Insulin(Human) Isophane (Premixed), 27% Metformin HCL, 2% Metformin HCL+Vildagliptin, 0.12% Metformin HCL +Pioglitazone, 1% Metformin HCL+Sitagliptin, 2% Linagliptin, 3% Sitagliptin, 9% Insulin Aspart Biphasic, 3% Regular Insulin Human and 1% Vidagliptin generic drugs are prescribed from 500 prescription.

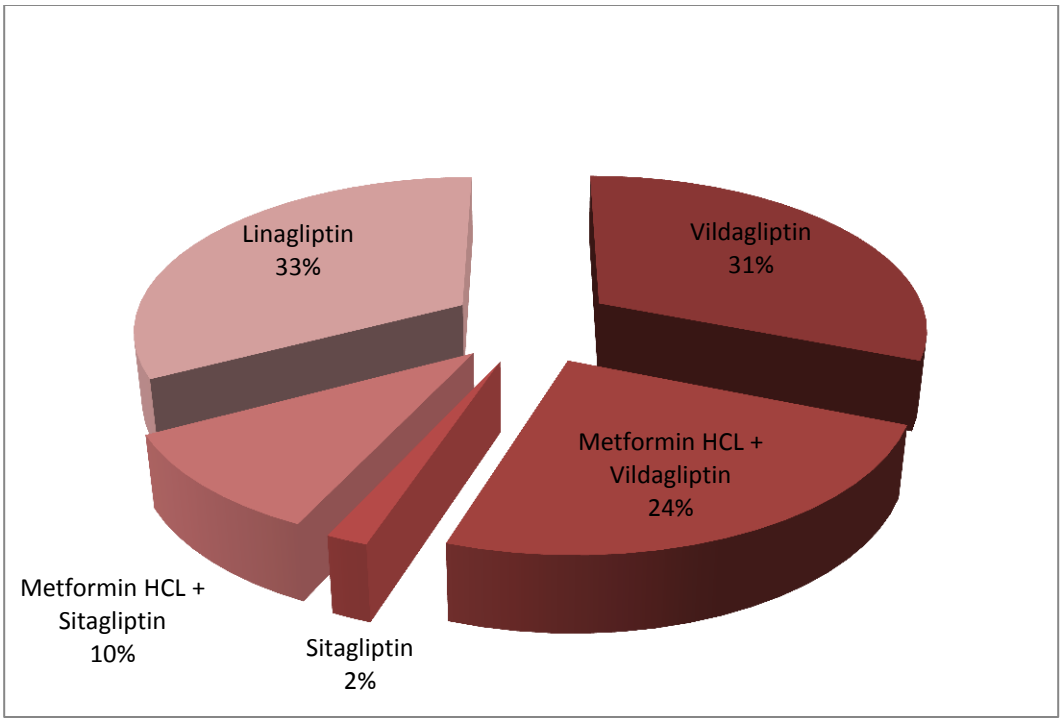


Figure 6: Distribution of New Anti-Diabetic Drugs

This Figure shows that, Linagliptin 33%, Metformin HCL+Vildagliptin 24%, Metformin HCL+Sitagliptin 10% ,Sitagliptin 2%, Vidagliptin 31% generic drugs are prescribed from 500 prescription.

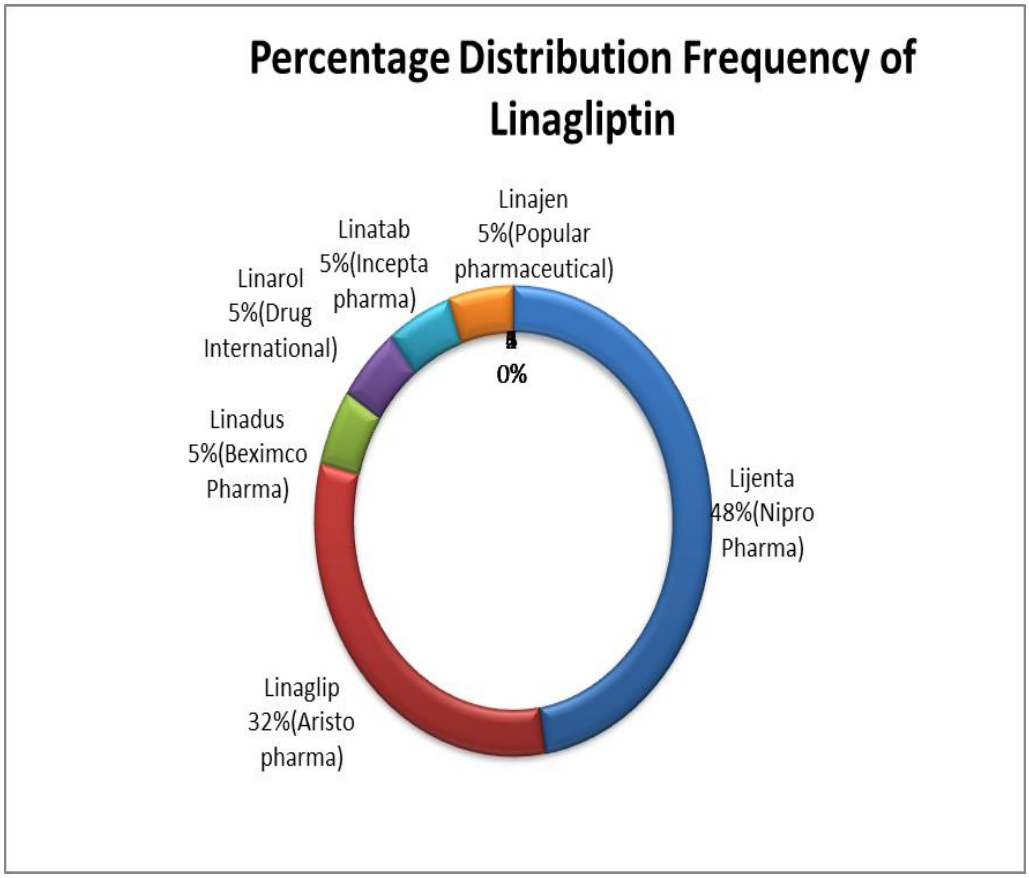


Figure 7: Percentage Distribution Frequency of Linagliptin

This Figure shows that Linagliptin 8%, Metformin 4% and Metformin HCL 88% generic drugs are prescribed from 500 prescriptions.

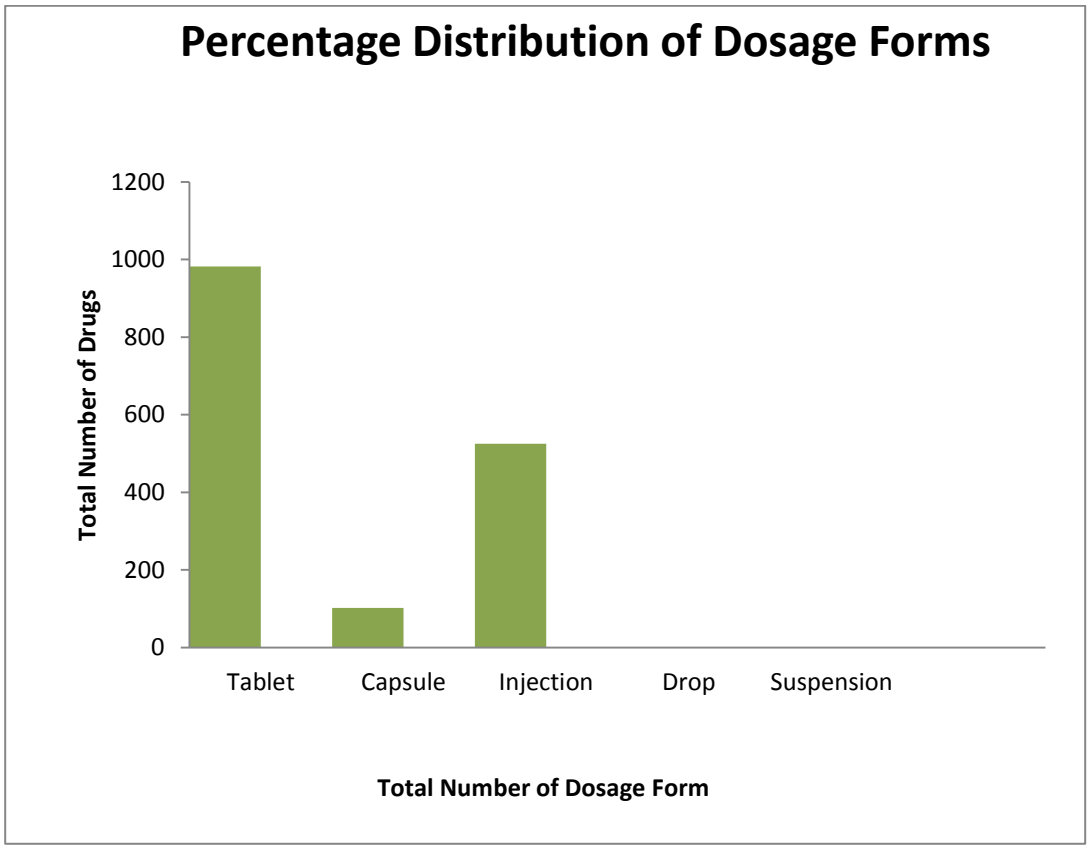


Figure 8:Percentage Distribution of Dosage Form

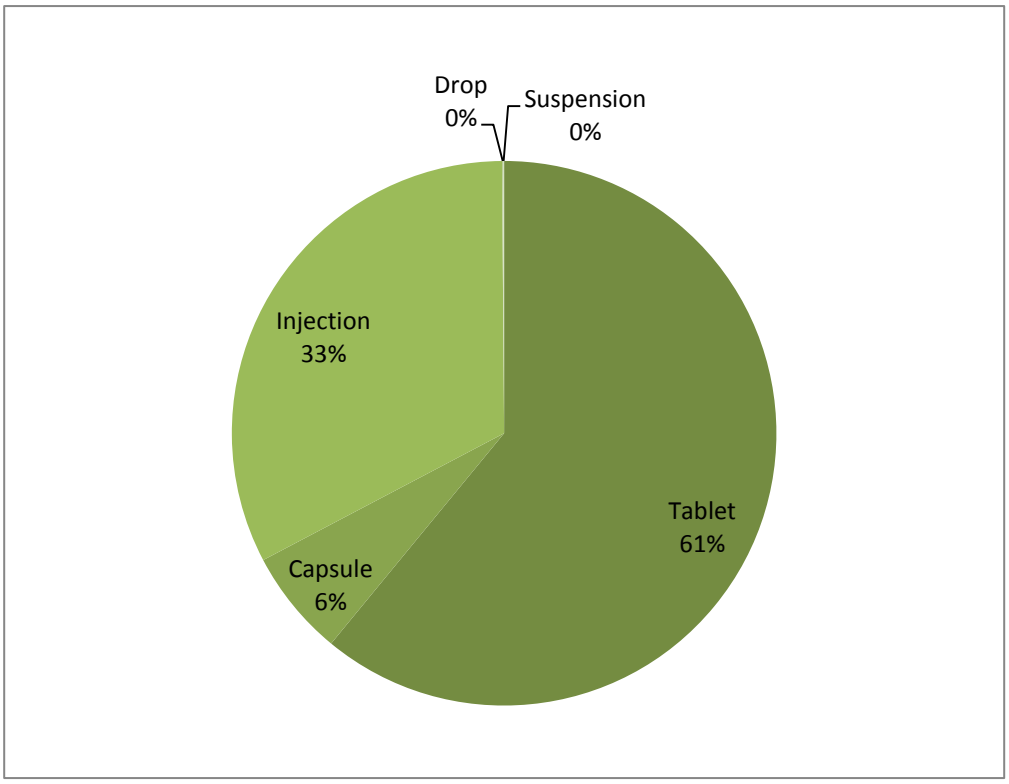


Figure 9:Distribution of Dosage form

This Figure shows that 33% Insulin(Human)Regular +Insulin(Human) etc, Capsule 6%,. Tablet 61%, Suspension 0% and Drop 0% of generic drugs are prescribed from 500 prescription.

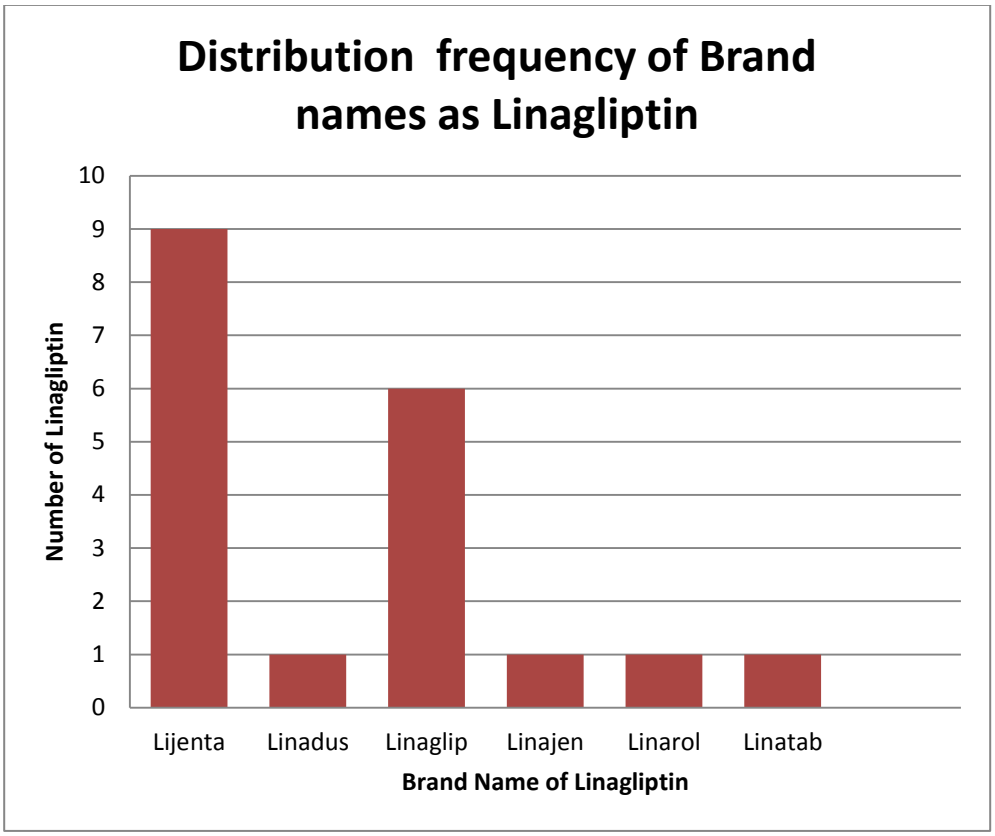


Figure 10: Distribution Frequency of Brand name as LINAGLIPTIN

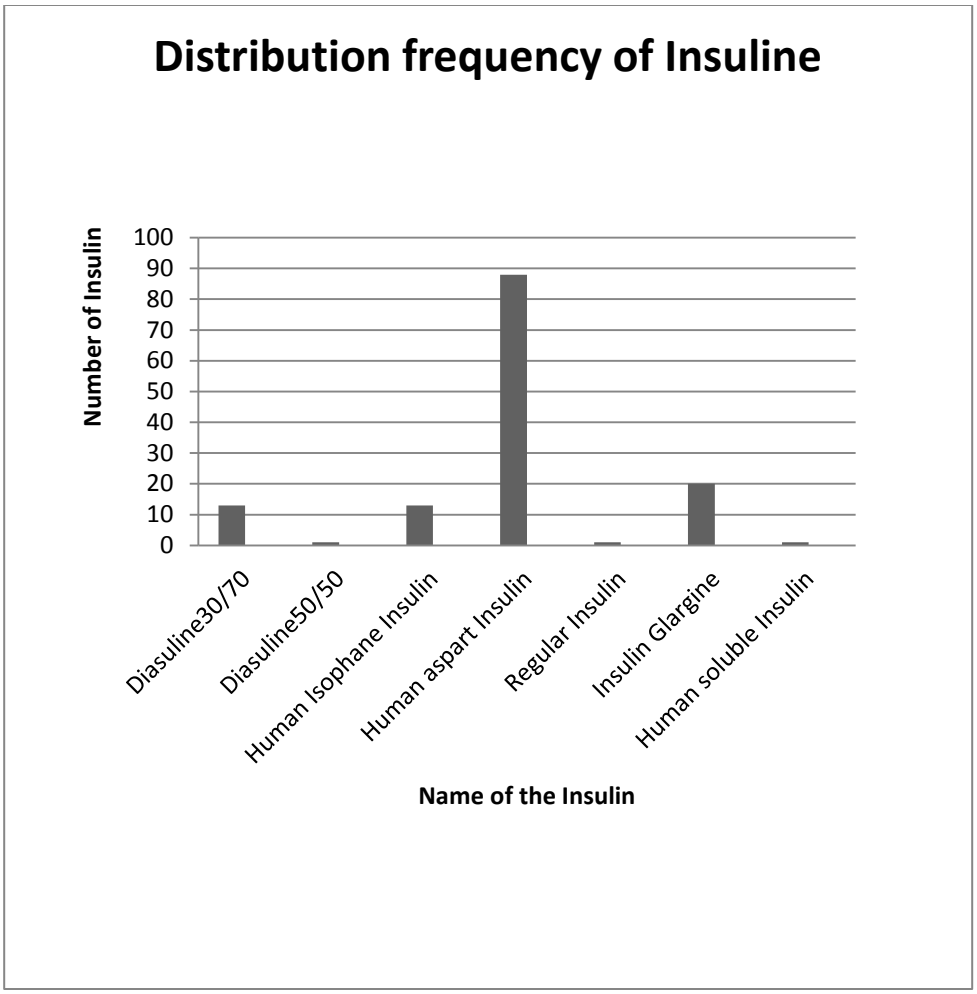


Figure 11:Distribution Frequency of All Insulin

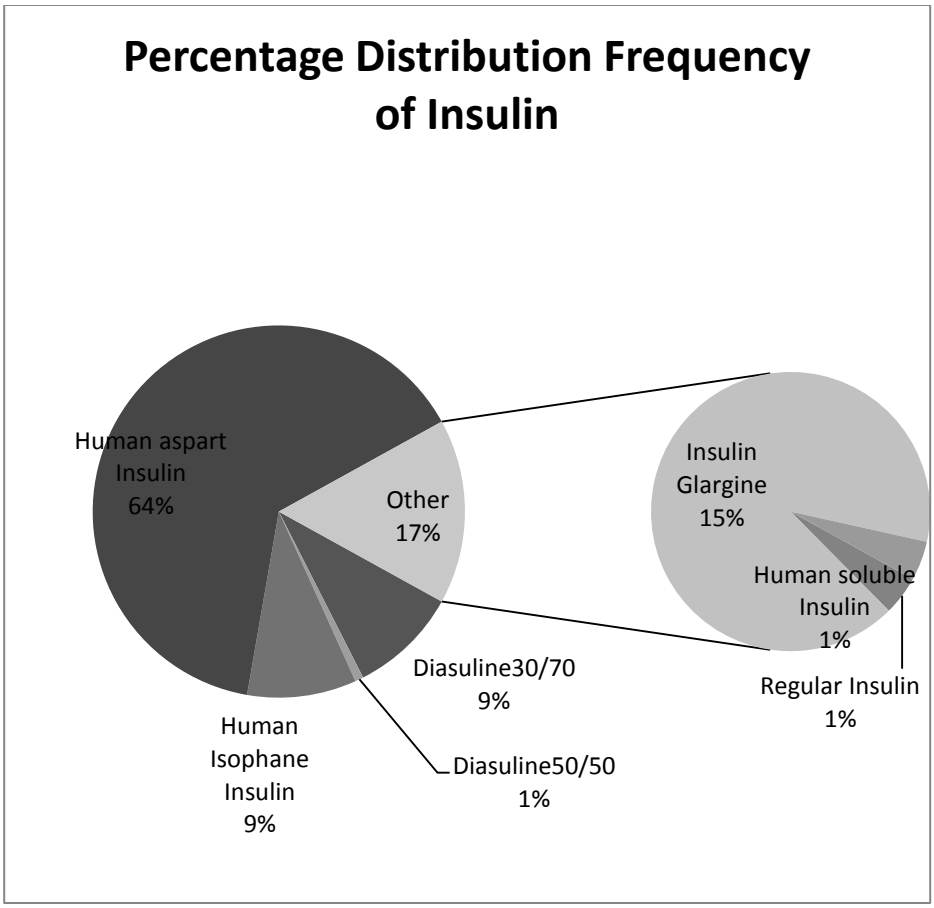


Figure 12: Percentage distribution of All Insulin

This Figure shows that 64% Human aspart Insulin,Human Isophane Insulin 9%,Insuline Glargilne 15%,Human soluble Insulin 1%,Regular Insulin 1%,Diasuline 30/70, 9%,and Other 17% of generic drugs are prescribed from 500 prescription.

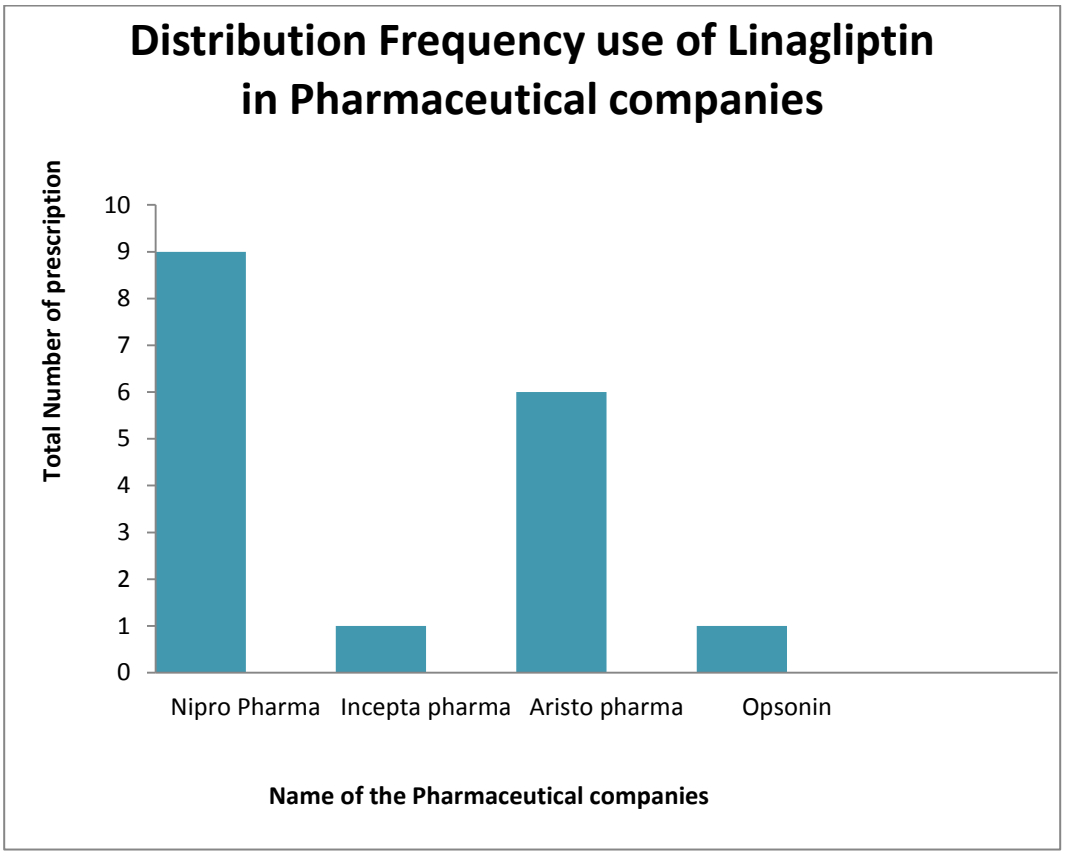


Figure 13: Distribution Frequency of Linagliptin in pharmaceutical companies

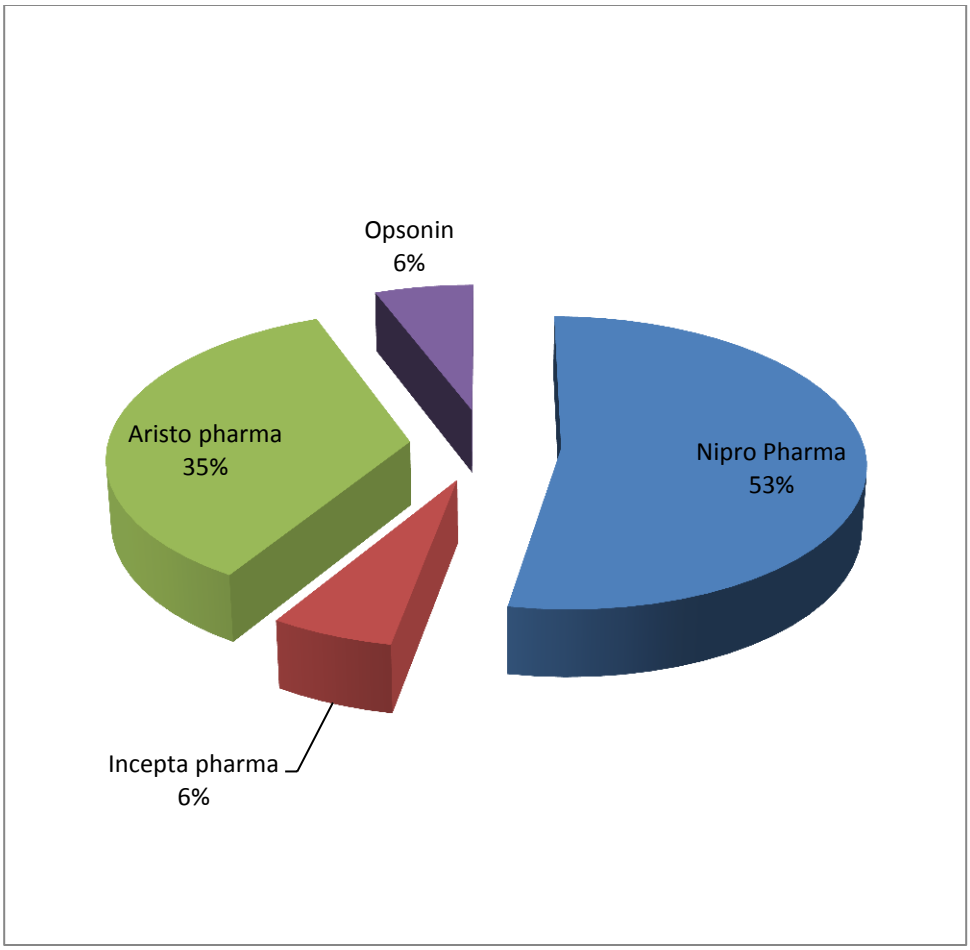


Figure 14: Percentage Distribution Frequency of Linagliptin in Pharmaceutical companies

In this Figure 14, shows that Aristo pharma 35%,opsonin 6%,Nipro pharma 53%, Incepta pharma 6% are use in companies of linagliptin from 500 prescriptions.

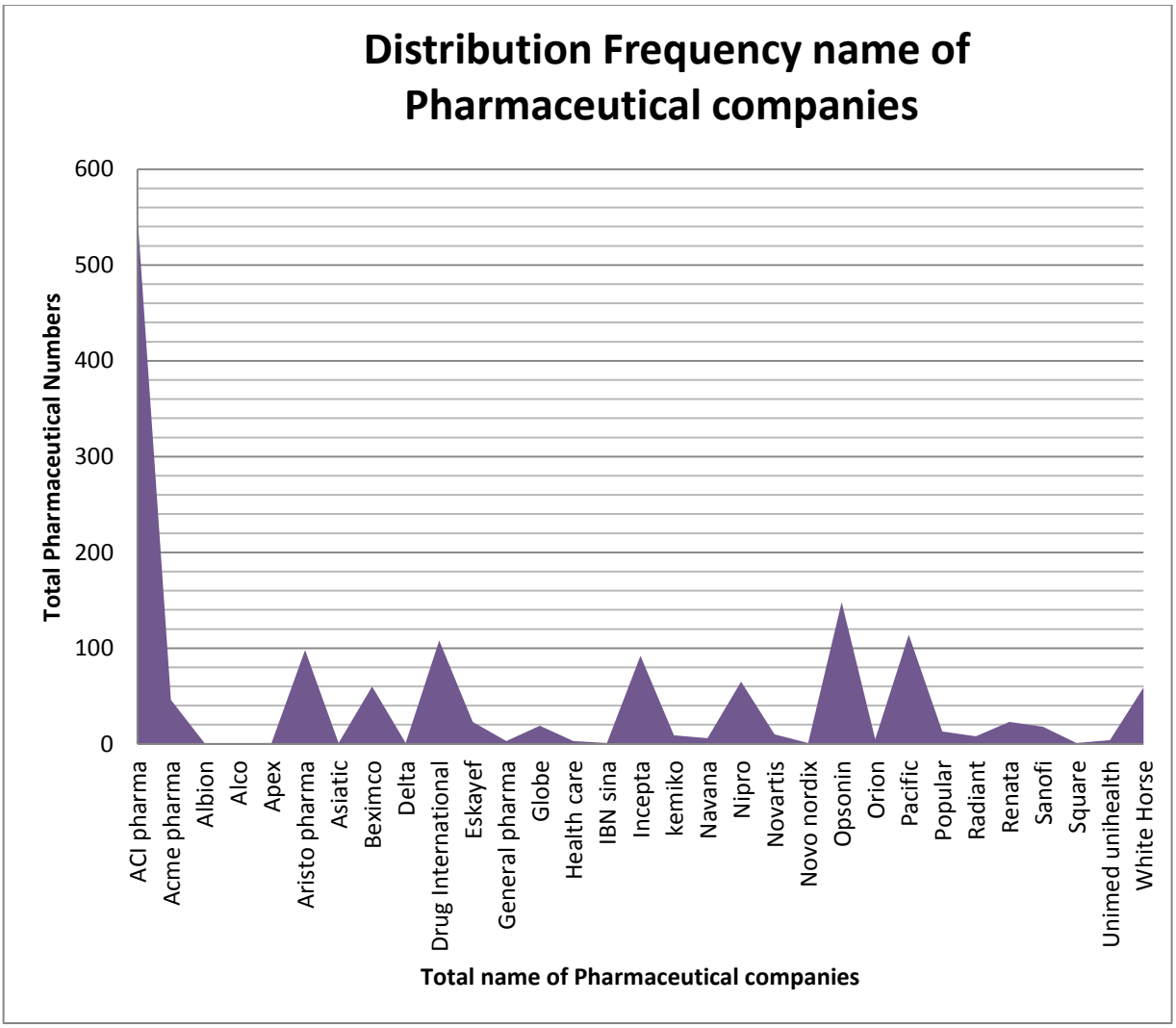


Figure 15: Distribution Frequency Name of total Pharmaceutical companies

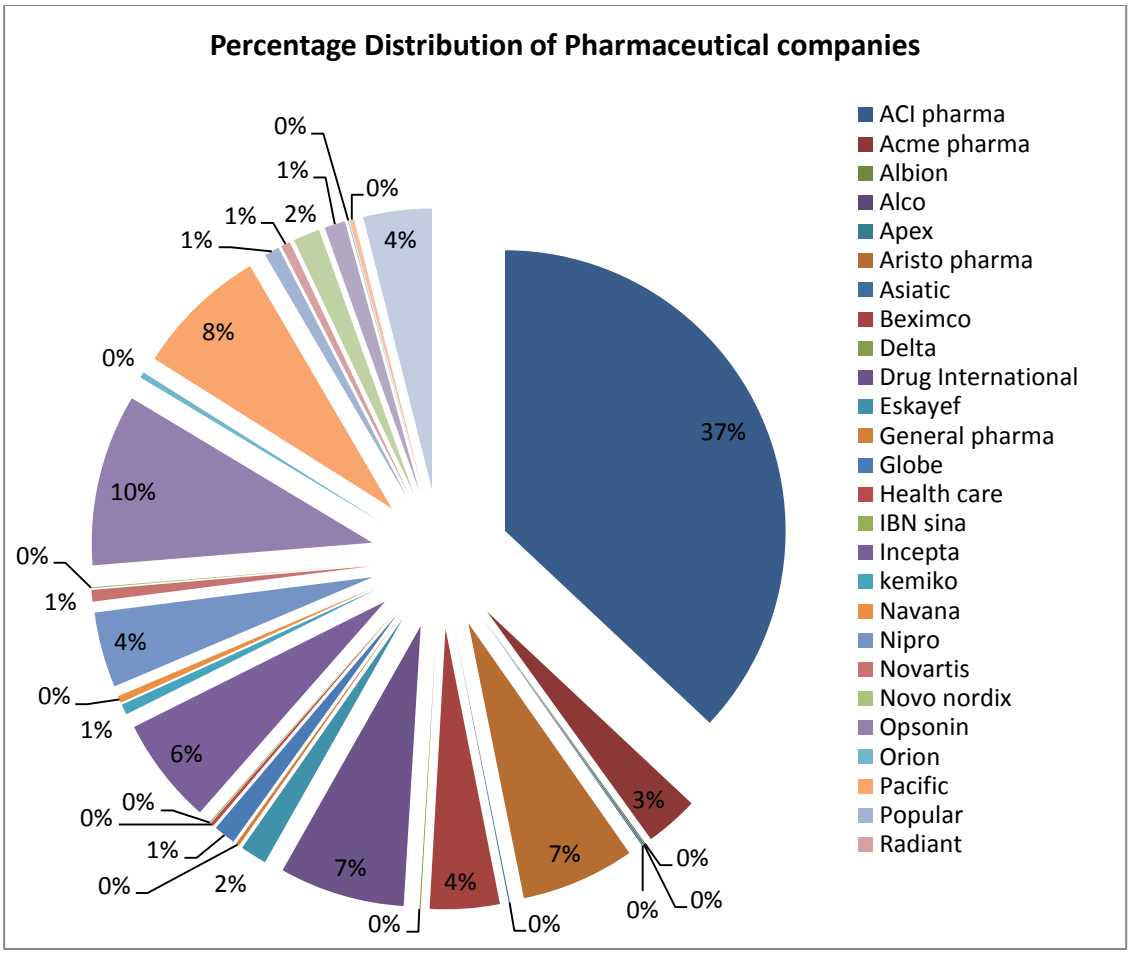


Figure 16: Percentage Distribution of total pharmaceutical companies in Prescription

This Figure shows that ACI pharma 553,Acme 46,Albion 1,Alco 1,Apex 1,Aristo 98,Asiatic 1,Beximco 60,Delta 1,Drug International 108,Eskayfe 23,General pharma 3,Globe 19,Health care 3,IBN SINA 1,Incepta 92,Kemiko 9,Navana 6,Nipro 65,Novartis 10,Novo Nordix 1,Opsonin 148,Pacific 114,Popular 13,Radiant 8,Renata 23,Sanofi 18,Square 1Unimed Unihealth 4,White Horse 59 are used of total Pharmaceutical

Companies from 500 prescriptions.

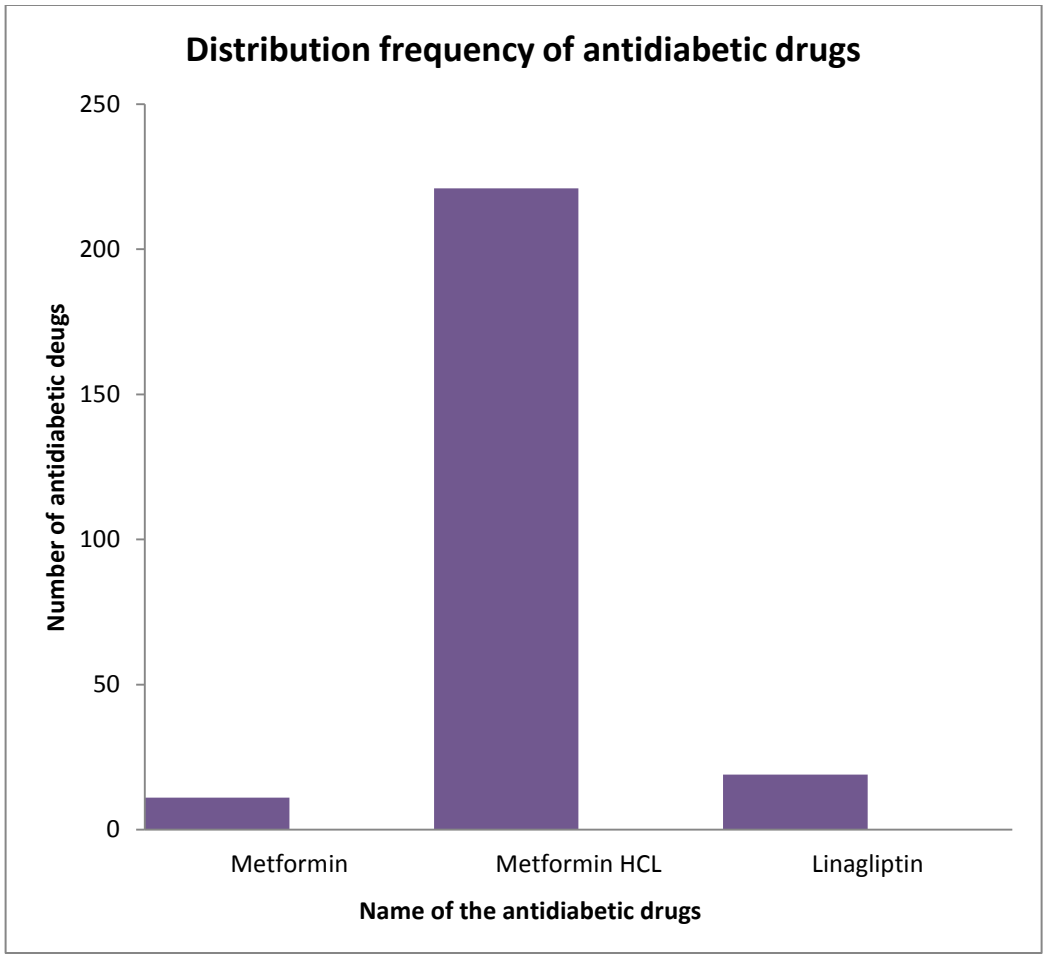


Figure 17: Distribution Frequency of Antidiabetic drugs

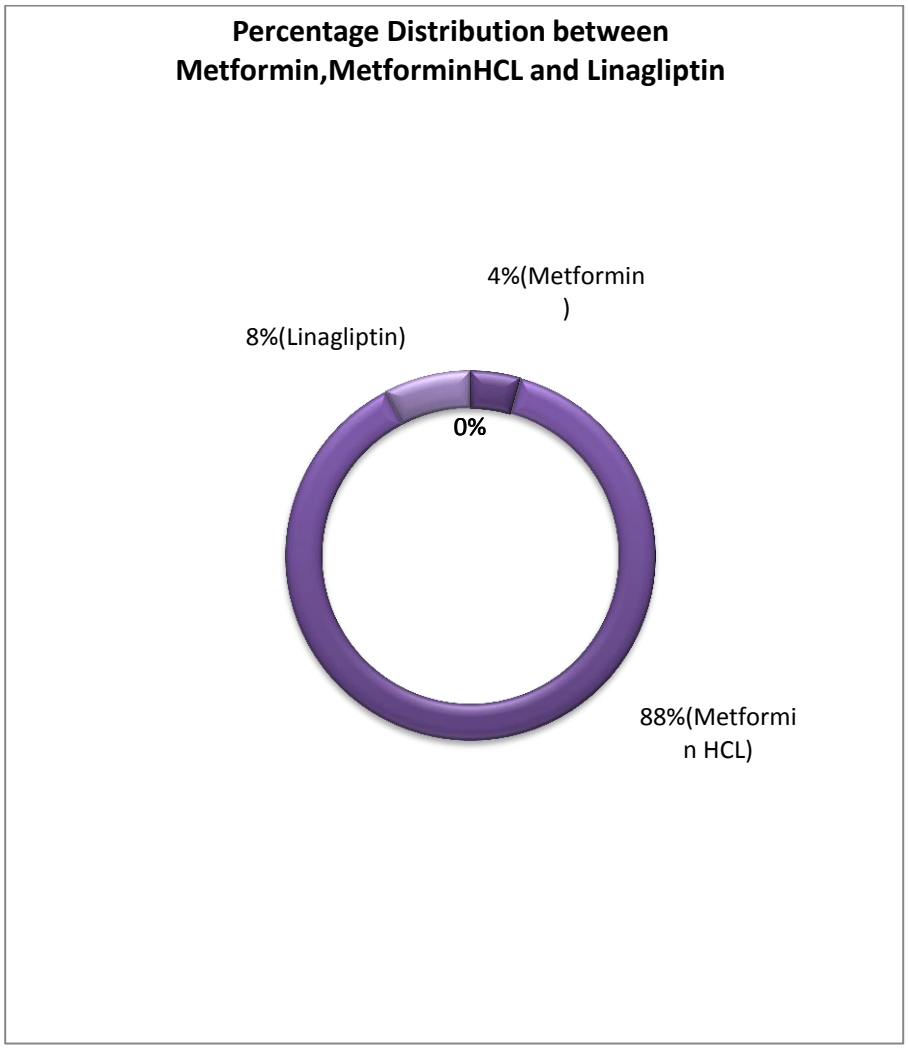


Figure 18: Percentage Distribution between Metformin, Metformin HCL and Linagliptin

This Figure shows that Metformin4%, Metformin HCL 88% And Linagliptin 8% of generic drugs are prescribed from 500 Prescriptions.

CHAPTER: FIVE

Discussion and Conclusion

Discussion:

Linaglipin is a novel dipeptidyl-peptidase 4 (DPP-4) inhibitor in clinical development for the treatment of type 2 diabetes. This thesis investigated the nonlinear pharmacokinetics of linagliptin as well as the relationship between linagliptin pharmacokinetics and plasma DPP-4 activity using nonlinear mixed-effect modelling. The developed models supported the clinical drug development of linagliptin by clinical trial simulations.Based on previous in vitro plasma protein binding studies, concentration-dependent protein binding was considered to be the most likely cause of the nonlinear pharmacokinetics of linagliptin. This hypothesis was tested by analysing linagliptin plasma concentrations and plasma DPP-4 activities from two phase IIa studies in type 2 diabetic patients. A model assuming concentration-dependent protein binding of linagliptin in plasma and tissues resulted in the best description of the linagliptin plasma concentrations, supporting the initial hypothesis. Several lines of evidence suggested that the binding partner of linagliptin responsible for the nonlinear pharmacokinetics is its target, DPP-4. Accordingly, plasma DPP-4 activity was included in the model in a semi-mechanistic way by relating it to the model-calculated plasma DPP-4 occupancy with linagliptin. The assumption of target-mediated drug disposition was confirmed in a subsequent nonclinical study. In this nonclinical study, wildtype rats exhibited a higher systemic exposure and a longer terminal half-life of linagliptin compared to DPP-4 deficient rats. These differences could be described by a single pharmacokinetic model assuming concentration-dependent protein binding in the plasma and tissue of wildtype rats and no binding for DPP-4 deficient rats.Taken together, both analyses suggest that concentration-dependent binding of linagliptin to plasma and tissue DPP-4 is responsible for the nonlinear pharmacokinetics of linagliptin.The nonlinear pharmacokinetics of linagliptin complicate predictions that are based solely on noncompartmental parameters. The availability of the target-mediated drug disposition model allowed simulations that greatly supported the design of future clinical studies. A twice-daily dosing strategy for a fixed dose combination of linagliptin with metformin was simulated. The simulations predicted that despite the nonlinear pharmacokinetics, 2.5 mg linagliptin twice daily would result in a bioequivalent extent of exposure (AUC24h,SS) as well as a similar DPP-4 inhibition compared to 5 mg linagliptin once daily. Other

simulations demonstrated that due to its nonlinear pharmacokinetics, the impact of impaired linagliptin clearance on the systemic exposure was sufficiently small to allow patients with a moderate renal impairment to participate in the phase IIb programme. Further simulations were performed to investigate the optimal duration of a treatment period in a changeover design to adequately test the dose-proportionality of linagliptin at steady-state. It was shown that a treatment period of seven days was sufficient to attain steady-state for 1, 2.5, and 5 mg linagliptin once daily in each sequence. Thus, linagliptin plasma concentrations after single oral administration of 10 mg linagliptin and single intravenous administrations of 0.5, 2.5, 5, or 10 mg linagliptin were analysed by the target-mediated drug disposition model. Using this approach, the absolute bioavailability could be estimated despite the nonlinear pharmacokinetics. The absolute bioavailability was estimated to be 29.5%.

In Figure-5, 43% Insulin(Human)Regular +Insulin(Human) Isophane (Premixed), 27% Metformin HCL, 2% Metformin HCL+Vildagliptin, 0.12% Metformin HCL +Pioglitazone, 1% Metformin HCL+Sitagliptin, 2% Linagliptin, 3% Sitagliptin, 9% Insulin Aspart Biphasic, 3% Regular Insulin Human and 1% Vidagliptin generic drugs are prescribed from 500 prescription.

In Figure-6, Linagliptin 33%, Metformin HCL+Vildagliptin 24%, Metformin HCL+Sitagliptin 10% ,Sitagliptin 2%, Vidagliptin 31% generic drugs are prescribed from 500 prescription.

In Figure-9 , 33% Insulin(Human)Regular +Insulin(Human) etc, Capsule 6%,. Tablet 61%, Suspension 0% and Drop 0% of generic drugs are prescribed from 500 prescription.

In Figure-7, Linagliptin 8%, Metformin 4% and Metformin HCL 88% generic drugs are prescribed from 500 prescription.

In Figure-12 , 64% Human aspart Insulin,Human Isophane Insulin 9%,Insuline Glargilne 15%,Human soluble Insulin 1%,Regular Insulin 1%,Diasuline 30/70, 9%,and Other 17% of generic drugs are prescribed from 500 prescription.

In Figure 14, Aristo pharma 35%,opsonin 6%,Nipro pharma 53%, Incepta pharma 6% are use in companies of linagliptin from 500 prescriptions.

In Figure 16 , ACI pharma 553,Acme 46,Albion 1,Alco 1,Apex 1,Aristo 98,Asiatic 1,Beximco 60,Delta 1,Drug International 108,Eskayfe 23,General pharma 3,Globe 19,Health care 3,IBN SINA 1,Incepta 92,Kemiko 9,Navana 6,Nipro 65,Novartis 10,Novo Nordix 1,Opsonin 148,Pacific 114,Popular 13,Radiant 8,Renata 23,Sanofi 18,Square 1Unimed Unihealth 4,White Horse 59 are used of total Pharmaceutical companies from 500 prescriptions.

In Figure 18, Metformin4%, Metformin HCL 88% And Linagliptin 8% of generic drugs was prescribed from 500 Prescriptions.

Conclusion

Therefore In conclusion, the work presented in this thesis contributes to a comprehensive understanding and characterization of the nonlinear pharmacokinetics of the novel DPP-4 inhibitor linagliptin and significantly supports the clinical development of this promising compound to be used for the treatment of type 2 diabetes.it will bring a great change in treatment of diabetic patients. Metformin, insulin and other supportive drugs are prescribed commonly as the treatment of diabetes in diabetic hospital. This research revealed that insulin alone or in combination with metformin or alone metformin or alone vildagliptin, sitagliptin, linagliptin or metformin in combination with vildagliptin, sitagliptin, linagliptin and other types of drugs which were prescribed for the treatment of patient suffering from diabetes. Among the metformin, insulin, vildagliptin, sitagliptin, linagliptin the mostly prescribed were insulin and metformin diabetic hospital of Bangladesh for the treatment of diabetes list of antidiabetic drugs is supposed to be updated regularly, however in Bangladesh no major review has been made after 2012. Our study found only 19 prescriptions with linagliptin among 500 prescriptions which was only 3.8%. In terms of updating the new antidiabetic drug list comprehensively according to the patients need for the treatment of diabetes, further follow up is required for the exclusion of the evidence based effective drugs. Concerted efforts are needed to motivate and updating the new antidiabetic drugs compare with previous antidiabetic drugs. So it can be calculated that linagliptin still seems to be not well accepted by most of the physicians. Another outcome of this study indicated that in 42% prescription there is a practice of old antidiabetic drugs. Furthermore, county wide multicenter research with a large sample is still needed to consolidate the observation of this study.

CHAPTER: SIX

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