Analyzing Market Potential of Gliptins

By

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TO WHOMSOEVER MAY CONCERN

This is to certify that **Avani Chauhan** student of MBA Pharmaceutical Management from The IIHMR University, Jaipur has undergone training at **IIHMR University** 1st February, 2016 to 5th May, 2016

The Candidate has successfully carried out the study designated to her during internship training and her approach to the study has been sincere, scientific and analytical. The Internship is in fulfillment of the course requirements

I wish her all success in all his future endeavors.

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CERTIFICATE BY SCHOLAR

This is to certify that the dissertation titled "**Analyzing Market Potential of Gliptins**" and submitted by **Avani Chauhan** under the supervision of **Dr. Sandeep Narula** for award of Master of Business Administration of the University carried out during the period from **1st February, 2016** to **5th May, 2016** embodies my original work and has not formed the basis for the award of any degree, diploma associate ship, fellowship, titles in this or any other Institute or other similar institution of higher learning.

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Executive summary

In today' s competitive world where cut-throat competition exists, everyone wants to know their position, their strength and weakness, so it is very essential to know opportunity to target the potential market, capture the market, evaluate from the marketing strategies.

The objective of the project was 'To analyze the market potential of Gliptins' in which I have studied patients of type 2 diabetes mellitus (T2DM), indication, pricing, response, top brands, competitors, sales value, sales volume, combinations, most preferred and effective strength & also prescription trend of gliptin. The project was undertaken in Mumbai city with respect to the survey with doctors, chemists & stockiest.

The project was started on 1st February after knowing all the relevant information regarding the project, under the guidance of Dr. SandeepNarula (Associate professor at The IIHMR University). The first part the project was to study of pharmacokinetic & pharmacodynamics of gliptin, its mechanism of action, indication for gliptin& combination therapy of gliptin in patients with type 2 diabetes mellitus (T2DM). For this I used Internet as a primary source of information for study.

The next part of the project was to develop the questionnaire for doctors, chemist & stockiest. Then the data was collected from the survey which was done by visiting them. Close ended as well as open ended questionnaire was made and statically analysis was carried to draw conclusion. The project was completed on 5th May.

During the study it was found that Sitagliptin is majorly prescribed gliptin for T2DM patients because of highest safety, efficacy & durability.

1. Introduction

1.1 Type 2 Diabetes mellitus (T2DM)

It is termed as metabolic discomfort of carbohydrate, fat &protein into body, a chronic condition characterized by the presence of abnormally high blood glucose levels

Occurs as a result of defects in insulin production and/or action

- Insulin resistance at level of liver resulting in hepatic outpouring of glucose into the hepatic venous system[1]
- Insulin resistance at peripheral tissue (skeletal muscles) resulting in inability in uptake of glucose[1]
- Beta-cell failure (five stages) resulting in declining insulin secretion capacity[1]

Based on data from the UKPDS[25] and Weir[2] by the time patient develops impaired glucose tolerance, between 50% and 66% of [beta]-cell function is lost. Between 75% and 80% of beta-cell function is lost once hyperglycemia fulfilling the definition of diabetes mellitus develops. After 10–15 years of diabetes duration <10% of endogenous insulin is present and exogenous insulin therapy becomes necessary.

It therefore makes sense that a paradigm shift to newer therapies is required that can help conserve beta-cell function. Until a few years ago only thiazolidinedione (TZD) therapy was shown to conserve beta-cell function [26,27] apart from its overwhelming insulin sensitizing benefits (at the level of liver and periphery/skeletal muscle).

1.2 Incretin

Glucose disposal is more efficient following an oral glucose meal as compared to an intravenous glucose infusion. This led some scientists to believe that the gastrointestinal tract was responsible for release of hormones that aided in glucose disposal. This theory was entertained more than 100 years ago.[14–19] These hormones were later identified as gut derived "incretins" (glucagons like peptide {GLP-1}and gastric insulotropic peptide {GIP}) which are responsible for > 99% of this incretin effect (enhanced glucose disposal following oral load).

Out of the two hormones it is GLP-1 that is the more active peptide in human beings. Patients with T2DM experience a blunting or even total loss of this incretin effect. Amplification of this incretin effect forms the basis of several incretin-based therapies.[14–19]

GIP is secreted by neuro-endocrine K-cells present in stomach and proximal small intestine. It has an amino acid sequence that is highly conserved across species, with over 90% homology. It has a half life of approximately 7 min in healthy individuals and 5 min in patients with T2DM. GIP is cleared through the kidney[3-10]

GLP-1 is a peptide that is secreted by neuro-endocrine L-cells present in the distal small intestine. GLP-1 circulates as two equipotent forms, GLP17-37 and GLP17-36 amide. GLP-1 (7-36) constitutes 80% of circulating GLP-1. The half-life of circulating native bioactive GLP1 is less than 2 min mostly because it is cleared by the kidney and degraded by dipeptidyl peptidase (DPP)-4. DPP-4 represents a single polypeptide chain of 766 amino acids and consists of four domains: an N-terminal cytoplasmic domain, a trans-membrane domain, an [alpha]/[beta]-hydrolase domain, and a [beta]-propeller domain. It is also called adenosine deaminase (ADA) binding protein, or CD26 (T-cell activation antigen).[14–19,31]

GIP and GLP-1 have distinct yet overlapping actions and act through specific G-protein receptor complexes, gastric inhibitory peptide receptor (GIP-R), and GLP-1 receptor (GLP-1R), respectively. Both GLP-1 and GIP are susceptible to cleavage at amino-terminus, position 2 (alanine), by the DPP-4. DPP-4 is a type II membrane peptidase resembling CD26 (marker of activated T-lymphocyte). It is the canonical representative of a family of genetically related peptidases. The DPP-4 gene family includes four enzymes DPP-4, DPP-8, DPP-9, fibroblast activation protein (FAP) and catalytically inactive proteins DPP-6 and DPP-10. DPP-4 has a widespread organ distribution (liver; gut; endothelial capillaries; acinar cells of mucous and salivary glands, pancreas; uterus; and immune organs such as thymus, spleen and lymph node) with the highest levels found in the kidney. DPP-4 regulates the activity of secretory hormones glucagon-like peptide (GLP)-1, and glucose-dependent insulinotropic peptide (GIP) to maintain

glucose homeostasis (enhanced insulin secretion and glucagons suppression), thereby improving post-prandial and fasting hyperglycemia.[14,18,19,29] Other physiological substrates of DPP-4 include neuropeptide-Y (NPY) (role in appetite, energy homeostasis, and blood pressure control), substance P (role in pain and inflammation).[33]

DPP-8 and DPP-9 enzyme levels are less well studied compared to DPP-4. Although DP8 and DP9 have no confirmed physiological substrates there is a growing body of evidence to suggest that they are actively involved in healing processes (skin, liver etc), play an important role in immune function (cleave chemokines), and hematopoiesis. They have been shown to predominate over DPP-4 in testis and brain tissue and have a wide area of organ distribution (gastrointestinal tract, skin, lymph node, spleen, liver and lung, as well as in pancreatic acinar cells, adrenal gland, spermatogonia and spermatids of testis, and in Purkinje cells and in the granular layer of cerebellum). Unlike DPP4, DPP8/9 are intracellular proteases responsible for T-cell activation and therefore off-target inhibition by selective DPP4 inhibitors can cause undesirable and serious side-effects (immune dysfunction, impaired healing, reticulocytopenias, skin manifestations).[33,34]

Following secretion, GLP-1 and GIP are both rapidly degraded by DPP-4. GLP-1 is degraded even before leaving the gut because of the presence of DPP-4 molecules anchored to the luminal surface of the endothelial cells of the mucosal capillaries. GIP is less susceptible to DPP-4 and leaves the gut un-degraded.

1.3 Anti-Hyperglycemic Drug

From the above pathogenetic discussion it would only seem logical that one chooses therapy that seems to address the ominous octet ie. a drug that can improve beta-cell health (TZD, incretin bases therapies {GLP analogues, DPP-4 inhibitors/Gliptins}, biguanides, alfa-glucosidase inhibitors), improve insulin resistance (biguanides, TZD's, possibly incretin based therapies) suppress glucagon secretion (incretin based therapies), suppress appetite (GLP-1 analogues, biguanides), improve lipid health (TZD), and suppress renal glucose reabsorption. The drug combination that seems most logical is incretin-based therapies (addressing 4 out of the 8 pathophysiological mechanisms) with biguanide (metformin) or TZD (addressing insulin resistance at liver and skeletal muscle).[2,26,27,39]

1.3.1 Dipeptidyl Peptidase-4 Inhibitors (Gliptins)

This new class of anti-diabetic agents seems like they have revolutionized the treatment of diabetes. Although various DPP-4 inhibitors have different pharmacokineic and pharmodynamic profiles, they are remarkably similar with regards anti-hyperglycemic properties with a very safe adverse effect profile (weight neutral without causing hypoglycemia)[20-26].

A list of available and expected gliptins is as follows:

Sitagliptin (Merck Sharp and Dohme Corp, approved as Januvia by US FDA in year 2006)

Vidagliptin (Novartis, approved as Galvus by EU in year 2007)

Saxagliptin (Bristol-Myers Squibb, approved as Onglyza by US FDA in 2010)

Linagliptin (BoerhingerIngelheim, approved as Tradjenta by US FDA in year 2011)

Alogliptin (developed by Takeda Pharmaceutical Company Limited, approved for use in Japan)

Dutogliptin (being developed by Phenomix Corporation)

Gemiglaptin (being developed by LG Life Sciences)

(Sitagliptin, Vidagliptin, Saxagliptin-are-approved-for-use-in-India)

The DPP-4 inhibitors based on their structure can be divided into those that mimic the DPP-4 molecule (peptidomimetics, vildagliptin and saxagliptin) and those that do not (non-peptidomimetics, sitagliptin, alogliptin, linagliptin) as shown in Tables Tables11 and and2.2. They are competitive reversible inhibitors of the DPP-4 substrate acting extra-cellularly. The molecules have varying affinities toward the DPP-4 substrate [17-29]. In general, the peptidomimetics have lesser selectivity toward DPP-4 compared to DPP8/9. Lesser the relative selectivity toward DPP-4 and greater the relative inhibition of DPP8/9 greater is the possibility of side effects (allergic skin manifestations etc).[14–18,28–34,40–43]

When compared to metformin, SU (glimerperide, glipizisde), thiazolidinediones (rosiglitazone, pioglitazone), and alfa-glucosidase inhibitors (voglibose), the use of gliptin has shown to be equally efficacious and non-inferior. When compared to SU the incidence of hypoglycemia was near negligible with the added advantage of being weight neutral.[44–51]

A meta-analysis comparing the efficacy of sitagliptin versus vildagliptin showed that the overall HbA1c reduction was ~0.74% and 0.73%, respectively. The glycemic outcomes were better if the initial HbA1c was higher >9% versus <8%.[40]

A recent meta-analysis suggested that using a gliptin (vildagliptin, sitagliptin, saxagliptin or alogliptin) in patients with T2DM was associated with a greater proportion of patients achieving their HbA1c goal of <7%, without any weight gain or hypoglycemia.[41]

As “add on therapy to metformin”

Data suggests that when a gliptin is added onto patients inadequately controlled with metformin there results a substantial improvement in HbA1c (range 0.50 – 0.75%) with as many twice as number of patients achieving an HbA1c of <7% compared to metformin alone. Furthermore, for the first time data has suggested that in patients with HbA1c between 7% and 8% while on metformin therapy, rather than optimizing the dose of metformin from 1 to 2 gm/day or greater, as most existing guidelines suggest, by adding a gliptin to an already existing dose of metformin the degree of HbA1c reduction is greater (additional HbA1c – 0.7% benefit) than that achieved by up-titrating the dose of metformin (additional HbA1c – 0.3% benefit), with far greater number of patients achieving HbA1c target of <7%..

The use of a gliptin compared to an SU as second line therapy added onto patients inadequately controlled on metformin therapy, provided non-inferiority data for use of gliptin suggesting that it might replace the use of traditionally used SU in the future.[5,50,52-54]

As “add on therapy to sulfonyureas”

Since the use of gliptin has shown to improve beta-cell health and promote insulin secretion in a glucose-dependent fashion, the concomitant use of SU can potentially be complicated by hypoglycemia. It is therefore suggested that the minimum possible dose of SU be started along with use of gliptin. If the patient is already on an SU and addition of gliptin is considered, the dose of SU should be halved and then up-titrated as required. Gliptins have been shown to non-

inferior in efficacy to SU (glipizide, glimeperide, gliclazide) with the added advantage of being weight neutral and being virtually free of hypoglycemia. Whether compared head to head with an SU (HbA1c reduction of approximately 0.8% in both groups) or added to an SU (further HbA1c reduction of approximately a gliptin was found to be effective (HbA1c reduction 0.5-0.8%) with significantly greater number of patients achieving the HbA1c of <7%.[1,33,48–53]

As add “on therapy to thiazolidinedione”

The addition of a gliptin to TZD therapy in patients inadequately controlled have been associated with average HbA1c reduction of approximately 0.7-1%. On the other hand, the use of gliptin along with TZD in drug-naïve T2DM patients has been shown to reduce HbA1c by up to 2% after 24 weeks, compared with 1.1% with pioglitazone monotherapy. Besides the reduction in HbA1c there have been other beneficial effects seen with this combination such as improvement in inflammatory markers, beta-cell health (homeostasis model assessment-beta-cell, HOMA-beta and pro-insulin/insulin ratio) and markers of insulin resistance (homeostasis model of insulin resistance, homeostasis model assessment-IR). This combination has however been plagued by an average weight gain of 2.5 – 5 kg and peripheral edema. The weight gain can however be dealt with a comprehensive lifestyle-weight-management program.[21,24,30,33–40]

As “add on therapy to insulin”

The addition of gliptin to insulin (long-acting, intermediate-acting insulin or premixed) has been associated with an additional HbA1c reduction of approximately 0.6%. A greater proportion of patients were seen to achieve HbA1c level < 7. Fasting plasma glucose improved by approximately 15.0 mg/dl (0.8 mmol/l) and 2-h post-meal glucose improved by approximately 36.1 mg/dl (2.0 mmol/l). The presumed improvement in glycemia is because of improvement in beta-cell health and suppression of glucagon predominantly.[11–14]

1.3.1.1 Sitagliptin

This is the first gliptin to be US FDA approved (October 2006). The recommended dose is 100 mg once a day. Its absorption is unaffected by food. For patients with moderate renal impairment (creatinine clearance 30 to 50 mL/min) the recommended dose is 50 mg/day and for severe renal impairment (creatinine clearance is <30 mL/min) the recommended dose is 25 mg/day. In a meta-analysis[40] it was shown to be more effective at reducing fasting blood sugar compared to vildagliptin, but overall efficacy was similar. For patients with hepatic impairment no change in dose is recommended for Childs grade A or B, however for Child grade C sitagliptin use in not recommended. The Asian study (China India Korea study) suggested that sitagliptin was more effective in the Indian population with greater HbA1c reductions of approximately 1.3% compared to placebo. Recent data is emerging that in addition to improving beta-cell health, DPP-4 inhibitors also help improve insulin resistance and plasma levels of triglyceride-rich lipoproteins of both intestinal and hepatic origin (cardiovascular benefit).[14–16,18,28,29,32]

1.3.1.2 Vildagliptin

This is the second gliptin to be approved for commercial use although still not US FDA approved. The recommended dose is 50 mg twice a day. Its absorption is unaffected by food. It is extensively metabolized by the liver and has >90% bioavailability following a single oral dose. No dosage adjustment is required for liver disease although a greater amount of inactive metabolites (30% greater) are retained in patients with severe liver disease (Childs grade C). In patients with renal impairment no dose adjustment is required for mild renal insufficiency however for moderate renal insufficiency half the recommended dose of 50 mg is suggested.[14–16,18,28,29,32,47]

1.3.1.3 Saxagliptin

This is the third gliptin to be approved for commercial use, and US FDA approved. The recommended dose is 5 mg once a day. Its absorption is unaffected by food. Saxagliptin is metabolized mainly by cytochrome P450 (CYP) 3A4 to a major active monohydroxylated metabolite, 5-hydroxy saxagliptin which is half as potent as saxagliptin. Approximately 75% of the total dose of saxagliptin is renally excreted (comprising 24% saxagliptin, 36% 5-hydroxy saxagliptin and minor metabolites of saxagliptin), while 22% of a saxagliptin dose was eliminated in the feces, mainly as metabolites. One-half the usual dose of saxagliptin 5 mg (i.e. 2.5 mg orally once daily) is recommended for patients with moderate (CLCR 30-50 mL/min) or severe (CLCR<30 mL/min not on dialysis) renal impairment or ESRD, but no dose adjustment is recommended for those with mild renal impairment or any degree of hepatic impairment.[14–16,18,28,29,32,51,52]

1.3.1.4 Linagliptin

Linagliptin is a new agent in the DPP-4 inhibitor class that is currently undergoing regulatory review in Japan, the EU, and the USA. It is recommended in the dose of 5 mg once a day. It has a favorable pharmacokinetic profile has a potential advantage over currently approved gliptins in that it primarily undergoes non-renal elimination. Linagliptin is predominantly excreted via the enterohepatic system, with 84.7% of the drug eliminated in the feces and only 5% eliminated via the urine. It therefore appears to be safe in patients with renal failure.[15,16,18,28,29,32,54]

Linagliptin has been shown to hasten wound healing in preclinical studies with evidence of improvement in wound re-epithelialization.[51]

1.3.1.5 Alogliptin

Alogliptin is a dipeptidyl peptidase-4 inhibitor that is approved in Japan for the treatment of adult patients with T2DM. It is recommended in the dose of 25 mg once a day. It is unaffected by food. Its predominant route of excretion is the kidneys. Caution must be used in patients with renal impairment with need for appropriate dose adjustments. As most of it is eliminated through the kidney, it is unlikely that hepatic impairment will affect its dosage.[14–16,18,28,29,32]

Adverse effects

Dipeptidyl peptidase 4 inhibitors were generally well tolerated in most studies. Adverse reactions have been associated with non-selective inhibition of other members of the DPP-4 gene family (DPP-8/9). Since DPP-4/CD26 is a marker of activated T-cell, initial concerns were related to immune dysfunction associated with DPP-4/CD26 inactivation. DPP-4 inactivation by a gliptin occurs extra-cellularly in comparison to DPP-8/9 which is intracellular. As long as other members of the DPP-4 gene family remain un-affected immune dysfunction is not seen.[14–16,18,28,29,32,47]

Their strength lies in the fact that they are weight neutral and do not cause any significant hypoglycemia. A meta-analysis[40] suggested an increased risk of nasopharyngitis (6.4% for DPP4 inhibitor {sitagliptin>vildagliptin} vs. 6.1% for comparator) headache (5.1% for DPP4 inhibitor (vildagliptin>sitagliptin} vs 3.9% for comparator), urinary tract infection (3.2% for DPP4 inhibitor {sitagliptin = vildagliptin} vs 2.4% for comparator). Although rare an increased incidence of extremity pain was seen with DPP-4 inhibitors. No increased incidences in gastro-intestinal side-effects were observed. Saxagliptin use has been linked with a reduction in lymphocyte count.[14–16,18,28,29,32,47]

No significant drug-drug interaction has been reported with DPP-4 inhibitors, except for saxagliptin where caution needs to be exercised when used along with drugs metabolized by hepatic CYP3A4/5 system (atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin). They are otherwise safe to use with commonly used anti-hyperglycemics (TZD, SU), anti-hypertensives, anti-hyperlipidemics, antibiotics, digoxin, warfarin, etc.[14–16,18,28,29,32,47]

The US FDA issued a warning in 2007 of risk of pancreatitis with use of drugs acting on the incretin system, following reports of pancreatitis with use of GLP-1 analogues (http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm079781.htm). Post-marketing surveillance has identified isolated rare cases of pancreatitis with use of DPP-4 inhibitors. No direct cause and effect relationship has been found though between the two. It must be emphasized that diabetes and hypertriglyceridemia are itself independent risk factors for development of pancreatitis and an analysis of a US healthcare database showed that rates of pancreatitis with exenatide or sitagliptin were no different from metformin or glyburide.[45]

In preclinical studies an increased risk of medullary carcinoma of the thyroid was seen however as human thyroid has a low expression of GLP-1 receptors unlike the mice it is not surprising that it appears to be safe in human beings.[46,47]

Although clinical studies with DPP-4 inhibitors havn't shown any adverse skin reaction, post-marketing survellance programs have suggested isolated rare cases of serious hypersensitivity skin reactions including Stevens–Johnson syndrome.[48]

Although not approved for use in cardiovascular patients there is some suggestion that DPP-4 inhibitors like GLP-1 analogues have a cardiovascular friendly profile Preclinical studies have suggested endothelial benefit, anti-atherosclerotic effects[49] and blood pressure lowering effects.[90] Several large cardiovascular outcome trials are currently underway which will specifically address the impact of the incretin-based therapies on macrovascular risk.

For patients with hepatic insufficiency except for vildagliptin no dose adjustment is necessary for gliptins. Vildagliptin is not recommended for patients with alanine aminotransferase or aspartate aminotransferase more than three times the upper limit of normal.[32,41,42]

For patients with renal insufficiency, sitagliptin, vildagliptin, and saxagliptin can be used in patients with mild renal insufficiency without dose adjustment; however only sitagliptin and saxagliptin can be used in patients with moderate or severe renal insufficiency. In the European Union, however sitagliptin and saxagliptin is not currently recommended for use in patients with more moderate or severe renal impairment. Linagliptin appears to be safe in renal insufficiency.[32,47]

1.3.2 Current Position of Gliptins in Diabetes Management Guidelines

The American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), European Society, and NICE (UK) guidelines suggest that gliptins should be considered over other anti-diabetic therapies especially if the patient is experiencing an increased incidence of hypoglycemias and/or weight gain. It is clear that even major guidelines appreciate their usefulness with the only apprehension being that they haven't withstood the test of time and therefore classified under less well-validated therapies. As data emerges suggesting sustained

anit-hyperglycenic benefits they should replace current practices that include popular use of SU +/– insulin as second and third line agents to metformin.[15–17]

1.3.3 Current indications for use of gliptins are:

First line in T2DM with HbA1c <7%

Second line as add-on therapy in T2DM patients already on 1 out of the following {metfromin, SU, TZD, alfa-glucosidase inhibitor, miglitinide})for uncontrolled T2DM with HbA1c >7%

Third line as add-on therapy in T2DM patients already on combination therapy (2 out of the following {metfromin, SU, TZD, alfa-glucosidase inhibitor, miglitinide)

Contraindications or indication for stopping gliptin therapy includes previous or current adverse reaction to gliptins (hypersensitivity) or failure to achieve an HbA1c reduction of greater than 0.5% over a 6 month period.[25–27]

2. Need for Study

T2DM is a growing problem in world, especially in India. So, analysis of market potential & prescription trends is needed to find out unmet medical needs.

The study helps to find:

- ✓ Useful information to company prior launching an oral anti-hyperglycemic (OAH) molecule (gliptin).
- ✓ Market scenario of gliptin in treatment of T2DM
- ✓ Indication for usage of gliptin
- ✓ Most commonly prescribed gliptin for T2DM with efficacy, safety & durability parameters.
- ✓ Most prescribed combination therapy with gliptin
- ✓ Identification of highest stock & sale of gliptin
- ✓ Most prescribed brands
- ✓ Major competitors
- ✓ Unmet Medical Need in case of T2DM with future scopes of gliptin

3. Research Question

- What is the market potential of gliptins in patients with type 2 diabetes in Mumbai city?

4. Objectives

- To identify the market scenario of gliptins in type 2 diabetes mellitus
- To analyze the prescription pattern of gliptins in type 2 diabetes mellitus
- To determine highest sales volume & stock of gliptins
- To identify the unmet needs of gliptins in in type 2 diabetes mellitus

5. Methodology

5.1 Sample design

The research conducted was descriptive (Cross-sectional)

5.2 Sampling method

The sampling method was Non-Probability (Purposive) sampling

5.3 Study Area

The study was carried out in Mumbai city.

5.4 Sample population

It includes all doctors (general physician, consultant physician, dialectologist, cardiologist, and endocrinologist), chemists & stockiest

5.5 Sample size

Sample size for the study was 184:

Doctors: 67

Chemist: 75

Stockiest: 42

5.6 Data collection

Primary and secondary data

Primary data- The primary data for this project was gathered through survey using questionnaire, face to face interview.

Secondary data- The secondary data for this project was gathered through different dependable articles and research reports.

5.7 Research Instrument (tools and techniques)

Research instrument is the structured questionnaire consists of both open and close ended questions.

The information was collected by interviewing with doctors, chemist & stockiest. All the questions could not find included in the questionnaire as it would have resulted in to a lengthy format which results into negative response of the sample population. Hence some data was collected with the help of informal talk with the doctors, chemist & stockiest.

5.8 Study duration

3 months (1st February to 5th May)

6. Data Analysis (Findings & Inferences)

a. Analysis of Doctors' views

Market scenario of gliptins in T2DM

6.1.1 Number of Patients per doctor weekly

It was found out that approximately 49% of doctors examined above 40 patients weekly followed by 21% in the range 30-40.

Table number 1as well as figure number 1 gives a data of number of patients and percentage of doctor's response in each range.

No.of T2DM patients	Total number of patients	%number of patients
Less than 10	3	4%
10 to 20	7	10%
20 to 30	10	15%
30 to 40	14	21%
above 40	33	49%

Table 1: Number of T2DM patients examine by doctors weekly

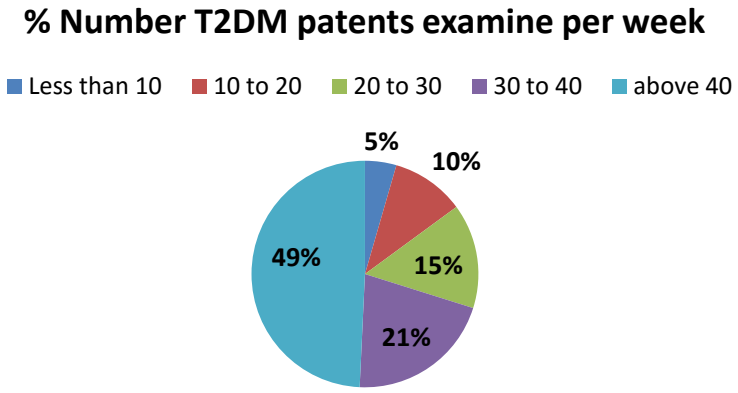

Figure 1: Number of T2DM patients examine by doctors weekly

6.1.2 Treatment used to cure T2DM

It was found out that approximately 46% of doctors use oral medication for treatment of T2DM followed by 34% both oral & I.V.

Table number 2 as well as figure number 2 gives a data of number of treatment used to cure T2DM and percentage of doctor's response in each range.

Treatent used to cure T2DM	in numbers	in %
Oral	31	46%
I.V.	13	19%
Both oral & I.V.	23	34%

Table 2: Treatment used to cure T2DM

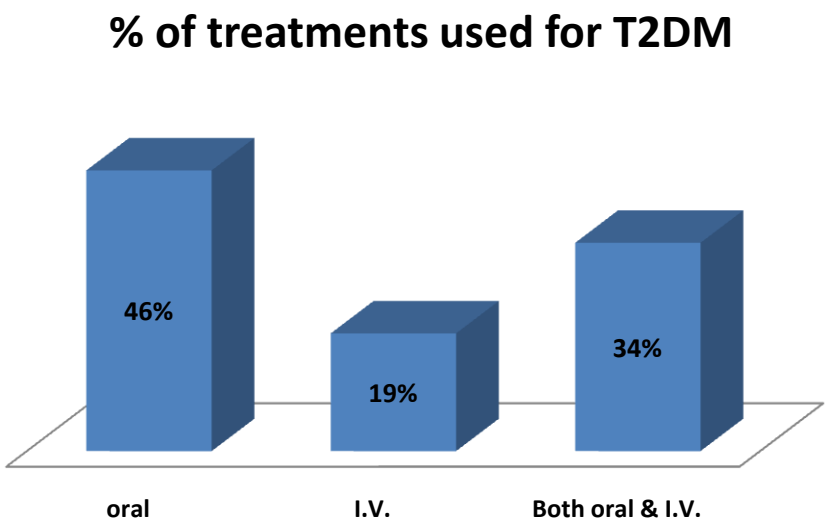

Figure 2: Treatment used to cure T2DM

6.1.3 Type of drug used in T2DM

It was found out that approximately 67% of doctors use branded medication for treatment of T2DM followed by 33% generic.

Table number 3 as well as figure number 3 gives a data of type of drug used to cure T2DM and percentage of doctor's response in each range.

Type of drug used	in numbers	in %
Generic	22	33%
Branded	45	67%

Table 3: Type of dug used in T2DM

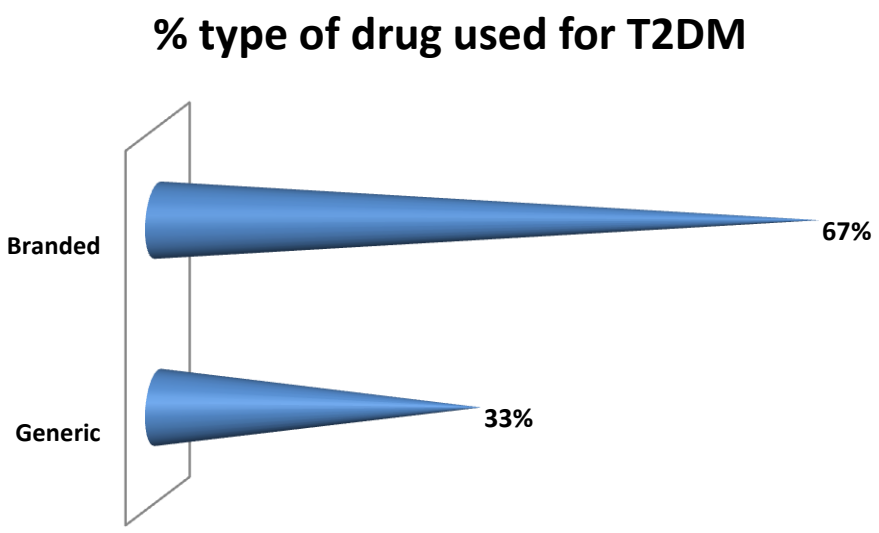

Figure 3: Type of dug used in T2DM

6.1.4 Indication for usage of gliptins

As per table 2, Patients with T2DM requires oral medication to cure disease and according to 60% doctors underlying indication for patients requiring gliptins therapy was add on to metformin that is followed by add on to sulfonylurea according to 15% of doctors.

The following table 4 and figure 4 give a description about various indications with number of patients in percentage.

Indication	in numbers	in %
Initial therapy	10	15%
Add on therapy with Metformin	40	60%
Add on therapy with sulfonylurea	10	15%
Add on therapy with Insulin	7	10%

Table 4: Indication for usage of gliptins

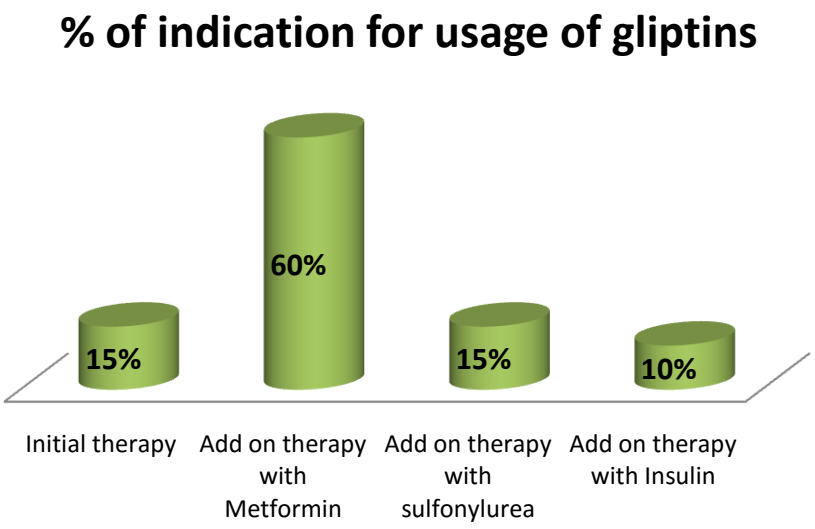

Figure 4: Indication for usage of gliptins

Prescription pattern of gliptins in T2DM patients

During the study it was found that sitagliptin is the best choice ofgliptins among doctors in termes of onset of action, DPP4 inhibition, CV safety, hepatic & renal safety, efficacy & durability. The only drawback with sitagliptin is its cost [Figure 12]

Sitagliptin is having highest onset of action that is DPP4 selectivity according to 46% doctors in all the gliptin class followed by 39% of vildagliptin [Table 5 & figure 5]

Sitagliptin is having duration of action that is DPP4 inhibition even after 24hr according to 52% doctors in all the gliptin class followed by 39% of sexagliptin.[Table 6 & figure 6]

Sitagliptin is having highest CV safety according to 54% doctors in all the gliptin class followed by 31% of linagliptin. [Table 7 & figure 7]

Linagliptin is having highest hepatic & renal safety according to 39% doctors in all the gliptin class followed by 27% of sitagliptin. [Table 8 & figure 8]

Vildagliptin is having highest efficacy according to 42% doctors in all the gliptin class followed by 40% of sitagliptin. [Table 9 & figure 9]

Sitagliptin is having highest durability according to 42% doctors in all the gliptin class followed by 21% of vildagliptin. [Table 10 & figure 10]

Teneligliptin is highly cost effective according to 78% doctors in all the gliptins, while others are pretty costlier. [Table 11 & figure 11]

6.1.5 Onset of action

Molecule	Onset of action	% onset of action
Sitagliptin	31	46%
Vildagliptin	26	39%
Teneligliptin	2	3%
Linagliptin	5	7%
Saxagliptin	3	4%

Table 5: onset of action of gliptins

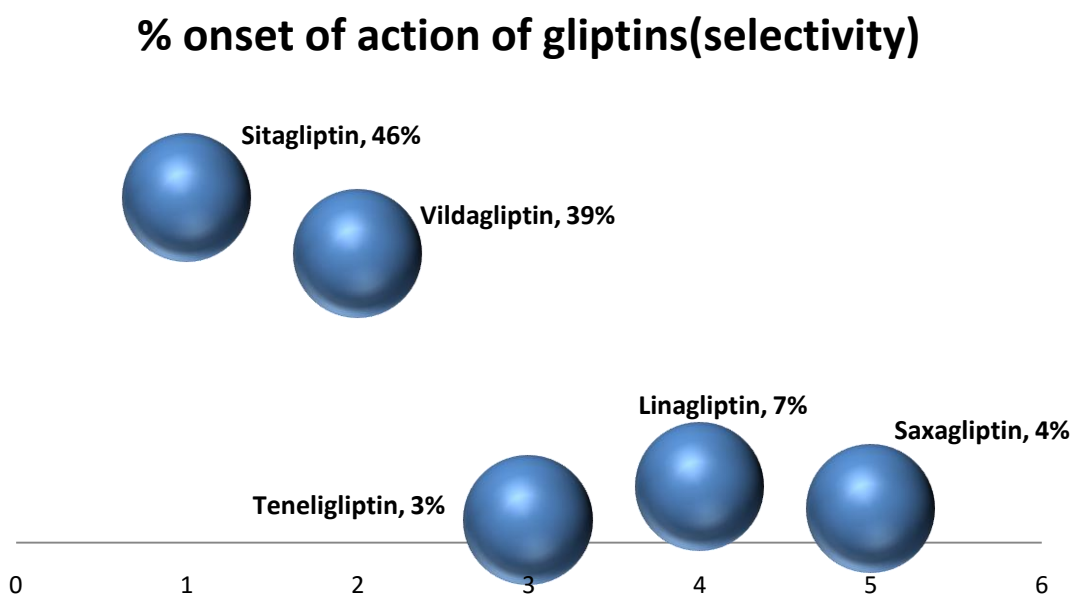

Figure 5: onset of action of gliptins

6.1.6 DPP4 inhibition after 24hrs

Molecule	DPP4 inhibition	% DPP4 inhibition
Sitagliptin	35	52%
Vildagliptin	1	1%
Teneligliptin	2	3%
Linagliptin	3	4%
Saxagliptin	26	39%

Table 6: DPP4 inhibition after 24hrs

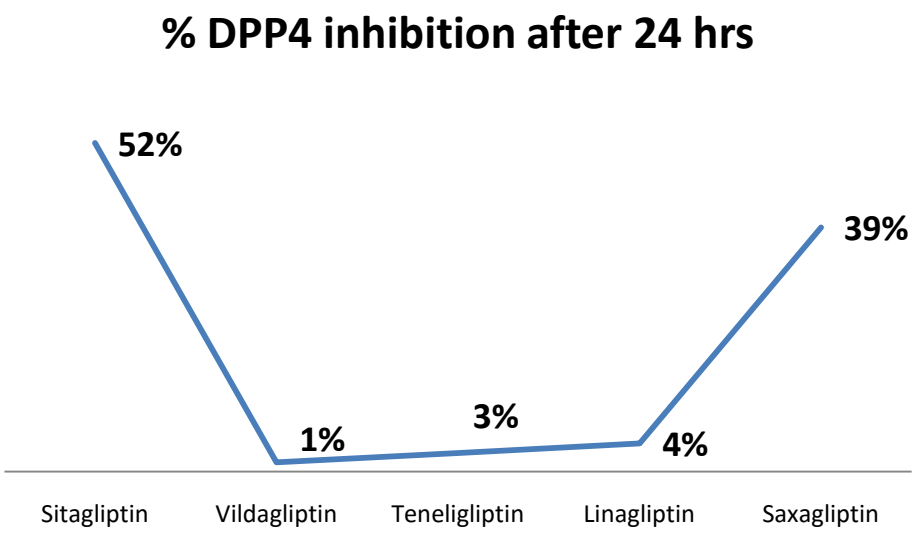

Figure 6: DPP4 inhibition after 24hrs

6.1.7 CV safety of all gliptins

Molecule	CV safety	% of CV safety
Sitagliptin	36	54%
Vildagliptin	1	1%
Teneligliptin	6	9%
Linagliptin	21	31%
Saxagliptin	3	4%

Table 7: CV safety with gliptins

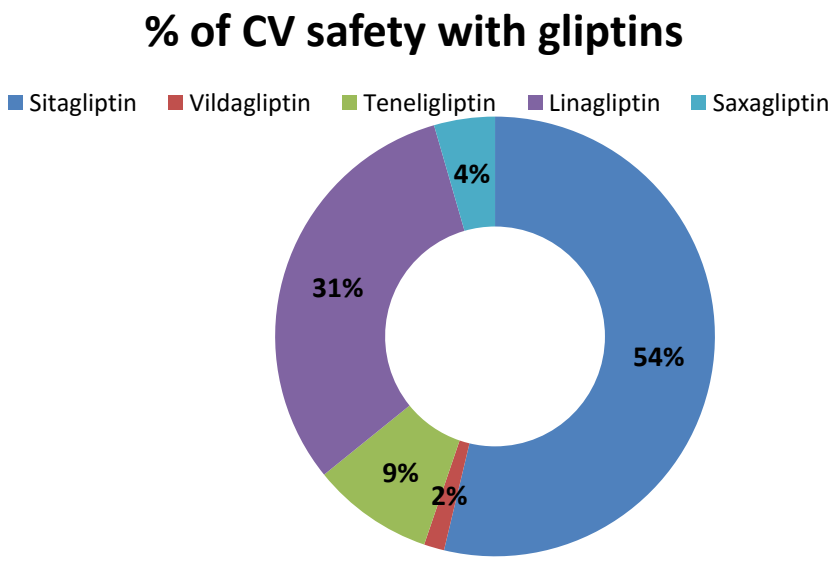

Figure 7: CV safety with gliptins

6.1.8 Hepatic & renal safety of all gliptins

Molecule	Hepatic & renal safety	% of hepatic & renal safety
Sitagliptin	18	27%
Vildagliptin	3	4%
Teneligliptin	17	25%
Linagliptin	26	39%
Saxagliptin	3	4%

Table 8: Hepatic & renal safety with gliptins

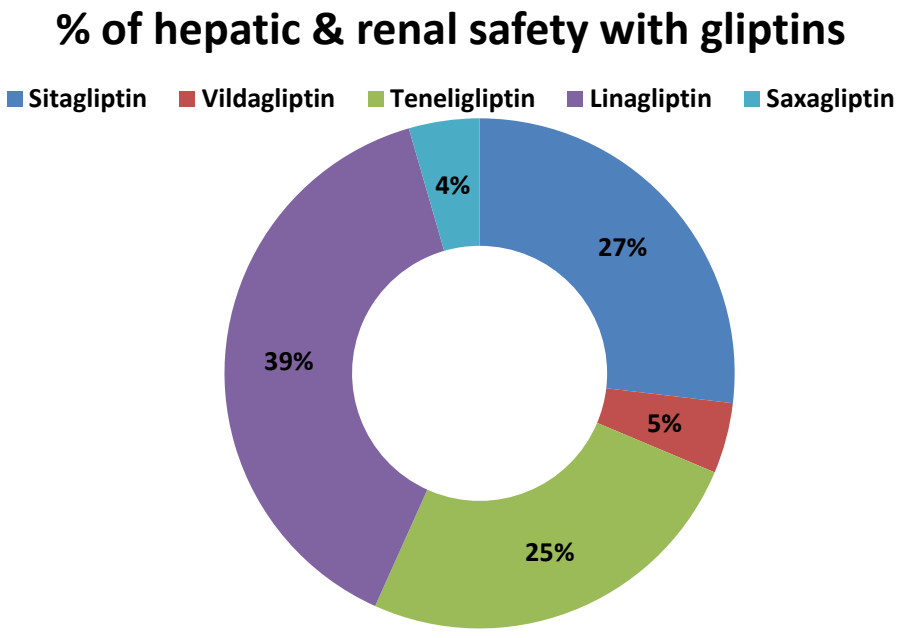

Figure 8: Hepatic & renal safety with gliptins

6.1.9 Efficacy of all gliptns

Molecule	Efficacy	% efficacy
Sitagliptin	27	40%
Vildagliptin	28	42%
Teneligliptin	4	6%
Linagliptin	5	7%
Saxagliptin	3	4%

Table 9: Efficacy with gliptins

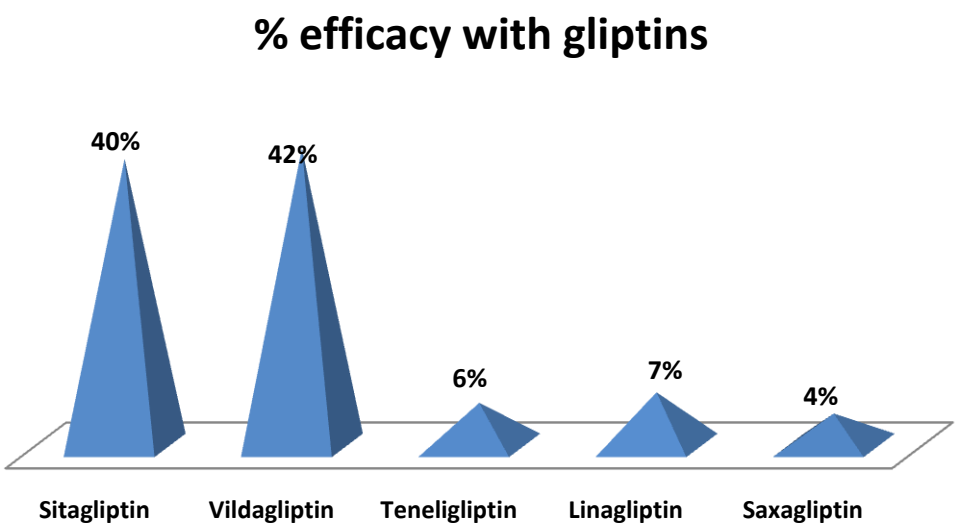

Figure 9: Efficacy with gliptins

6.1.10 Durability with gliptins

Molecule	Durability	% Durability
Sitagliptin	28	42%
Vildagliptin	14	21%
Teneligliptin	13	19%
Linagliptin	7	10%
Saxagliptin	5	7%

Table 10: Durability with gliptins

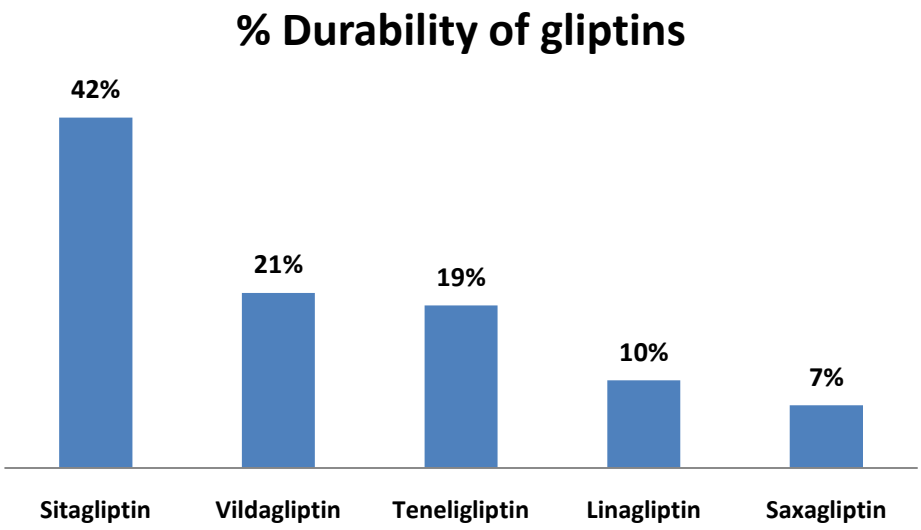

Figure 10: Durability with gliptins

6.1.11 Cost with gliptins

Molecule	cost	% cost
Sitagliptin	5	7%
Vildagliptin	1	1%
Teneligliptin	52	78%
Linagliptin	1	1%
Saxagliptin	8	12%

Table 11: Cost with gliptins

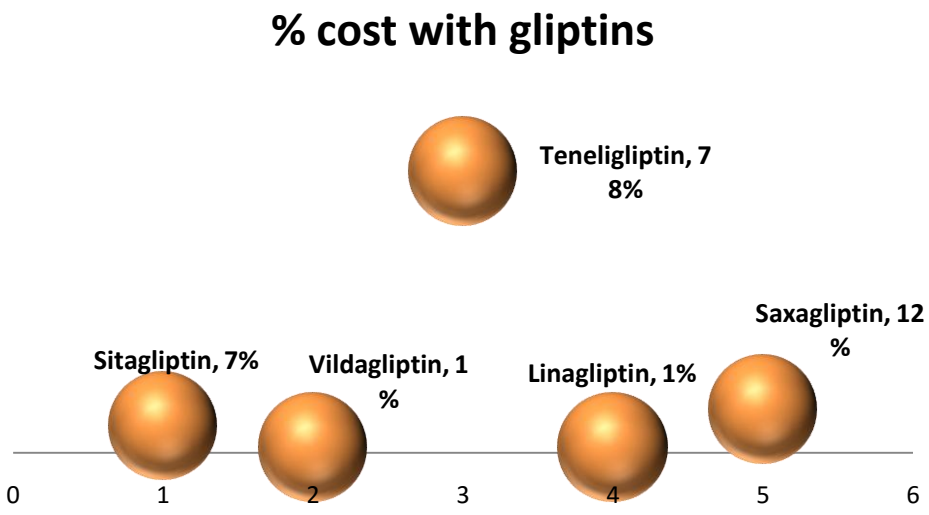

Figure 11: Cost with gliptins

6.1.12 Comparison of gliptins

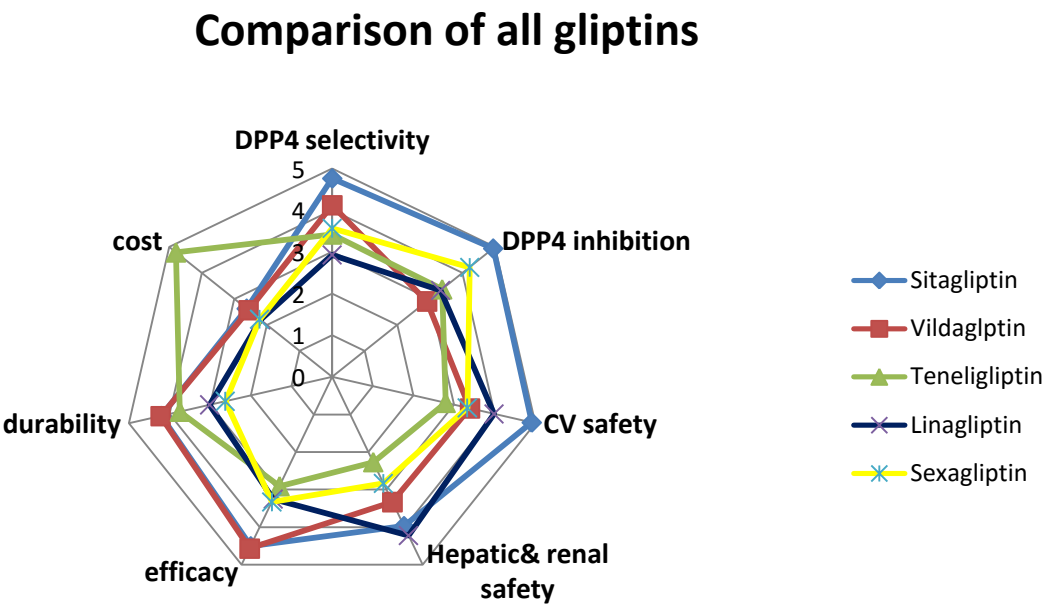

Figure 12: Comparison of all the gliptins

6.1.13 Factors influencing to prescribe any brand of gliptin

It was found out that approximately 49% of doctors find highest efficacy with sitagliptin followed by 30% in vildagliptin.

Table number 12 as well as figure number 13 gives a data of number of patients and percentage of doctor's response in each range.

Factors	In numbers	in %
Efficacy	33	49%
Safety	20	30%
Cost	5	7%
Durability	5	7%
Clinical evidence	4	6%

Table 12: Factors influencing to prescribe any brand of gliptin

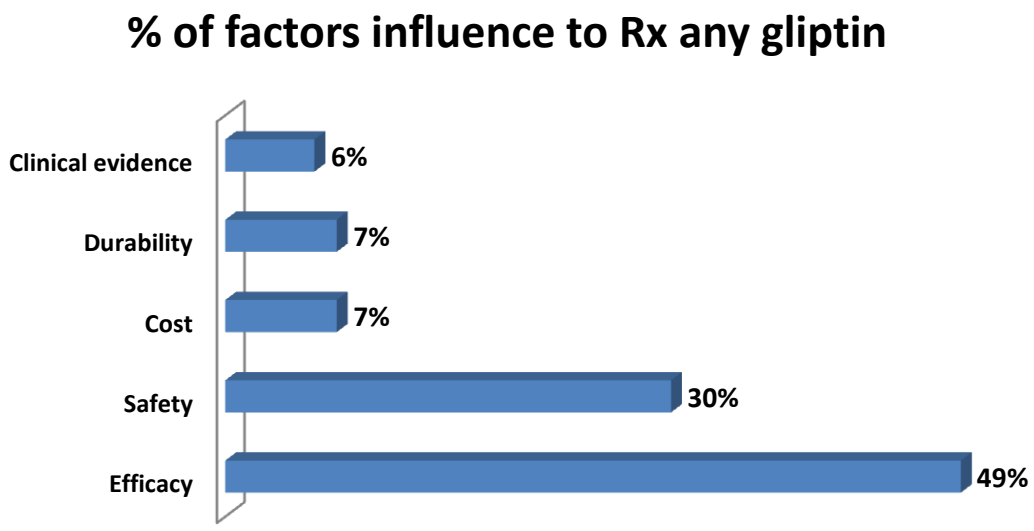

Figure 13: Factors influencing to prescribe any brand of gliptin

6.1.14 Most preferred brand of gliptins

It was found out that approximately 54% of doctors say most preferred brand of gliptin is from Januvia family followed by 19% of ziten.

Table number 13 as well as figure number 14 gives a data of number of most preferred brand and percentage of doctor's response in each range

Brands	Most preffered brand	% of most preferred brands
Januvia/Janumet/Janumet XRCP	36	54%
Galvus	10	15%
Onglyza	4	6%
Zomelis	2	3%
Ziten	13	19%
Tregenta	2	3%

Table 13: Most preferred brand of gliptin

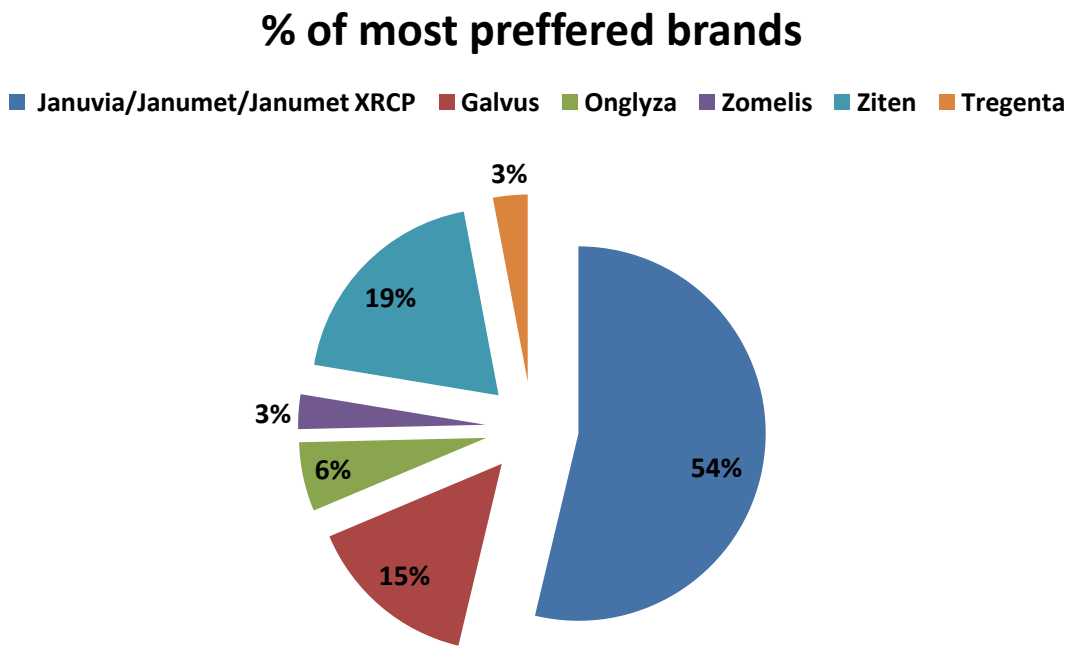

Figure 14: Most preferred brand of gliptin

6.1.15 most preferred combination therapy

It was found out that approximately 76% doctors prefer combination therapy with gliptinsFrom these 76% doctors 54% use metformin as combination with gliptins followed by sulfonylurea 26%.

Table number 14, 15 as well as figure number 15 gives a data of number of doctors preference for combination therapy and percentage of doctor's response in each range

Combination therapy	Preferred combination therapy	% of combination therapy
No	16	24%
Yes	51	76%

Table 14: Combination therapy preference

Combination therapy	% Response
Sulfonylurea	26%
Metformine	54%
TZD	11%
Insulin	9%

Table 15: Preferred combination therapy

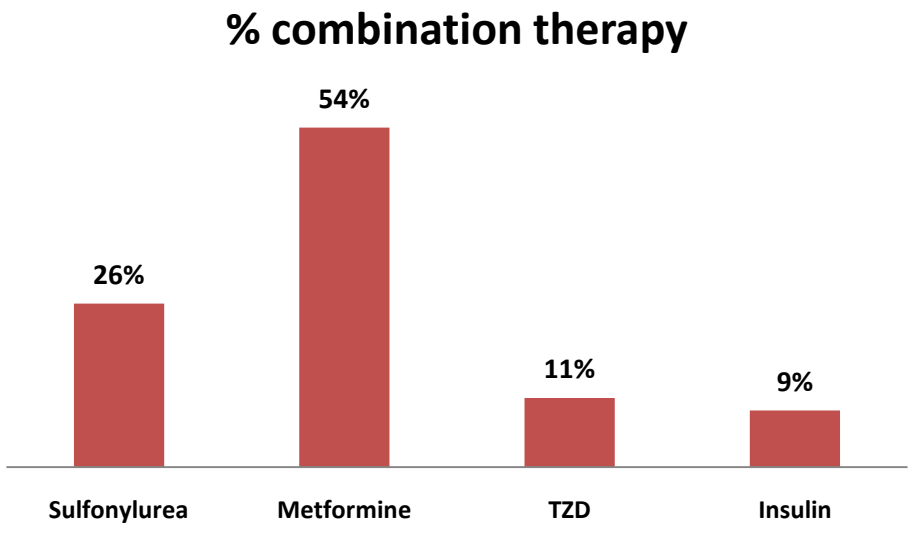

Figure 15: Preferred combination therapy

Unmet needs of gliptins in patients with T2DM

During the survey, most of the doctors had opinion that:

- ✓ Molecules with minimum side effects with cost effectiveness are need for market
- ✓ Combination therapy could be better than single molecule

6.2 Analysis of Chemists' views

Market scenario of gliptins in T2DM

6.2.1 Number of brands in stock

It was found out that approximately 49% of chemists keep more than 6 brands.

Table number 16 as well as figure number 16 gives a data of number of brands keep by chemist and percentage of chemist's response in each range.

No.ofgliptin brands	Response	%Response
1 to 3	12	16%
4 to 6	26	35%
above 6	37	49%

Table 16: Number of gliptin brands in stock

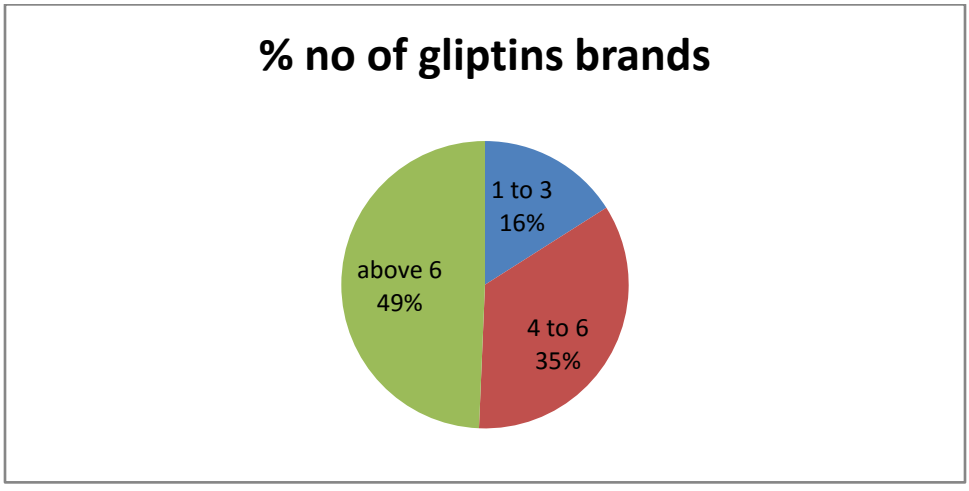

Figure 16: Number of gliptin brands in stock

6.2.2 Brands in stock by chemist

It was found out that approximately 41% of chemists keep Januvia family brands instock followed by ziten 35%.

Table number 17 as well as figure number 17 gives a data of brands keep by chemist and percentage of chemist's response in each range.

Brands of gliptin	Response	% Response
Januvia	31	41%
Galvus	10	13%
Onglyza	5	7%
Zomelis	3	4%
Ziten	26	35%

Table 17: Brands in stock by chemist

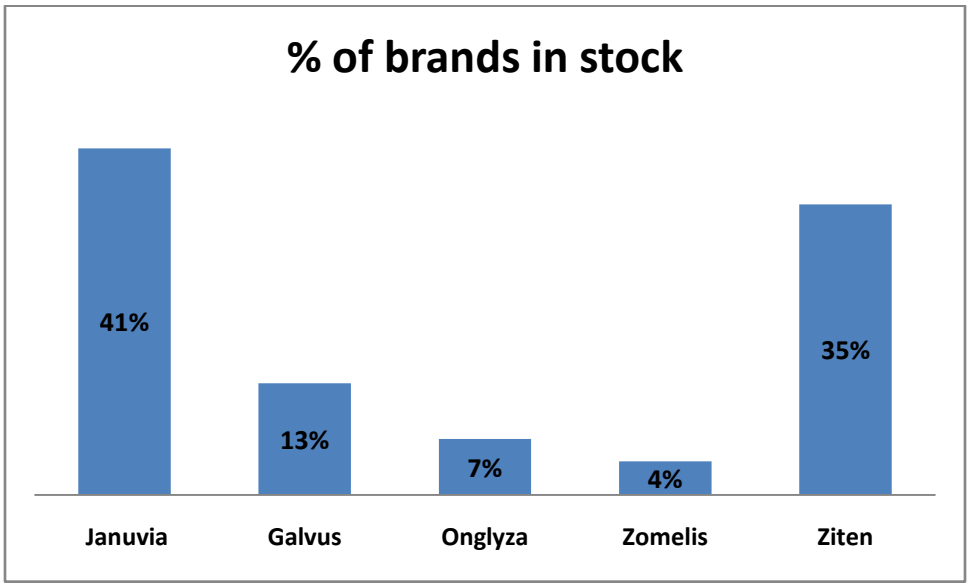

Figure 17: Brands in stock by chemist

6.2.3 Most prescribed brand by doctors

It was found out that approximately 47% of doctors prescribe Januvia family brands followed by ziten.

Table number 18 as well as figure number 18 gives a data of most prescribed brand of by doctors and percentage of chemist's response in each range.

Most prescribed brand	Response	% Resonse
Januvia	35	47%
Galvus	10	13%
Onglyza	2	3%
Zomelis	2	3%
Ziten	26	35%
Tregenta	0	0%

Table 18: Most prescribed brand of gliptin

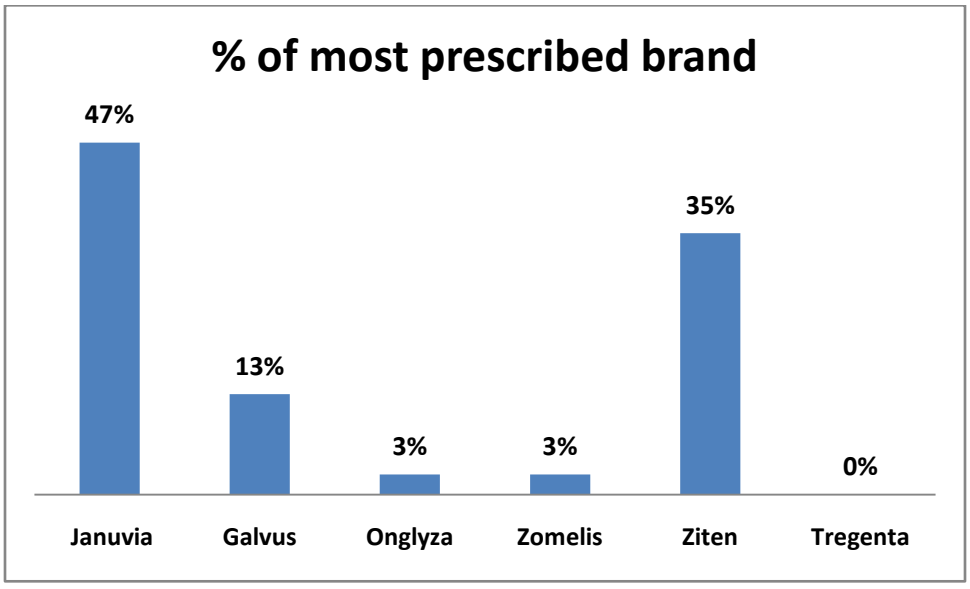

Figure 18: Most prescribed brand of gliptin

6.2.4 Major competitor of sitagliptin

It was found out that approximately 47% chemist suggest teneligliptin as major competitor followed by vildagliptin 37%

Table number 19 as well as figure number 19 gives a data of major competitor of sitagliptin and percentage of chemist's response in each range.

Competitor ofsitagliptin	Response	% Response
Vildagliptin	28	37%
Teneligliptin	35	47%
Linagliptin	4	5%
Sexagliptin	8	11%

Table 19: Competitor of sitagliptin

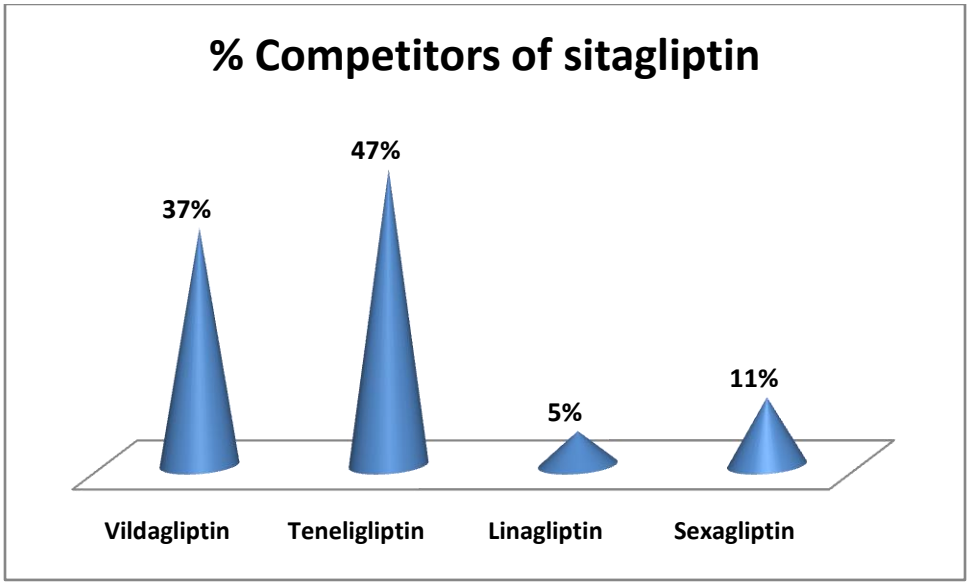

Figure 19: Competitor of sitagliptin

Sales Volume

6.2.5 Sales profile of Januvia family brand per week

It was found out that according to 43% of chemist sales of Januvia per week are 20-30 strips followed by 31% of chemist who suggest it is 10-20 strips per week

Table number 20 as well as figure number 20 gives a data of number of Januvia sale per week and percentage of chemist's response in each range.

No.Januvia sold/week	Response	% Response
less than 10	2	3%
10 to 20	23	31%
20 to 30	32	43%
30 to 40	8	11%
more than 40	10	13%

Table 20: number Januvia sale per month

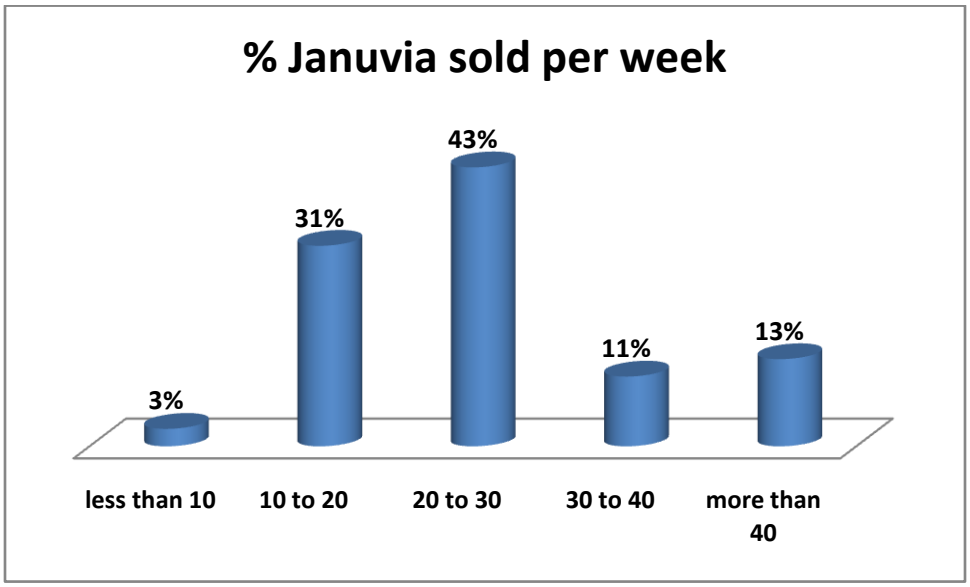

Figure 20: number Januvia sale per month

6.2.6 Sales profile of Januvia family brand on prescription

It was found out that according to 49% of chemist sales of Januvia on prescription per week are less than 10 strips followed by 28% of chemist who suggest it is 10-20 strips per week

Table number 21 as well as figure number 21 gives a data of number of Januvia sale per week and percentage of chemist's response in each range.

No. of januvia sold on Rx	Respose	% Response
less than 10	37	49%
10 to 20	21	28%
20 to 30	12	16%
30 to 40	3	4%
more than 40	2	3%

Table 21: Number of Januvia sale on prescription

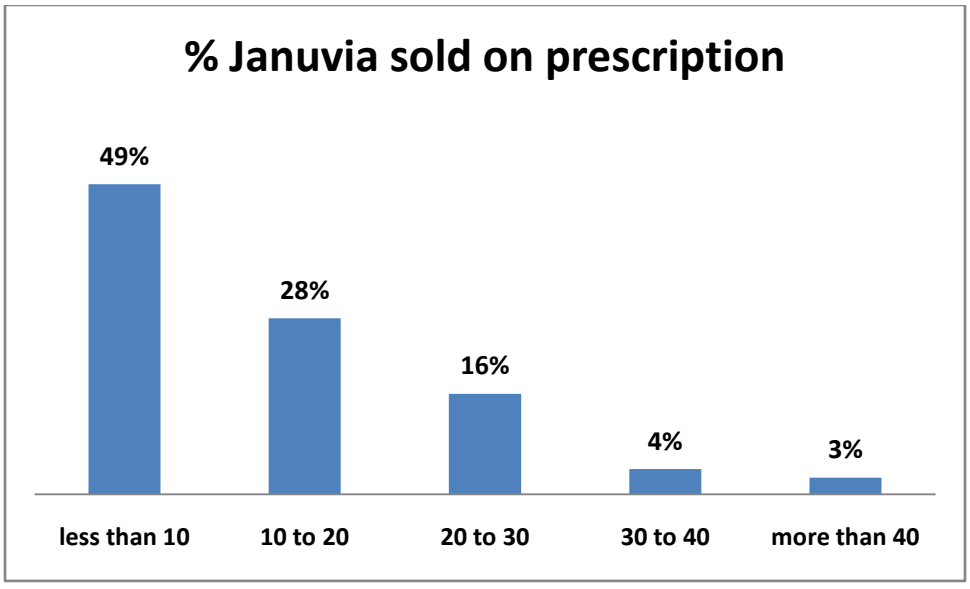

Figure 21: Number of Januvia sale on prescription

6.2.7 Sale other brand of same molecule in absence of prescribed brand

It was found out that according to 65% of chemist they do not sale other brand of same molecule if the prescribed brand is not present.

But the 13% chemist who sale other brands say they sale teneligliptin brands 83% as it is a generic molecule

Table number 22, 23 as well as figure number 22 gives a data of number other brands sale & percentage of chemist's response in each range.

sale of other brand than Rx	Response	% Response
No	65	87%
Yes	10	13%

Table 22: sale of other brands than prescribe

sale of other brand	% response
Teneligliptin	83%
Vildagliptin	17%

Table 23: sale of molecule other than prescribed

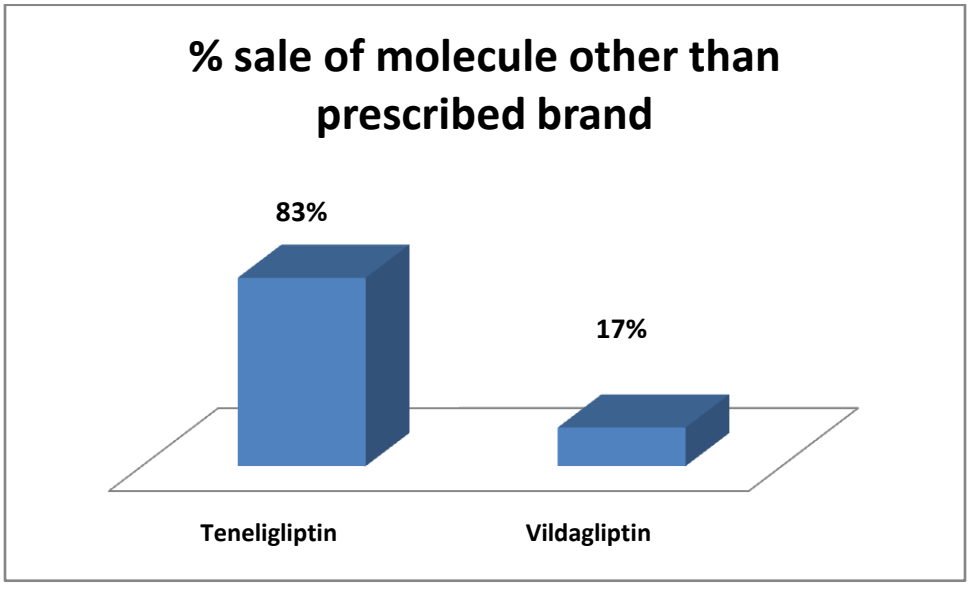

Table 22: sale of molecule other than prescribed

6.2.8 Combination therapy with sitagliptin

It was found out that according to 67% of chemist sale metformin with sitagliptin followed by 25% of sulfonylurea

Table number 24 as well as figure number 23 gives a data of combination therapy with sitagliptin and percentage of chemist's response in each range.

Combination with sitagliptin	Response	% Response
Metformin	50	67%
Sulfonylurea	19	25%
TZD	3	4%
Insulin	3	4%
Vildagliptin		17%

Table 25: combination with sitagliptin

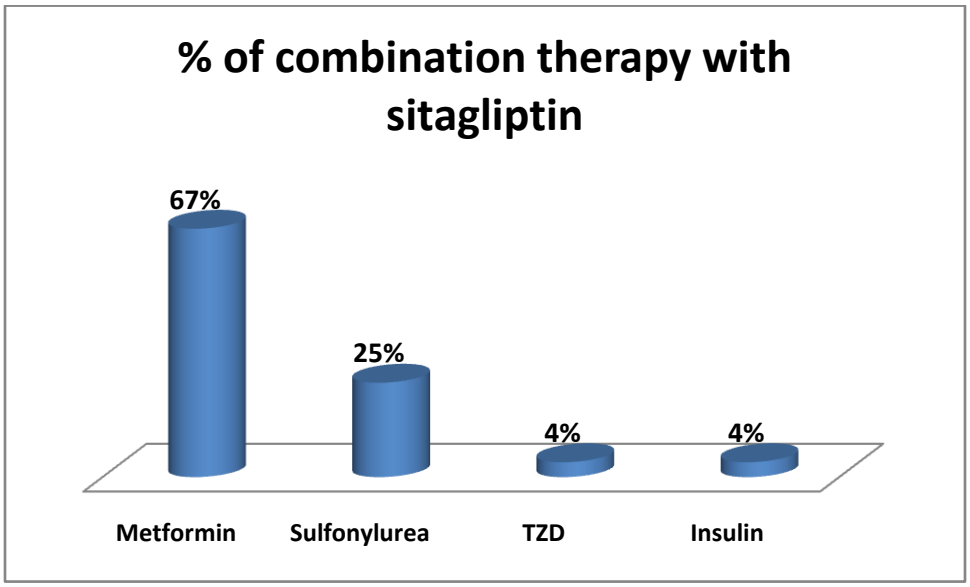

Figure 24: combination with sitagliptin

6.2.9 Most prescribed dose of sitagliptin

It was found out that according to 72% of chemist most prescribed dose of sitagliptin is 100mg followed by 50 mg

Table number 26 as well as figure number 25 gives a data of most prescribed dose with sitagliptin and percentage of chemist's response in each range.

Dose of januvia	Response	% Response
100 mg	54	72%
50 mg	19	25%
25 mg	2	3%

Table 26: Most prescribed dose of sitagliptin

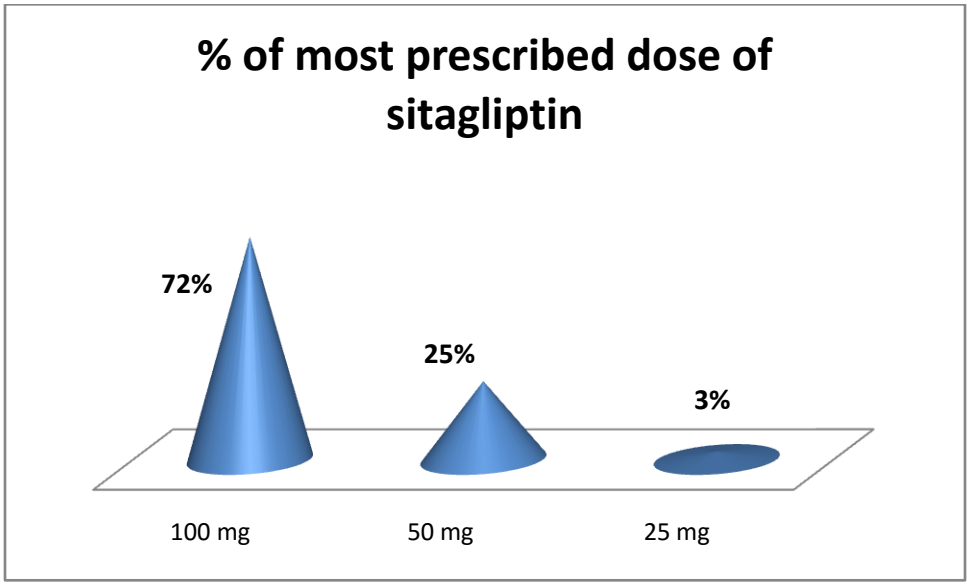

Table 25: Most prescribed dose of sitagliptin

6.3 Analysis of Stickiest' views

Market scenario of gliptins in T2DM

6.3.1 Number of brands in stock

It was found out that approximately 55% of stockiest keep 4 to 5 gliptin brands.

Table number 27as well as figure number 26 gives a data of number of brands keep by stockiest and percentage of stockiest response in each range.

No. of Brands in stock	Response	% Response
less than 3	11	26%
4 to 5	23	55%
More than 5	8	19%

Table 27: Number of brands in stock

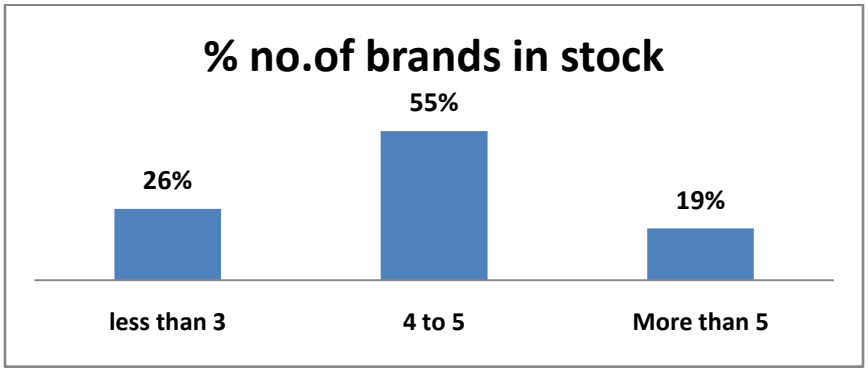

Figure 26: Number of brands in stock

6.3.2 Most prescribed brand of gliptins

It was found out that approximately 43% of stockiest say Januvia is the most prescribed brand folloed by ziten 40%

Table number 28 as well as figure number 27 gives a data of number of most prescribed brands of gliptins and percentage of stockiest's response in each range.

Most prescribed brand	Response	% response
Januvia	18	43%
Galvus	3	7%
Onglyza	2	5%
Ziten	17	40%
Tregenta	0	0%
Zomelis	2	5%

Table 28: Most prescribed brand of gliptins

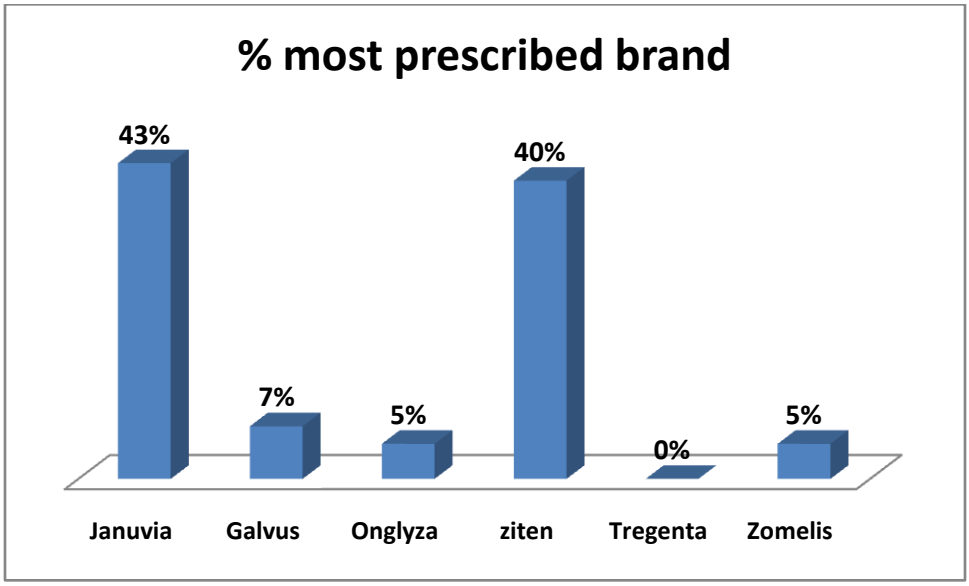

Figure 27: Most prescribed brand of gliptins

6.3.3 Stock of sitagliptin per month

It was found out that approximately 50% of stockiest keeps 500-700 strips of sitagliptin/month

Table number 29 as well as figure number 28 gives a data of number of stock of brands of gliptins and percentage of stockiest's response in each range.

stock of sitagliptin/month	Response	% Response
Less than 100	1	2%
100-300	3	7%
300-500	6	14%
500-700	21	50%
700-1000	5	12%
More than 1000	6	14%

Table 29: stock of sitagliptin per month

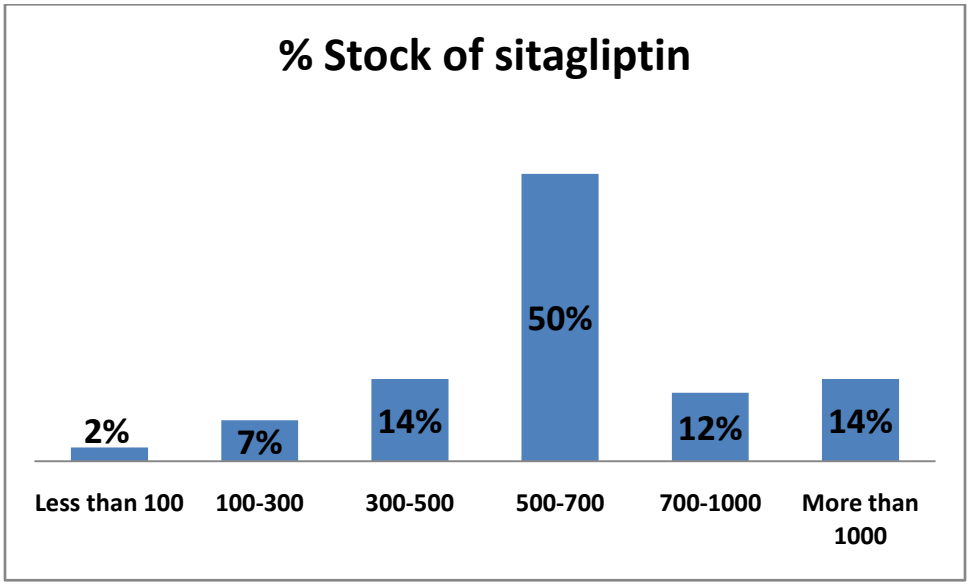

Figure 28: stock of sitagliptin per month

6.3.4 Sale of sitagliptin per month

It was found out that approximately 43% of stockiest sale 500-700 strips of sitagliptin/month

Table number 30 as well as figure number 29 gives a data of number of sale of brands of gliptins and percentage of stockiest's response in each range.

Sale of sitagliptin/month	Response	% Response
Less than 100	2	5%
100-300	3	7%
300-500	8	19%
500-700	18	43%
700-1000	7	17%
More than 1000	4	10%

Table 30: sale of sitagliptin/month

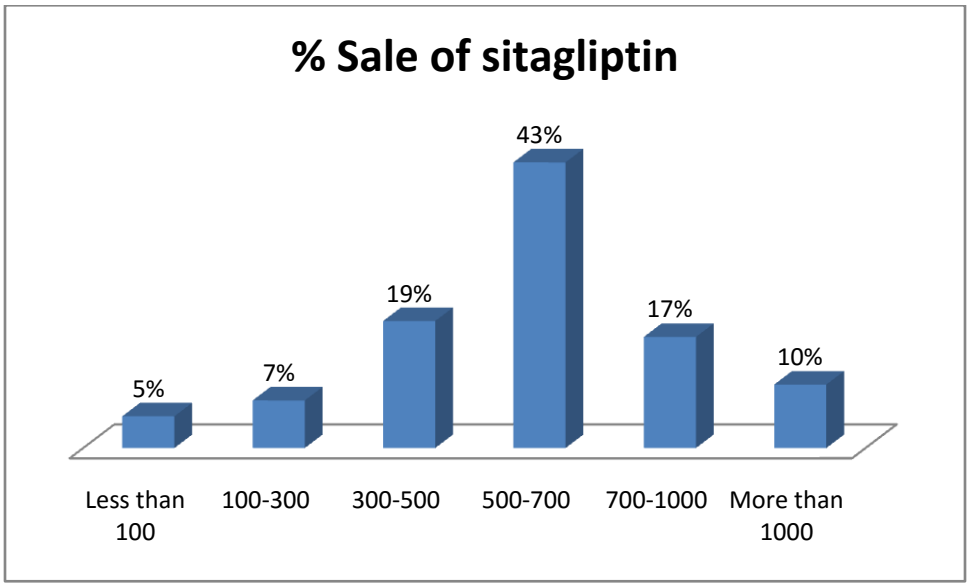

Figure 29: sale of sitagliptin/month

6.3.5 Scheme available in any gliptin brands

It was found out that approximately 33% of stockiest keeps scheme for gliptin brands

From this 33% of stockiest, 53% give scheme like free strips followed by 47% discount scheme.

Table number 31 & 32 gives a data of scheme in stock of brands of gliptins and percentage of stockiest's response in each range.

Scheme for brands	% Response
No	67%
Yes	33%

Table 31: Scheme for brand

Scheme	% Response
Discount	47%
Free strips	53%

Table 32: Preferred scheme for brands

6.3.6 Competitor of januvia

According to 57% stockiest, ziten is a major competitor of Januvia, followed by galvus 31%

Table number 33 & Figure number 30 gives a data of major competitor of januvia and percentage of stockiest's response in each range.

Competitor of Januvia	Response	% Response
Galvus	13	31%
Onglyza	2	5%
Ziten	24	57%
Tregenta	1	2%
Zomelis	2	5%

Table 33: Competitor of januvia

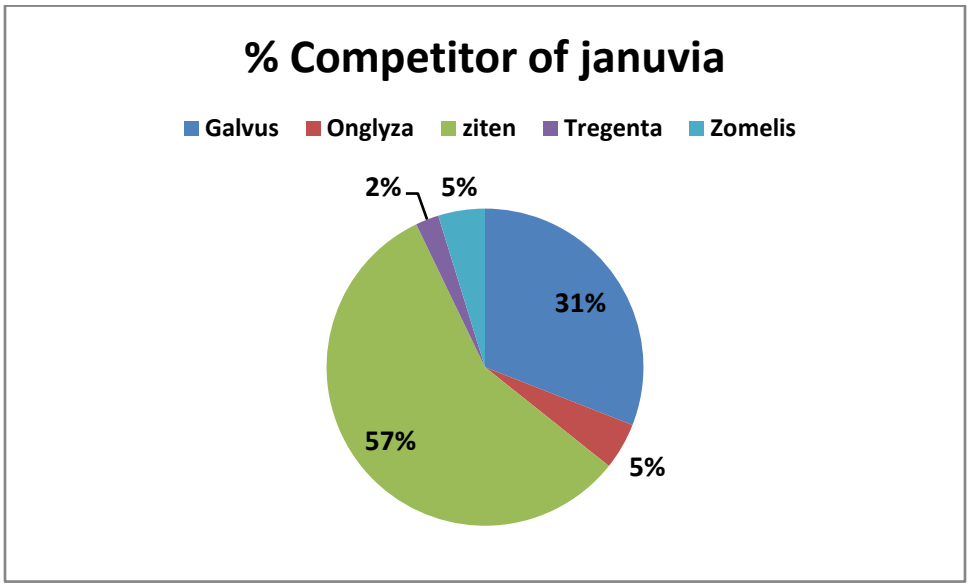

Figure 30: Competitor of januvia

7. Findings based on observation & key opinions

- Number of patients with diabetes therapy is increasing exponentially.
- Prescription pattern follows efficacy, safety & durability.
- Prescription pattern follows minimum side effects of the molecule
- Prescription pattern follows economy status of the patients.
- According to some doctors prescription trend never remains same, it keeps on changing.
- Many doctors prefer USFDA approved products.

8. Suggestions

1) As India is developing country, with a large population not being financially strong, Teneligliptin is choice of drug because of cost-effectiveness in majority of the clinics, but teneligliptin is having certain side effects. While prescribing any product complication cost can be taken in consideration rather than therapy cost.

2) Sitagliptin is the best choice in all gliptins among doctors in termes of onset of action, DPP4 inhibition, CV safety, hepatic & renal safety, efficacy & durability.

3) Sitagliptin with Add on therapy with Insulin could be future market driver as it is having good efficacy.

4) Cost effectiveness of sitagliptin could help a molecule to become market leader according to some doctors.

5) During the study it was found that language is a major constraint. For awareness of a particular product among doctors, company's representatives should know the local languages.

6) Stockiest and chemist could give more schemes to attract customers

9. Limitations

1) Sample unit are limited for survey, it affect the accuracy of outcomes.

2) Survey was carried out in one region only (Mumbai).

3) Time duration of the survey did not allow collecting more data.

4) The respondents were very busy and could not afford more time to answer.

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11. Annexure

11.1 Doctor's questionnaire

Questionnaire for Doctors

S.No.			

Date: _____

Name: _____ Location: _____

Q1) How many Type 2 diabetes patients you examine weekly?

a) Less than 10

b) 10-20

c) 20-30

d) 30-40

e) More than 40

Q2) which of the following treatment you use to cure/treat them?

a) Oral

b) I.V.

c) Both

Q3) which type of drug you used in T2DM?

a) GENERIC

b) BRANDED

Q4) In which indication you use Gliptins mostly?

a) Initial therapy

b) Add on therapy with Metformin

c) Add on therapy with sulfonylurea

d) Add on therapy with Insulin

Q5) Among the given parameter, which parameter you consider, best define the mentioned T2DM molecule(gliptin)?

(5=very good, 4=good, 3=average, 2=poor , 1=very poor)

S.no	Molecule(Gliptin)	Onset of action (DPP4 selectivity)	Duration of action (DPP4 inhibition after 24 hrs)	CV safety	Hepatic & Renal safety	Efficacy (HBA1C Reduction)	Durability	Cost
1	Sitagliptin							
2	Vildagliptin							
3	Teneligliptin							
4	Linagliptin							
5	Saxagliptin							

Q6) While prescribing any brand, which are the factors you consider the most?

a) Efficacy
b) Safety
c) Cost
d) Durability
e) Clinical evidence

Q.7) Which is the most preffered brand of gliptin you use in T2DM patients?

a) Januvia/Janumet/Janumet XRCP
b) Galvus
c) Onglyza
d) Zomelis
e) Ziten
f) Tregenta
g) Other

Q.8) Any combination therapy you preferred with sitagliptin?

a) No
b) Yes

If Yes: _____

Q.9) According to you, Which is the current unmet need in T2DM?

_____
_____
_____
_____
_____
_____
_____

11.2 Chemist's Questionnaire

Questionnaire for chemist

S.No.			

Date: _____

Name: _____Location:_____

Q.1 How many brands of Gliptins do you have in your stock?

a) 1-3

b) 4-6

c) More than 6

Q2) what brands do you have in stock?

h) Januvia/Janumet/Janumet XRCP

i) Galvus

j) Onglyza

k) Zomelis

l) Ziten

m) Tregenta

n) Other

Q3) which is the most prescribe brand of gliptins?

a) Januvia/Janumet/Janumet XRCP
b) Galvus
c) Onglyza
d) Zomelis
e) Ziten
f) Tregenta
g) Other

Q4) Who is the major competitor of Sitagliptin(Januvia Family)?

_____

Q5) How many tablets of Januvia family you sale in one month?

A) Less than 10
B) 10-20
C) 20-30
D) 30-40
E) more than 40

Q6) how many tablets of Januvia family are sold on Prescription?

A) Less than 10
B) 10-20
C) 20-30

D) 30-40

E) more than 40

Q7) Do you provide another brand of same molecule if prescribed brand is not available in your stock?

a) No

b) Yes

If yes, then which brand?

_____

Q.8) what combinations with Sitagliptin are most prescribed?

a) Metformin

B) Sulfonylurea

c) TZD

e) Insulin

f) Others

Q 9) What strength of Januvia is most prescribed?

A) 25mg B)50mg C)100 mg

11.3 Stockiest Questionnaire

Questionnaire for stockiest

S.No.			

Date: _____

Name: _____ Location:_____

Q1) How many brands of Gliptins do you have in your stock?

d) Less than 3
e) 4-5
f) More than 5

Q2) Which is the most prescribe brand of Gliptins?

o) Januvia/Janumet/Janumet XRCP
p) Galvus
q) Onglyza
r) Zomelis
s) Ziten
t) Tregenta
u) Other

Q.3) How much stock of Sitagliptin you keep in one month?

a) Less than 100

b) 100-300

c) 300-500

d) 500-700

e) 700-1000

f) More than 1000

Q4) How many strips of sitagliptin you sale in one month?

g) Less than 100
h) 100-300
i) 300-500
j) 500-700
k) 700-1000
l) More than 1000

Q5) Do you provide any scheme for the sale of above mentioned brands?

a) no
b) yes

If yes, what type of scheme you provide for different brands?

a) Januvia/Janumet/Janumet XRCP

b) Galvus

c) Onglyza

d) Zomelis

e) Ziten

f) Tregenta

g) others

Q6) Who is the major competitor of Januvia family?

a) Galvus

b) Onglyza

c) Zomelis

d) Ziten

e) Tregenta

f) others