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A REVIEW: DIPEPTIDYLPEPTIDASE-4 INHIBITORS (GLIPTINS)

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ABSTRACT

Dipeptidyl peptidase-4 inhibitors (DPP-4s), also commonly called gliptins. The need of the hour is a refreshing class of drugs whose effects on hyperglycemia can be sustained, without adversely affecting the survival of beta-cells and are weight neutral and free of hypoglycaemia, a true class of anti-hyperglycemics, a dream too good to be true. Classification of gliptins involve 1. Peptidomimetics: Which mimic the DPP-4 enzyme E.g.-vildagliptin and saxagliptin 2. Non-Peptidomimetics-Which those that do not mimic DPP4 enzyme. E.g. Sitagliptin, Alogliptin, Linagliptin. SAR (Structural Activity Relationship), pharmacology, mechanism of action of drugs of gliptin classes are explain in th following review.

KEYWORDS: Dipeptidyl peptidase-4 inhibitors (DPP-4), glucagon-like peptide-1 (GLP-1), type 2 diabetes mellitus (T2DM).

1. INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (DPP-4s), also commonly called gliptins, are a relatively new class of drugs for the treatment of type 2 diabetes. These agents work in a unique way to improve insulin secretion from the β-cells of the pancreas in response to an increase in blood sugar and simultaneously decrease glucagon output from the α-cells of the pancreas, which results in decreased hepatic glucose output.

In order to understand how gliptins work, it is essential to understand the normal physiology of glucose homeostasis in both the fasting and fed states. When a person is fasting, the tissues extract glucose from the bloodstream to use as fuel.[4,5] If this extraction were to continue without glucose being replaced into the circulation, that person would die of hypoglycaemia

within a matter of hours. The blood glucose does not fall to hypoglycemic levels during fasting, however, because the liver replaces glucose to maintain normal glycaemia. It does so under the influence of glucagon, a hormone that is produced from the α-cells of the pancreas.

Glucagon signals the liver to release glucose into the circulation, either from glycogenolysis or from gluconeogenesis. Normally, this balance of blood glucose works very well to maintain normal glycaemia in the range of 60 to 90 mg/dL in the fasting state Basal insulin is necessary at all times to maintain normal metabolism, including metabolism of fat and protein, as well as glucose.[2] Similarly, basal glucagon secretion is necessary to maintain normal fasting glucose levels. When a person eats, a neural stimulus from the act of eating triggers the brain to send signals to the gut which leads to the release of intestinal hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP).

Patients with type 2 diabetes also have decreased α-cell sensitivity to glucose, so their glucagon secretion is not appropriately suppressed as blood glucose rises postprandial and it may even be paradoxically stimulated. The importance of suppressing glucagon has been recognized for many years, but not until recently have drugs with a potent effect on postprandial glucagon secretion become available.

In 2006, a new class of medicine for Type 2 diabetes was introduced to the U.S. market. Called DPP-4 inhibitors, These drugs work in a way that is different from any previous diabetes.

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 hypoglycaemia).[1]

1.1. Need of Dpp4 Inhibitor

The treatment of type 2 diabetes mellitus (T2DM) has included the use of metformin (particularly in the overweight patient) and sulfonyurea (SU) (in both lean and overweight patient), as first line anti-diabetic therapies world over.

Sulfonylurea- Prior to 1995, the use of it was the most popular anti-diabetic therapy in the USA (United States). SU′s act by increasing insulin secretion in a glucose-independent manner, thereby risking severe unpredictable hypoglycaemia, particularly if the meal is delayed or if its carbohydrate quantity reduced.

Metformin: The use of only became popular in the US post 1995. It only makes sense that they continue to remain mainstay therapy as despite their problems they are best suited to deal with the original pathogenic triumvirate theory for T2DM proposed by Ralf Defranzo, (qualitative and quantitative beta cell failure and insulin resistance at level of liver and peripheral tissue).

This was particularly true since there was no agent that could help improve health of the beta cell and cause insulin release in a glucose dependant manner. This all changed once it was learnt that the incretin system was involved in the pathogenesis of T2DM. Failure of this incretin system has been implicated in progression of beta-cell failure and therefore any therapy that can augment this system has been shown to promote beta cell health and insulin release in a glucose-dependent manner.

Although the use of metformin therapy has been associated with several advantages (non-hypoglycemic, weight-loss promoting, anti-ischemic to cardiac tissue, improvement in non-alcoholic hepatosteatosis, anti-neoplastic etc), its use has been associated with gastrointestinal adverse effects, precluding or limiting its use, particularly in the non-overweight patient. Use of SU′s on the other hand although effective in lowering plasma glucose can be associated with variable severities of hypoglycemia, weight gain, beta-cell death and possibly adverse cardiac outcomes as proposed originally by the UKPDS and later by other groups.

The UKPDS was the first to show that the combination of SU and metformin resulted in a progressive decline in [beta]-cell function and by 3 years up to 50% of diabetic patients can require an additional pharmacological agent to maintain the glycosylated haemoglobin<7.0%. Moreover, the percentage of diabetic patients classified as adequately controlled while mostly on these therapies still remains a challenge with a majority (> 50%) of diabetic patients having a HbA1c > 7%. From the above data it seems clear that existing popular therapies are not only ineffective but are associated with a significant amount of morbidity (weight gain and hypoglycaemia). The need of the hour is a refreshing class of drugs whose effects on hyperglycemias can be sustained, without adversely affecting the

survival of beta-cells and are weight neutral and free of hypoglycaemia, a true class of anti-hyperglycemics, a dream too good to be true.[2]

1.2. Discovery and Development of Dpp-4 Inhibitors

It is important to find a fast and accurate system to discover new DPP-4 inhibitors with ideal therapeutic profiles.

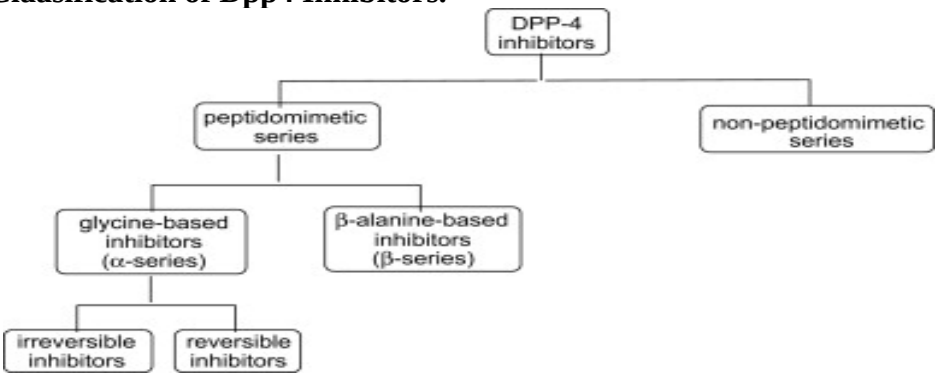
Virtual screening has for example been used to screen for small primary aliphatic amines to identify fragments that could be placed in S1 and S2 sites of DPP-4. On the other hand, these fragments were not very potent and therefore identified as a starting point to design better ones. 3D models can provide a useful tool for designing novel DPP-4 inhibitors. Pharmacophore models have been made based on key chemical features of compounds with DPP-4 inhibitory activity. These models can provide a hypothetical picture of the primary chemical feature responsible for inhibitory activity]. The first DPP-4 inhibitors were reversible inhibitors and came with bad side effects because of low selectivity. Researchers suspected that inhibitors with short half-lives would be preferred in order to minimize possible side effects. However, since clinical trials showed the opposite, the latest DPP-4 inhibitors have a long-lasting effect.

One of the first reported DPP-4 inhibitor is P32/98 from Merck. It used thiazolidide as the P1-substitute and is the first DPP-4 inhibitor that showed effects in both animals and humans. Another old inhibitor is DPP-728 from Novartis, where 2-cyanopyrrolidine is used as the P1-substitute. The addition of the cyano group generally increases the potency.

2. Classification of Dpp4 Inhibtors

2.1. The DPP-4 Inhibitors Based On Their Mechanism Of Action Can Be Divided As.

Table 1: Claasification of Dpp4 Inhibitors.[3]



1. Peptidomimetics

Which mimic the DPP-4 enzyme

E.g.-vildagliptin and saxagliptin

2. Non-Peptidomimetics

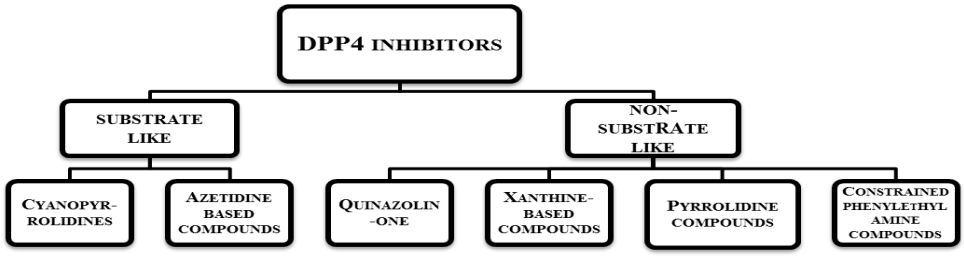
Which those that do not mimic DPP4 enzyme

E.g. Sitagliptin, Alogliptin, Linagliptin.

They are competitive reversible inhibitors of the DPP-4 substrate acting extra-cellularly. The molecules have varying affinities toward the DPP-4 substrate.[4]

2.2. Classification of Dpp4 Inhibitors Based Upon Chemical Group Present

Table 2: Clasification of DPP4 Based On Chemical Moiety Present.



2.2.1-Substrate-Like Inhibitors

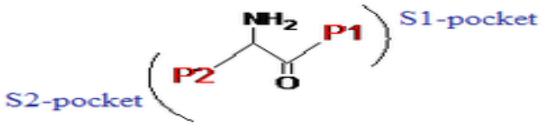


Figure 1: Substrate Like Inhibitor.

Substrate-like inhibitors are more common than the non-substrate-like. They bind either covalently or non-covalently and have a basic structure where the P1-substituent occupies the S1-pocket and the P2-substituent occupies the S2-pocket. Usually they contain a proline mimetic that occupies the S1-pocket.

Large substituent on the 2-cyanopyrrolidine ring is normally not tolerated since the S1-pocket is quite small. Since DPP-4 is identical with the T-cell activation marker CD26 and DPP-4 inhibitors are known to inhibit T-cell proliferation, these compounds were initially thought to be potential immunomodulators.[3]

When the function against type 2 diabetes was discovered, the cyanopyrrolidines became a highly popular research material. A little later vildagliptin and saxagliptin, which are the most developed cyanopyrrolidineDPP-4 inhibitors to date, were discovered.

2.2.1.1: Cyanopyrrolidines

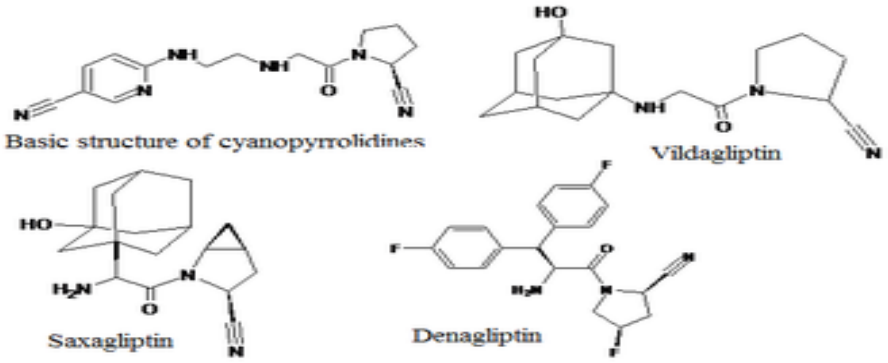


Figure 2: Structure of Cyanopyrrolidine and Drugs Involve In This Class.

Cyanopyrrolidines have two key interactions to the DPP-4 complex:

1. Nitrile in the position of the scissile bond of the peptidic substrate that is important for high potency. The nitrile group forms reversible covalent bonds with the catalytically active serine hydroxyl (Ser630), i.e. cyanopyrrolidines are competitive inhibitors with slow dissociation kinetics.

2. Hydrogen bonding network between the protonated amino group and a negatively charged region of the protein surface, Glu205, Glu206 and Tyr662. All cyanopyrrolidines have basic, primary or secondary amine, which makes this network possible but these compounds usually drop in potency if these amines are changed. Nonetheless, two patent applications unveil that the amino group can be changed, i.e. replaced by a hydrazine, but it is claimed that these compounds do not only act *via* DPP-4 inhibition but also prevent diabetic vascular complications by acting as a radical scavenger.[3]

2.2.1.2.: Azetidine Based Compounds

Information's for this group of inhibitors are quite restricted. Azetidine-based DPP-4 inhibitors can roughly be grouped into three main subcategories; 2-cyanoazetidines, 3-fluoroazetidines and 2-ketoazetidines. The most potent ketoazetidines and cyanoazetidines have large hydrophobic amino acid groups bound to the azetidinenitrogen and are active below 100nM.

2.2.2. Non-Substrate-Like Inhibitors

Non-substrate-like inhibitors do not take after dipeptidic nature of DPP-4 substrates. They are non-covalent inhibitors and usually have an aromatic ring that occupies the S1-pocket, instead of the proline mimetic.

Development: In 1999, Merck started a drug development program on DPP-4 inhibitors. When they started internal screening and medicinal chemistry program, two DPP-4 inhibitors were already in clinical trials, isoleucyl thiazolidide (P32/38) and NVP-DPP728 from Novartis. Merck in-licensed L-*threo*-isoleucyl thiazolidide and its *allo*stereoisomer. They found that both isomers had similar affinity for DPP-4, similar *in vivo* efficacy, similar pharmacokinetic and metabolic profiles. Nevertheless, the *allo* isomer was 10-fold more toxic. The researchers found out that this difference in toxicity was due to the *allo* isomer's greater inhibition of DPP-8 and DPP-9 but not because of selective DPP-4 inhibition.

More research also supported that DPP-4 inhibition would not cause compromised immune function. Once this link between affinity for DPP-8/DPP-9 and toxicity was discovered, Merck decided on identifying an inhibitor with more than a thousand fold affinity for DPP-4 over the other dipeptidases. For this purpose, they used positional scanning libraries. From scanning these libraries, the researchers discovered that both DPP-4 and DPP-8 showed a strong preference for breaking down peptides with a proline at the P1 position but they found a great difference at the P2 site; i.e., they found that acidic functionality at the P2 position could provide a greater affinity for DPP-4 over DPP-8.Merck kept up doing even more research and screening.

They stopped working on compounds from the α-amino acid series related to isoleucyl thiazolidide due to lack of selectivity but instead they discovered a very selective β-amino acidpiperazine series through SAR studies on two screening leads. When trying to stabilize the piperazine moiety, a group of bicyclic derivatives were made, which led to the identification of a potent and selective triazolopiperazine series. Most of these analogs showed excellent pharmacokinetic properties in preclinical species. Optimization of these compounds finally led to the discovery of sitagliptin.

E.g.-Sitagliptin

Sitagliptin (Januvia) has a novel structure with β-amino amide derivatives.

Since sitagliptin has shown excellent selectivity and *in vivo* efficacy it urged researches to inspect the new structure of DPP-4 inhibitors with appended β-amino acid moiety. Further studies are being developed to optimize these compounds for the treatment of diabetes. Crystallographic structure of sitagliptin along with molecular modeling has been used to continue the search for structurally diverse inhibitors. A new potent[selective and orally bioavailable DPP-4 inhibitor was discovered by replacing the centralcyclohexylamine in sitagliptin with 3-aminopiperidine. A 2-pyridyl substitution was the initial SAR breakthrough since that group plays a significant role in potency and selectivity for DPP-4.[5]

2.2.2.1.: Constrained Phenylethylamine Compounds

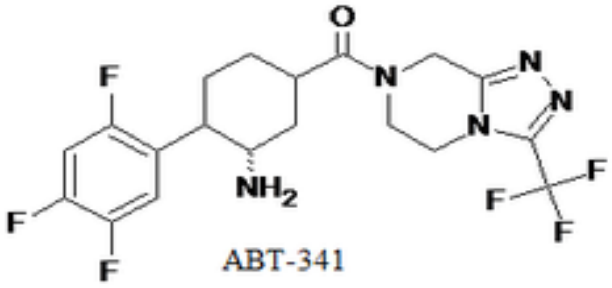


Figure 3: Phenylethylamine Compound E.G.-The Structure of Abt-341.

Researchers at Abbott Laboratories identified three novel series of DPP-4 inhibitors using HTS. After more research and optimization ABT-341 was discovered. It is a potent and selective DPP-4 inhibitor with a 2D-structure very similar to sitagliptin. However, the 3D-structure is quite different. ABT-341 also has a trifluorophenyl group that occupies the S1-pocket and the free amino group, but the two carbonyl groups are orientated 180° away from each other. ABT-341 is also believed to interact with the Tyr547, probably because of hindrance between the cyclohexenyl ring and the tyrosine side-chain.[3]

2.2.2.2: Pyrrolidine Compounds

The pyrrolidine type of DPP-4 inhibitors was first discovered after HTS. Research showed that the pyrrolidine rings were the part of the compounds that fit into the binding site. Further development has led to fluoro substituted pyrrolidines that show superior activity, as well as pyrrolidines with fused Cyclopropylrings that are highly active.[38]

2.2.2.3: Xanthine-Based Compounds

This is a different class of inhibitors that were identified with HTS. Aromaticheterocyclic-based DPP-4 inhibitors have gained increased attention recently. The first patents describing

xanthines as DPP-4 inhibitors came from Boehringer-Ingelheim(BI) and Novo Nordisk. When Xanthine based DPP-4 inhibitors are compared with sitagliptin and vildagliptin it has shown a superior profile. Xanthines are believed to have higher potency, longer-lasting inhibition and longer-lasting improvement of glucose tolerance.[39]

E.g.-Linagliptin

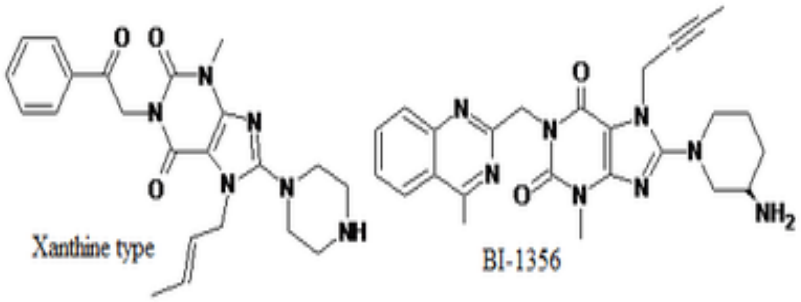


Figure 4: The Structure of Xanthine Type Inhibitors & Linagliptin (Known As Bi-1356 In Clinical Trials).

Researchers at BI discovered that using a buty-2-nyl group resulted in a potent candidate, called BI-1356. In 2008 BI-1356 was undergoing phase III clinical trials; it was released as linagliptin in May 2011. X-ray crystallography has shown that that Xanthine type binds the DPP-4 complex in a different way than other inhibitors:

- The amino group also interacts with the Glu205, Glu206 and Tyr662
- The buty-2-nyl group occupies the S1-pocket
- The uracil group undergoes a π-stacking interaction with the Tyr547 residue
- The quinazoline group undergoes a π-stacking interaction with the Trp629 residue [3]

2.2.2.4.: Quinazolinone

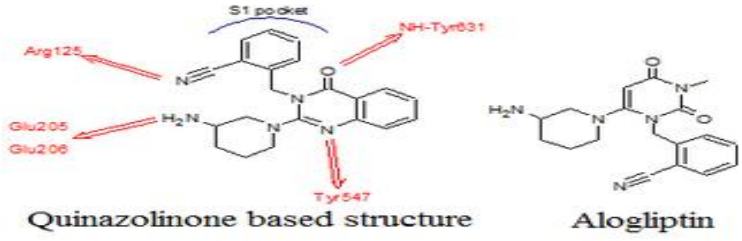


Figure 5: Quinazolinone Structure and Alogliptin.

Alogliptin is a novel DPP-4 inhibitor developed by the Takeda Pharmaceutical Company. Researchers hypothesized that a quinazolinone based structure would have the necessary

groups to interact with the active site on the DPP-4 complex. Quinazolinone based compounds interacted effectively with the DPP-4 complex, but suffered from low metabolic half-life.

It was found that when replacing the quinazolinone with a pyrimidinedione, the metabolic stability was increased and the result was a potent, selective, bioavailable DPP-4 inhibitor named alogliptin. The quinazoline based compounds showed potent inhibition and excellent selectivity over related protease, DPP-8. However, short metabolic half due to oxidation of the A-ring phenyl group was problematic.

At first, the researchers tried to make a fluorinated derivative. The derivative showed improved metabolic stability and excellent inhibition of the DPP-4 enzyme. However, it was also found to inhibit CYP 450 3A4 and block the hERG channel. The solution to this problem was to replace the quinazolinone with other heterocycles, but the quinazolinone could be replaced without any loss of DPP-4 inhibition.

X-ray crystallography has shown that that Xanthine type binds the DPP-4 complex in a different way than other inhibitors.
The amino group also interacts with the Glu205, Glu206 and Tyr662
The buty-2-nyl group occupies the S1-pocket
The uracil group undergoes a π-stacking interaction with the Tyr547 residue
The quinazoline group undergoes a π-stacking interaction with the Trp629 residue 5

3. Mechanism of Action of Dpp-4 Inhibitors

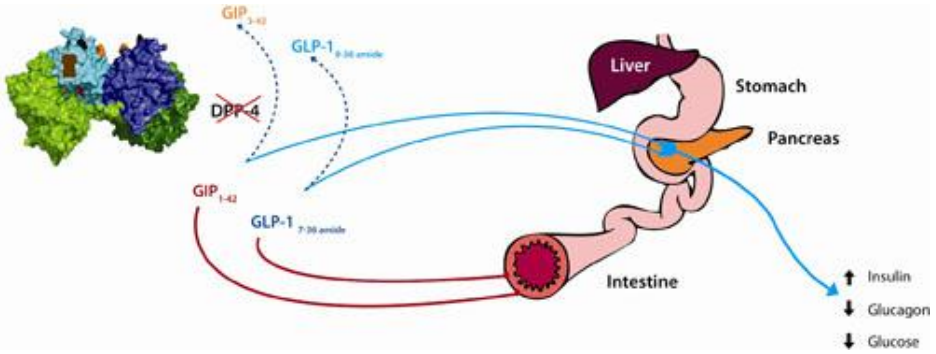


Figure 6: Effects of Dpp-4 Inhibitors Occur Predominantly Through GLP-1 and GIP.[4,5]

Drugs that inhibit the action of DPP-4 enzyme are intervening in a complex set of reactions that occur when food is eaten. In response to meals, specialized cells in the intestines called L

cells secrete GLP-1. L cells are mainly found in the ileum, the last segment of the small intestine and in the large intestine (also known as the colon). GLP-1 appears to be secreted, however, before food from a meal reaches these areas of the intestines. The L cells have receptors for a variety of hormones secreted by the digestive system, which helps them determine the type of nutrients that have been consumed and control the amount of GLP-1 they release.

It is thought that hormonal signals from the upper intestine, as well as a chemical released by nerves in response to eating, stimulate the release of GLP-1.

GLP-1 has several effects in the body other than stimulating the release of insulin. It also slows stomach emptying, inhibits the release of glucagon (glucagon is a hormone that signals the liver to release glucose and is usually elevated in people with Type 2 diabetes) and enhances the survival and growth of pancreatic beta cells, which secrete insulin.

DPP-4 is a protein that is found both circulating in the blood and attached to cell membranes. It breaks down several hormones, not just GLP-1 and helps transmit signals from outside cells to the inside. DPP-4 was originally identified as a protein on lymphocytes, a type of white blood cell in the immune system. It was later found on many different types of tissue, including the kidneys, lungs, liver, intestines, pancreas, blood vessels and brain. The breakdown of GLP-1 occurs within several minutes of DPP-4 being released into the blood.

Since DPP-4 inhibitors only enhance the body's own ability to release insulin and regulate blood glucose, these drugs can only treat Type 2 diabetes. Their effect is dependent on some function of the insulin-releasing beta cells in the pancreas and people with Type 1 diabetes generally do not have a significant number of functioning pancreatic beta cells.

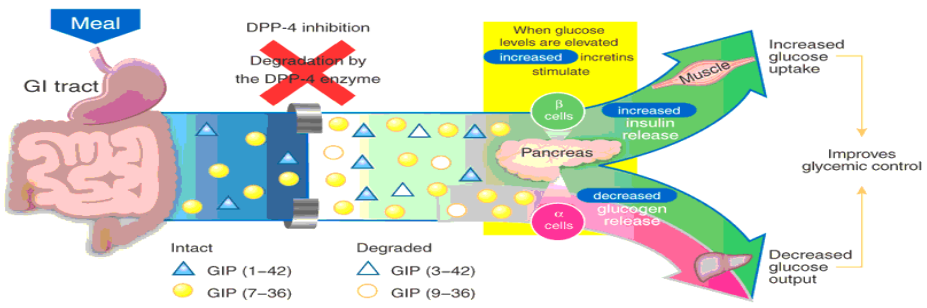


Figure 7: Effect of DPP4 Inhibitors on action on glp and gip.[5,3]

Glucagon-like peptide-1 (GLP-1) is an incretin hormone that results in glucose-dependent insulin secretion, suppression of glucagon secretion, a delay in gastric emptying and a decrease in caloric intake likely secondary to centrally mediated signaling. It arises from posttranslational processing of proglucagon primarily in intestinal L cells and k-cells is secreted in two major forms: GLP-1(7,36) and GLP-1(7,37). The majority of known biological actions of GLP-1 depend on the presence of the two N-terminal amino acids; these are removed by the enzyme, dipeptidyl peptidase-4 (DPP-4), whose substrates are polypeptides with an alanine or a proline at the second position from the N-terminal side. Hence, the intact (7,36) and (7,37) peptides are often referred to as "active" GLP-1, whereas the truncated (9,36) and (9,37) peptides are known as "inactive" GLP-1.

The class of agents that use the incretin system are DPP-4 inhibitors, which inhibit the principal enzyme responsible for the degradation of endogenous GLP-1. By decreasing clearance of GLP-1, concentrations of active GLP-1 are increased, resulting in a lowering of fasting and postprandial glucose concentrations. There are differences in the glucose-lowering efficacy, the effect on body weight and the side effect profiles between DPP-4 inhibitors and GLP-1 receptor agonists. These differences have led to speculation that alternative mechanisms of action may explain the effects of DPP-4 inhibition.[56,57]

In practice, DPP-4 inhibitors increase concentrations of both active incretin hormones, GLP-1 and glucose-dependent insulinotropic polypeptide (secreted by the enteroendocrine L and K cells, respectively, which are substrates for DPP-4). This results in improved b cell responsiveness to prevailing glucose concentrations and suppression of glucagon secretion. That the incretin hormones mediate these effects has been conclusively demonstrated in the double-incretin receptor knockout (DIRKO) mouse. Despite increases in active GLP-1concentrations, there are no effects, however, of these compounds on directly measured gastric emptying and gastric accommodation. This is a significant difference from GLP-1 receptor agonists that is not as yet completely understood. Although it is true that concentrations of active GLP-1may not be high enough or sustained enough during DPP-4 inhibition to alter gastrointestinal motility, this is not always the case. Indeed DPP-4 is necessary for the activation of some pro-satiety factors (such as peptide YY) also produced by the L cell. In such cases, it is conceivable (but not proven) that the net result of DPP-4 inhibition on satiation is neutral because the increase in active GLP-1 is countered by a decrease in activated peptide YY. It has been suggested that decreased incretin secretion may

play a part in the pathogenesis of type 2 diabetes. However, the direct measurement of GLP-1 concentrations in response to an oral challenge across the spectrum of prediabetic and in established diabetes suggests that this is not the case. Given the decline in b-cell function associated with increasing glucose intolerance and frank diabetes, despite normal incretin hormone concentrations, it stands to reason that b -cell responsiveness to these secretagouges is progressively impaired.

4. Structure-Activity Relationship (Sar)

Strict steric constraint exists around the pyrrolidine ring of cyanopyrrolidine-based inhibitors, with only hydrogen, fluoro, acetylene, nitrile, or methano substitution permitted.

Presence of a nitrile moiety on the pyrrolidine ring is critical to achieving potent activity Also, systematic SAR investigation has shown that the ring size and stereochemistry for the P2 position is quite conditioned.

A 5-membered ring and L-configuration has shown better results than a 4-membered or 6-membered ring with D-configuration.

Only minor changes on the pyrrolidine ring can be tolerated since the good fit of the ring with the hydrophobic S1 pocket is very important for high affinity.

Some trials have been made, e.g. by replacing the pyrrolidinewith a thiazoline. That led to improved potency but also loss of chemical stability.

Efforts to improve chemical stability often led to loss of specificity because of interactions with DPP-8 and DPP-9. These interactions have been connected with increased toxicity and mortality in animals.

There are strict limitations in the P1 position and hardly any changes are tolerated, on the other hand a variety of changes can be made in the P2 position.

In fact, substitution with quite big branched side chains, e.g. *tert*-butylglycin, normally increased activity and chemical stability, which could lead to longer-lasting inhibition of the DPP-4 enzyme.

It has also been noted that biaryl-based side-chains can also give highly active inhibitors.

It was originally believed that only lipophilic substitution would be tolerated. Now it is stated that also the substitution of polar negatively charged side-chains as well as hydrophilic substitution can lead to excellent inhibitory activity.

Vildagliptin: The adamantyl group worked as a steric bulk and slowed intramolecular cyclisation while increasing chemical stability. Furthermore, the primary metabolites were highly active. To avoid additional chiral centre a hydroxylation at the adamantyl ring was carried. The product, vildagliptin, was even more stable, undergoing intramolecular cyclisation 30-times slower and having high DPP-4 inhibitory activity and longer-lasting pharmacodynamic effect.

Saxagliptin-Researchers at Bristol-Myers Squibb found that increased steric bulk of the N-terminal amino acidside-chain led to increased stability. To additionally increase stability the *trans*-rotamer was stabilized with a *cis*-4,5-methano substitution of the pyrrolidine ring, resulting in an intramolecularvan-der-Waals interaction, thus preventing intramolecular cyclisation.[7]

5. Pharmacodynamics

In sitagliptin given in a range of doses, dose-dependent inhibition of DPP-4 activity occurred. The difference in inhibition, was more than 80% for 100 mg over a 24-hour period. In patients with type-2 diabetes, similar results were noted with 80% inhibition of plasma DPP-4 activity 24 hours after oral administration as well as up to a two-fold increase in GLP-1 levels. Similarly, diabetic patients, plasma DPP-4 levels were inhibited by 50% for saxagliptin 2.5 mg. Postprandial GLP-1 levels were increased 1.5-fold to three-fold, compared with placebo. A meta-analysis comparing the efficacy of sitagliptin versus vildagliptin showed that the overall HbA1c reduction was ~0.74% and 0.73%, respectively. The glycaemic outcomes were better if the initial HbA1c was higher >9% versus <8%. 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 hypoglycaemia.[8]

6. Pharmacokinetics

Table 3: Pharmecokinetics Dpp4 Inhibitors.

	Chemistry	Metabolism	Elimination route
Sitagliptin (US, FDA approved)	Non-peptidomimetic (β-amino acid-based)	Not appreciably metabolized	Renal (~80% unchanged as parent)
Vildagliptin (EU, approved)	Peptide-like	Hepatically hydrolyzed to inactive metabolite	Renal (22% as parent, 55% as metabolite)
Alogliptin (Japan, approved)	Non-peptidomimetic (modified pyrimidinedione)	Not appreciably metabolized	Renal (>70% unchanged as parent)
Saxagliptin (US FDA approved)	Peptide-like	Some metabolism to active metabolite	Renal (12-29% as parent, 21-52% as metabolite)
Linagliptin (US, FDA approved)	Non-peptidomimetic (xanthine)	Not appreciably metabolized	Biliary (unchanged as parent); <6% via kidney

Pharmacokinetic profile of DPP-4 inhibitors/gliptins.

Available DPP-4 inhibitors have been studied to determine parameters of absorption, distribution, metabolism and excretion.

6.1. Absorption

A study of oral and IV administration of sitagliptin in healthy volunteers demonstrated 87% bioavailability of the oral dose.

6.2. Distribution

The distribution of sitagliptin and saxagliptin generally depends on a variety of factors, such as plasma protein binding. Both drugs demonstrate low binding to proteins in the serum. Disease states that may alter levels of proteins, therefore, are not expected to lead to wide variations in disposition of these agents.

6.3. Metabolism

Sitagliptin and saxagliptin differ in the transformation of their original biochemical structures. After ingestion of radiolabeled sitagliptin, approximately 87% was excreted as unchanged drug. Metabolites were detected in low levels, although these are not expected to add to the DPP-4 inhibitory action of sitagliptin. Saxagliptin, however, has a metabolite that retains 50% of the activity of the original compound. Metabolism is mediated primarily by the cytochrome P450 (CYP 450) 3A4/5 system; therefore, inhibitors and inducers of this system are expected to affect the concentration of saxagliptin.

6.4. Excretion

Renal and hepatic pathways are involved in the elimination of oral doses of sitagliptin and saxagliptin. After administration of oral carbon 14–labeledsitagliptin, approximately 13% was recovered in the faeces and 87% was recovered in the urine. After administration of carbon 14–labeledsitagliptin, percentages of the drug excreted in the urine, as unchanged drug and active metabolites, were 24% and 36%, respectively. Of the administered radioactivity, 22% of saxagliptin was recovered in the faeces. Active tubular secretion is involved in the elimination of both agents. The terminal half-life of sitagliptin is approximately 12.4 hours, compared with 2.5 hours for saxagliptin and 3.1 hours for its metabolite.[9,10]

7. Drug–Drug Interactions

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-hypertensive, anti-hyperlipidemics, antibiotics, digoxin, warfarin, etc. 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 Post-marketing surveillance has identified isolated rare cases of pancreatitis with use of DPP-4 inhibitors.[11]

8. Contraindication

- The dipeptidyl peptidase-4 (DPP-4) inhibitors are contraindicated with hypersensitivity to the individual agents or any components of the formulations.
- DPP-4 inhibitor fixed-dose combination products that contain metformin are also contraindicated with renal impairment and acute or chronic metabolic acidosis. Sitagliptin/simvastatin is also contraindicated with concomitant administration of strong cytochrome P450 3A4 inhibitors, gemfibrozil, cyclosporine, or danazol; active liver disease; pregnancy; and nursing
- The concurrent use of a DPP-4 inhibitor and an insulin secretagogue (e.g., sulfonylurea) may increase the risk of hypoglycaemia; therefore, blood glucose should be monitored closely and a dosage reduction of the insulin secretagouges may be required. should be initiated.

- Patients should be warned against excessive alcohol intake while receiving metformin-containing products. Lactic acidosis is a serious, metabolic complication that can occur due to metformin accumulation during treatment with all of the metformin-containing DPP-4 inhibitor fixed-dose combination products.[12]

9- Adverse Effects

There have been numerous individual trials and 3 large meta-analyses to examine the safety and tolerability of the DPP-4 inhibitors as a class.

- ✓ HYPOGLYCEAMIA-
- ✓ UPPER RESPIRATORY TRACT INFECTION-
- ✓ URINARY TRACT INFECTION-
- ✓ HYPERSENSITIVITY REACTION-
- ✓ HEPATIC DYSFUNCTION-
- ✓ ACUTE PANCREATITIS-
- ✓ CARDIOVASCULAR RISK.[13]

10. Drugs of Gliptin Series Available In Market

10.1. Sitagliptin

Tablets contain sitagliptin phosphate, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

Sitagliptin phosphate monohydrate is described chemically as

- **Iupac Name** -7-[(3R)-3-amino-1-oxo-4-(2,4,5trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate.
- **Empirical Formula**- $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$
- **Molecular Wieght**- 523.32.
- **The Structural Formula is**

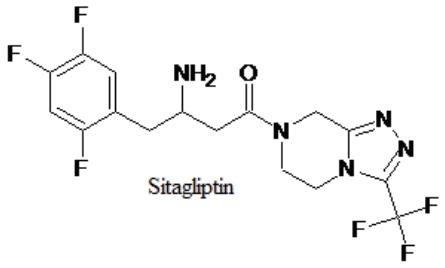


Figure 8: Structure of Sitagliptin.

- **Physical Properties**

Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N, N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

- **Brand Name**- JANUVIA
- **Pharmokinetics**

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.

- **Side Effects**

When used in combination with a sulfonylurea, hypoglycaemias occurred in 12.2% of patients, but no severe events were reported Gastrointestinal events rarely occur. Headaches (incidence of 1.8% to 5.7%), nasopharyngitis (2.9% to 9.1%) and upper respiratory tract infection (0% to 8.8%) have been reported.

- **Doses and Indication**

Sitagliptin is available commercially in 25-mg, 50-mg and 100-mg tablets. It is indicated for mono- or combination therapeutic management of hyperglycaemia in patients with type 2 diabetes. In patients with normal renal function, it is dosed at 100 mg daily; the dose is 25 mg daily. It can be taken with or without food.[14]

10.2. Vildagliptin

It is chemically,

- **Iupac Name**- (NVP-LAF237/(2S)-{[(3-hydroxyadamantan-1-yl)amino]acetyl}-pyrrolidine-2-carbonitrile)
- **Molecular Formula**- $C_{17}H_{25}N_3O_2$
- **Molecular Weight**-303.40
- **Structure**

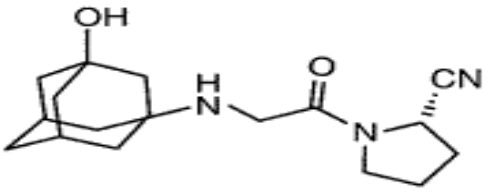


Figure 9: Structure of Vildagliptin.

Vildagliptin (Galvus) was first synthesized in May 1998 and was named after Edwin B. Villhauer.

It was discovered when researchers at Novartis examined adamantylderivatives that had proven to be very potent. This is the second gliptin to be approved for commercial use although still not US FDA approved.

- **Pharmokinetics**- 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).
- **Brand Name**- GALVUS
- **Recommended Dose-** VILDAGLIPTIN 50 mg twice a day.
- **Dose for Renal Impairement**- 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.[15]

10.3- Saxagliptin

- **Iupac Name**- (1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo[3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate.
- **Empirical Formula**- C18H25N3O2•H2O
- **Molecular Weight**- 333.43:
- **The Structural Formula Is**

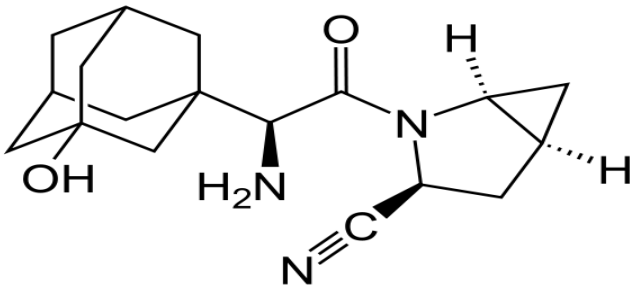


Figure 10: Structure of Saxagliptin.

- **Recommended Dosing**

The recommended dose of is 2.5 mg or 5 mg once daily taken regardless of meals.

- **Brand Name-Onglyza**
- **Physical Properties**

Saxagliptin monohydrate is a white to light yellow or light brown, non-hygroscopic, crystalline powder. It is sparingly soluble in water at 24°C ± 3°C, slightly soluble in ethyl acetate and soluble in methanol, ethanol, isopropyl alcohol, acetonitrile, acetone and polyethylene glycol 400 (PEG 400).

- **Dose With Renal Impairment**

No dosage adjustment for ONGLYZA is recommended for patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min).

The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment.

This is the third gliptin to be approved for commercial use, and US FDA approved.

- **Pharmacokinetics**

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 faeces, mainly as metabolites.

- **Side Effects**

Headache, painful, burning urination, stomachpain, nausea, vomiting, diarrhea, bloating.[16]

10.4- Linagliptin

TRADJENTA (linagliptin) tablets contain, as the active ingredient, an orally-active inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.

- **Chemical Name** - 1H-Purine-2,6-dione, 8-[(3R)-3-amino-l-piperidinyl]-7-(2-butyn-l-yl)-3,7-dihydro-3-methyl-l-[(4-methyl-2-quinazolinyl)methyl]-
- **Empirical Formula**- $C_{25}H_{28}N_8O_2$
- **Molecular Weight** is 472.54 g/mol.
- **Structural Formula**

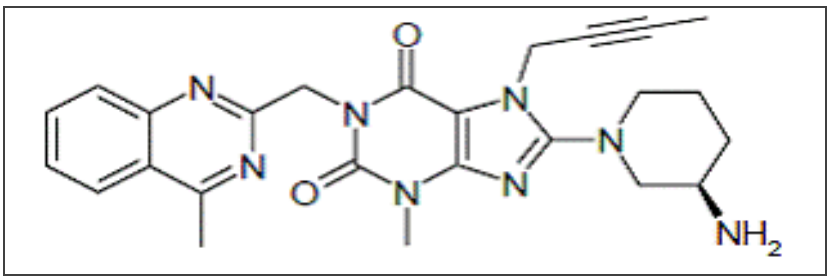


Figure 11: Structure of Linagliptin.

- **Physical Properties**

Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water (0.9 mg/mL). Linagliptin is soluble in methanol (ca. 60 mg/mL), sparingly soluble in ethanol (ca. 10 mg/mL), very slightly soluble in isopropanol (< 1 mg/mL) and very slightly soluble in acetone (ca. 1 mg/mL).

- **Brand Name**- Tradjenta tablets
- **Recommended Dose** -5 mg once a day.
- **Pharmacokinetic**- It has a favourable 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 faeces and only 5% eliminated via the urine.
- **Side Effects**- Low blood sugar levels (when used with a sulphonylurea such as glibenclamide and metformin), Cough (frequency unknown if taken in combination with

a sulphonylurea such as glibenclamide and metformin), Inflammation of the nose and throat, causing a blocked or runny nose and sore throat (nasopharyngitis). Inflammation of the pancreas (pancreatitis).

- **Contraindication-** Certain medicines should not be used during pregnancy or breastfeeding. However, other medicines may be safely used in pregnancy or breastfeeding providing the benefits to the mother outweigh the risks to the unborn baby.

- The following medicines may increase the breakdown of linagliptin and so could reduce its effect at controlling blood sugar:
- carbamazepine
- Phenobarbital
- Rifampicin.[17]

10.5- Alogliptin

- **Molecular Formula: $C_{18}H_{21}N_5O_2$**
- **Molecular Mass**: 339.169525
- **Chemical Name**

2-({6-[(3R)-3-Amino-1-piperidinyl]-3-methyl-2,4-dioxo-3,4-dihydro-1(2H)-pyrimidinyl}methyl)benzonitrile

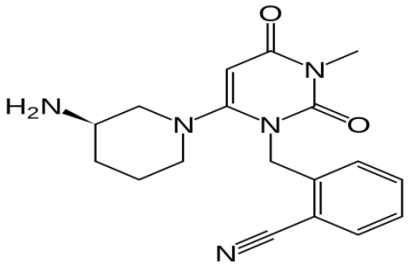


Figure 12: Structure of Alogliptin.

- Alogliptin is a Dipeptidyl peptidase-4 inhibitor that is approved in Japan for the treatment of adult patients with T2DM.
- **Recommended Dose-** of 25 mg once a day.
- **Pharmokinetics**- 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.

- **Brand Name-** Nesina, KAZANO
- In 2013 the FDA approved the drug in three formulations: As a stand-alone with the brand-name Nesina. Combined with metformin using the name Kazano and when combined with pioglitazone as Oseni.
- On January 25, the FDA announced approval of 3 drugs —*Nesina* (alogliptin) tablets, the fixed-dose combinations *Kazano* (alogliptin and metformin hydrochloride) tablets, and *Oseni* (alogliptin and pioglitazone) tablets for use with diet and exercise to improve blood glucose control in adults with type 2 diabetes. All 3 are manufactured by Takeda Pharmaceuticals America, Inc.[18]

11-As "Add on Therapy of Gliptin''

11.1- Biguanides

From the Biguanides metformin is drug usually used with dpp4 inhibitors combination therapy. 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.[19]

11.2-Sulfonylurea- 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 hypoglycaemia.

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, Glimepride, gliclazide) with the added advantage of being weight neutral and being virtually free of hypoglycaemia.

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%.[20]

11.3- Thiazolidinediones

The addition of a gliptin to TZD therapy in patients inadequately controlled has 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 oedema. The weight gain can however be dealt with a comprehensive lifestyle-weight-management program.[21]

11.4- 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 glycaemia is because of improvement in beta-cell health and suppression of glucagon predominantly.[22]

Table 4: Dosage Form, Trade Name and Strenght of Combination.

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength
Linagliptin/ metformin (Jentadueto®)	Adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes*	Tablet: 2.5/500 mg 2.5/850 mg 2.5/1,000 mg
Saxagliptin/ metformin (Kombiglyze XR®)	Adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes†	Tablet (saxagliptin/metformin ER): 5/500 mg -2.5/1,000 mg 5/1,000 mg -
Sitagliptin/ metformin (Janumet®, Janumet XR®)	Adjunct to diet and exercise to improve glycaemic control in adults with type 2 diabetes‡	Tablet (sitagliptin/metformin IR): 50/500 mg 50/1,000 mg Tablet (sitagliptin/metformin ER): 50/500 mg 50/1,000 mg 100/1,000 mg
Sitagliptin/ simvastatin (Juvisync®)	Patients for whom treatment with both sitagliptin and simvastatin is appropriate§	Tablet: 100/10 mg 100/20 mg 100/40 mg

Therapy

ER=extended-release, IR=immediate-release

*When treatment with both linagliptin and metformin is appropriate.

†When treatment with both saxagliptin and metformin is appropriate.

‡When treatment with both sitagliptin and metformin or metformin extended-release is appropriate.[23]

12- Gliptin Drugs Under Development

Table 5: Drugs Under Development.

INHIBITORS	NAME	COMPANY	CLINICAL PHASE	TYPE OF ACTION
R1438	Aminomethylpyridine	Roche	2	Reversible inhibitors
Nvpdpp728	?	Novartis	2	Covalently bonded
Psn9301	Isoluecinthiazolidin	Prosidion	3	Reversible inhibitors
P32/98	Denagliptin	Probiodrug	3	Reversible inhibitors
Gsk823093c	?	Glaxo Smith Kline	3	Reversible inhibitors
nn-7201	?	Novo Nordisk	1	Covalently bonded
Als 2-0426	?	Alantos	1	Reversible inhibitors

'?' = NOT REPORTED.

13- CONCLUSION

Gliptins have revolutionized the concept of diabetes management and have provided a breath of fresh air to healthcare professionals dealing with diabetes. They provide an effective and safe alternative to the management of diabetes. Shown to reduced HbA1c from 0.5 to up to 2% effectively and safely (weight neutral without any if at all hypoglycaemias) this new class of drugs is here to stay. Even major diabetes management guidelines have acknowledged them for their safe adverse effect profile and urge healthcare professionals to use gliptins should they be struggling with regards weight or hypoglycaemias with their patients. Although sitagliptin and saxagliptin are both approved as adjunctive therapies to diet and exercise in type-2 diabetes, current data suggest that metformin or a sulfonylurea is generally necessary as a first-line treatment for significantly lowering blood glucose levels. The potential benefits of DPP-4 inhibitors include their complementary mechanism of action with other antidiabetic medications, a favourable adverse-effect profile and a neutral effect on weight. With a low risk of hypoglycaemia, sitagliptin and saxagliptin are advantageous for patients who are close to their target HbA1c but who continually experience elevated glucose levels after meals. As to the advantages of selecting one DPP-4 inhibitor over another, comparative clinical data are unavailable. DPP-4 inhibitors are a new class of agents that improve long-term, 24-hour control of HbA_{1c}, FPG (before meal) levels, and PPG (after meal) levels through decreased DPP-4–mediated degradation of incretin hormones. DPP-4 inhibitors provide a complementary mechanism of action to existing OADs and including a low risk for hypoglycemia and weight neutrality. DPP-4 inhibitors have been studied in a broad range of patients and have demonstrated similar efficacy, regardless of age, gender, or race/ethnicity. These agents offer an important addition to the treatment of patients with T2D by providing another mechanism to address the multiple pathophysiologic defects present in this disease.

13- REFERENCE

1. Nancy Bohannon, Md1, 1monteagle Medical Center, San, Overview Of The Gliptin Class (Dipeptidylpeptidase-4 Inhibitors) In Clinical Practice, Studied By Francisco, Postgraduate Medicine, January 2009; 121(1). Issn – 0032-5481, E-Issn – 1941-9260.
2. Galina Smushkin, Adrian Vella; Inhibition Of Dipeptidyl Peptidase-, The Mechanisms Of Action And Clinical Use Vildagliptin For The Management Of Type 2 Diabetes,; Division Of Endocrinology, Diabetes, Metabolism And Nutrition, Mayo Clinic College

Of Medicine, Rochester, Mn, Usa, Diabetes Metabolic Syndrome And Obesity: Targets And Therapy.

3. Diabetes, Metabolism And Nutrition, Mayo Clinic, Rochester, Minnesota, Jcem. Endojournals. Org, J Clin Endocrinol Metab, August 2012; 97(8): 2626–2628. issn, Issn Online 1945-7197 2012. Page No. 281.
4. S Leo Thomas, Matthias Eckhardt, Elke Langkopf, Moh Tadayyon, Frank Himmelsbach, And Michael Mark; Dipeptidyl Peptidase-4 Inhibitorsis Studied By Departments Of Metabolic Diseases Research (L.T., M.T., M.M.) And Chemical Research (M.E., E.L., F.H.), Boehringer, Ingelheim Pharma Gmbh & Co. Kg, From The Journal Of Pharmacology And Experimental Therapeutics Vol. 325, No. 1, By The American Society For Pharmacology And Experimental Therapeutics, 135723.
5. Gaba Monika, Singh Sarbjot, Gaba Punam, John R; Dipeptidyl Peptidase-4 Inhibitors: A Newapproach In Diabetes Treatment, Dipeptidyl Peptidase-Iv Inhibitors, Pharmacological Profile And Clinical Use, Is Studied Form International Journal Of Drug Deve Lopment And Research received, 1(1): 146.
6. Dipeptidyl Peptidase-4 Inhibition In The Management Of Type 2 Diabetes A Report By Edoardo Mannucci Co-Ordinator Of The Diabetes Outpatient Clinic, Geriatric Unit, Careggi Teaching Hospital, University Of Florence Medical School From, Journal Touch Briefings 2007, European Endocrine Disease.
7. Jay Shubrook1, Randall Colucci1, Aili Guo2 And Frank Schwartz2, Saxagliptin: A Selective Dpp-4 Inhibitor For The Treatment Of Type 2 Diabetes Mellitus, Studied By, Department Of Family Medicine, Ohio University College Of Osteopathic Medicine (Ou-Com), From Journal Clinical Medicine Insights: Endocrinology And Diabetes, 2011; 4: 1–12. Http://Www.La-Press.Com.
8. By Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch C, Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors For Type 2 Diabetes Mellitus (Review), Studied This Is A Reprint Of A Cochrane Review, Prepared And Maintained By The Cochrane Collaboration And Published In The Cochrane Library 2009, Issue 3, Http://Www.Thecochranelibrary.Com
9. Http://Formularyjournal.Modernmedicine.Com/News/Dpp-Iv-Inhibitors-Review-Sitagliptin-Vildagliptin-Alogliptin-And-Saxagliptin, Studied By Pamela Kushner, Ma, Md, Faafp, From Journal Dpp-4 Inhibitors In Type 2 Diabetes: Importance Of Selective Enzyme Inhibition And Implication For Clinical Use, 2010; 59: 02.
10. By A. D. Dobrian, 1 Q. Ma, 2 J. W. Lindsay, 1 K. A. Leone, 2 K. Ma, 2 J. Coben, 1 E. V. Galkina, 3 And J. L. Nadler 2, Dipeptidyl Peptidase Iv Inhibitor Sitagliptin Reduces

Local Inflammation In Adipose Tissue And In Pancreatic Islets Of Obese Mice, Studied Departments Of 1physiological Sciences, 2internal Medicine, And 3microbiology And Molecular Cell Biology, Eastern Virginia, Medical School, Norfolk, Virginia 0193-1849/11 From Journal Of The American Physiological Society Http://Www.Ajpendo.Org.

11. Inger Brandt A, Jurgen Joossens B, Xin Chen C, Marie-Berthe Maes A, Simon Scharpe´ A, Ingrid De Meester A, Anne-Marie Lambeir I. Brandt Et Al., Inhibition Of Dipeptidyl-Peptidase Iv Catalyzed Peptide Truncation Byvildagliptin ((2s)-{[(3-Hydroxyadamantan-1-Yl)Amino]Acetyl}-Pyrrolidine-2-Carbonitrile) Is Studied By / From Journal Biochemical Pharmacology, 2005; 70: 134–143.
12. Qaseem A, Humphrey Ll, Sweet De, Starkey M, Shekelle P, Therapeutic Class Overview, Dipeptidyl Peptidase-4 (Dpp-4) Inhibitors Is Studied By; Clinical Guidelines Committee Of The American College Of Physicians. Oral Pharmacologic Treatment Of Type 2 Diabetes Mellitus: A Clinical Practice Guideline From The American College Of Physicians. Ann Intern Med., 2012; 156: 218-31.
13. Dpp-4 Inhibition And Islet Function, Is Studied By Ahrén* 2011 Asian Association For The Study Of Diabetes And Blackwell Publishing Asia Pty Ltd From Journal Of Diabetes Investigation Volume 3 Issue 1 February 2012, Cobble M. Dpp-4 Inhibitors: A New Therapeutic Class For The Treatment Of Type 2 Diabetes. J Fam A New Therapy Of Type 2.
14. Diabetes: Dpp-4 Inhibitors, Tatjana Ábel, National Health C0enter, Hungarypract. 2009; 58(10).
15. Http//Www.Jfponline.Com/Supplements_Cme.Asp?Id=8068. Accessed January 15, 2010.
16. Www.Intechopen.Com.
17. Australian Public Assessment Report For Saxagliptin Hydrochloride Proprietary Product Name: Onglyza Submission No: Pm-2008-03469-3-5 Sponsor: Bristol-Myers Squibb Australia Pty Ltd, April 2011 onglyza Saxagliptin Bristol-Myers Squibb Australia Pty Ltd Pm-2008-03469-3-5 Final 13 April 2011 Page 2 Of 130, Onglyza Saxagliptin Bristol-Myers Squibb Australia Pty Ltd Pm-2008-03469-3-5 Final 13 April 2011.
18. Tesfaye Biftu, Rational Design Of A Novel, Potent, And Orally Bioavailable Cyclohexylamine Dpp-4 Inhibitor By Application Of Molecular Modeling And X-Ray Crystallography Of Sitagliptin Is Studied By, From Journal Of Usa, Department Of Metabolic Disorders, Merck Research.

19. Jaime A. Davidson, Md, Clinical Professor Of Internal Medicine, Division Of Endocrinology, University Of Texas Southwestern Medical School, Dallas, Tx, Advances In Therapy For Type 2 Diabetes:Glp–1 Receptor Agonists And Dpp–4 Inhibitorss 28 Cleveland Clinic Journal Of Medicine Volume 76 • Supplement 5 December 200.
20. Japanese Clinical Medicine C As E R E Port, Japanese Clinical Medicine 2012: 3 1, Combination Therapy With A Dipeptidyl Peptidase-4 Inhibitor, Sulfonylurea And Metformin Markedly Improves Hba1c Levels, In Japanese Patients With Type 2 Diabetes Mellitus, Koichi Hirao1, Hajime Maeda1, Shin-Ichiro Shirabe1, Ritsuko Yamamoto1, Tetsuyuki Hirao1, Setsuko Hirao1, Mikio Yamauchi1 And Keiko Arai1, 21hec Science Clinic, 2arai Clinic, Yokohama, Japan.
21. Assessing The Binding Affinity Of A Selected Class Of Dpp4 Inhibitors Using Chemical Descriptor-Based Multiple Linear Regression Studied By Jose Isagani B. Janairo*A,D, Gerardo C. Janairob, D, Frumencio F. Coc And Derrick Ethelbhert C. Yu*B,D Physics Department, De La Salle University, 2401 Taft Avenue, Manila, Philippines Bchemistry Department, De La Salle University, 2401 Taft Avenue, Manila, Philippines Cmathematics Department, De La Salle University, 2401 Taft Avenue, Manila, Philippines Dmaterials Science And Nanotechnology Unit, Center For Natural Sciences And Environmental Research (Censer), De La Salle University, 2401 Taft Avenue, Manila, Philippines From Orbital Elec. J. Chem., Campo Grande, 2011; 3(1): 1-23 janairo Et Al. Vol 3 □ □ No. 1 □ □ January-March 2011.
22. Www.Drugs.Com/Monograph/Sitagliptinphosphate, Ahfs Drug Information, American Society Of Health-System Pharmacist, Dpp4 Inhibotors Benjamin J. Lamont, Bsc, Phd Daniel J, From Journal Of Orbital Chemistry, Md Www.Medscape.Org.Com, From.
23. Therapy For T2d:Riskc And Benefits With Long Acting Glp-1 Agonist, Medscape Today News & Prospective Business Of Medicine, Drug Interaction Checker Health Care Directory, Medline/Www,Medline.Com.
24. Ingenta Connect Pharmacology Of Dpp4 Innhibitors: Similarity And Differences, Studied By Baetta, Roberta; Corsini, Aiberto; From Journal Drugs, Volume 71,Pp.1441-1467(27), Adis International/Www.Ingentaconnect.Com.
25. Dpp4 Inhibitors, Studied By Bentham, From The Open Medicinal Chemistry Journal, Pubmed Central, Table 5a: Open Med Chem J., 2011; 5: 82-92 Published Online 2011 September 9.
26. Gliptins: Dpp-4 Inhibitors To Treat Type 2 Diabetes, Is Studied By Brian Green, Bsc (Hons), Phd, Cbiol Mibiol, Lecturer In Nutritional Biochemistry And Physiology, Queens

University, Belfast, Peter Flatt, Bsc (Hons), Phd, Frsc, Fbiol, Professor Of Biomedical Sciences And Head Of The Diabetes Research Group, University Of Ulster, Coleraine.