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Review on Drugs used in treatment of Diabetes Mellitus

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ABSTRACT: -

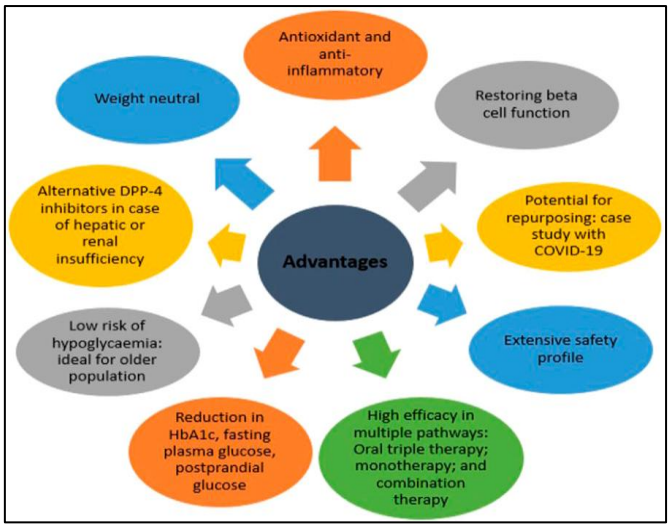
Significant advancements have been made in the treatment of diabetes in recent years. Diabetic patients are now receiving more attention to manage their risk factors overall rather than just blood glucose control, with individual blood glucose goals being adjusted. Additionally, new anti-diabetic medications that have undergone cardiovascular safety testing must be approved by regulators. Thus, it has been demonstrated that the newest class of medications, which includes some glucagon like peptide 1 receptor (GLP1) analog and sodium-glucose transporter 2 (SGLT2), reduces major adverse cardiovascular events. They therefore hold a significant position in the hyperglycemia treatment algorithms. The function of DPP4 inhibitors, or DPP4i, has changed in recent years. DPP4i do not result in hypoglycemia or weight gain, have a good safety profile, an anti-inflammatory profile, and do not need dose escalation. It can also be used with older diabetic patients and patients with certain forms of chronic kidney disease. Overall, there is substantial experience with the use of DPP4i, a class of safe oral hypoglycemic agents, in the management of diabetic patients.

Keywords:- DPP-4, Diabetes Mellitus, Hyperglycemia.

Introduction: -

Membrane glycoprotein Dipeptidyl-peptidase-4 (DPP4, or CD26) is well-known for its catalytic role in the breakdown of incretins. The antidiabetic drug class known as DPP4 inhibitors (DPP4i) has gained global acceptance due to its mild effects on HbA1c, lack of serious side effects, and ease of administration. The cardioprotective effects of DPP4 inhibition in experimental models have been consistently demonstrated. It is widely expected that these drugs will demonstrate a benefit in suitably designed efficacy trials from a cardiovascular (CV) standpoint because early meta-analyses of phase II/III data of DPP4i used in the context of glycemia lowering showed favorable protective effects of this class in terms of CV endpoints. Nevertheless, recently concluded phase III trials that were carefully planned and intended to demonstrate benefit from a cardiovascular standpoint have not demonstrated a statistically significant improvement in primary CV endpoints in patients treated with DPP4i when compared to placebo. We will provide an overview of DPP4's composition, functions, and recognized physiological roles in this review. Additionally, we will discuss its significance in the pathophysiology of cardiometabolic disorders and present data from recent clinical trials evaluating its effects.

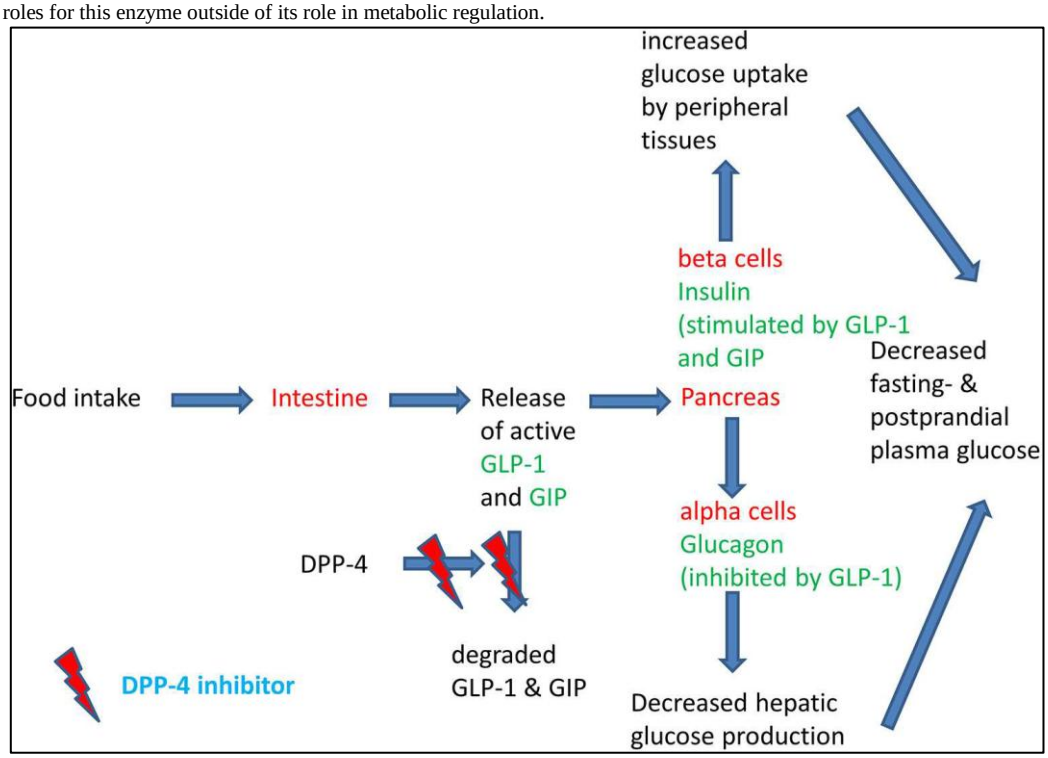
Advantages: -



Mechanism of action: -

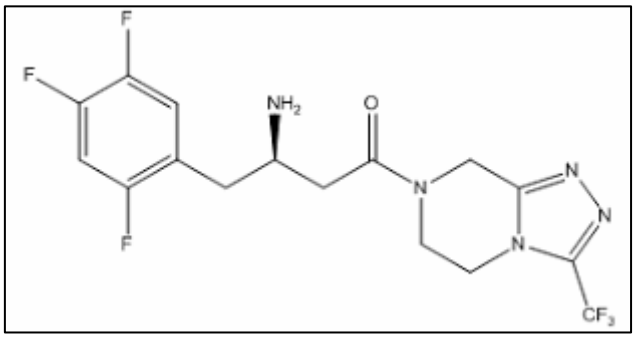
The physiological function of DPP-4 in controlling the incretin hormones GLP-1 and GIP is well-established. Animals with DPP-4 genetic deficiencies or those treated pharmacologically with DPP-4 inhibitors showed enhanced glucose tolerance, increased GIP, and improved active GLP-1. Moreover, DPP-4-deficient mice and rodents and humans treated pharmacologically with inhibitors showed increased insulin and decreased glucagon levels, which is consistent with the function of this enzyme in incretin regulation and metabolic control. In mice lacking both GLP-1 and GIP receptors, DPP-4 inhibitors do not increase glucose tolerance; this suggests that these incretins alone are in charge of the increased glucose tolerance seen in these animals. These findings, when combined, clearly show that these incretins are endogenous substrates for DPP-4.

More peptides than just GLP-1 and GIP have been linked to this enzyme's regulation: pituitary adenylate cyclase-activating polypeptide (PACAP), gastrin-releasing peptide (GRP), glucagon-like peptide 2 (GLP-2), growth-hormone-releasing hormone (GHRH), and PACAP. This enzyme also has a number of neuropeptides and chemokines as in vitro substrates. It is challenging to ascertain whether DPP-4 regulates these peptides in vivo, even though many of them cleave effectively in vitro. This is primarily due to the lack of adequate assays for measuring the endogenous levels of the putative substrates and products. To gain a thorough understanding of this enzyme's biology, more work will be needed. Since DPP-4-deficient mice are robust and able to procreate, if additional This enzyme controls the production of proteins and/or peptides; it has no discernible negative effects on development, reproduction, or overall health. Clinical research findings also show that selective DPP-4 inhibitors are well tolerated and do not point to any additional roles for this enzyme outside of its role in metabolic regulation.



DPP4 inhibitors: -

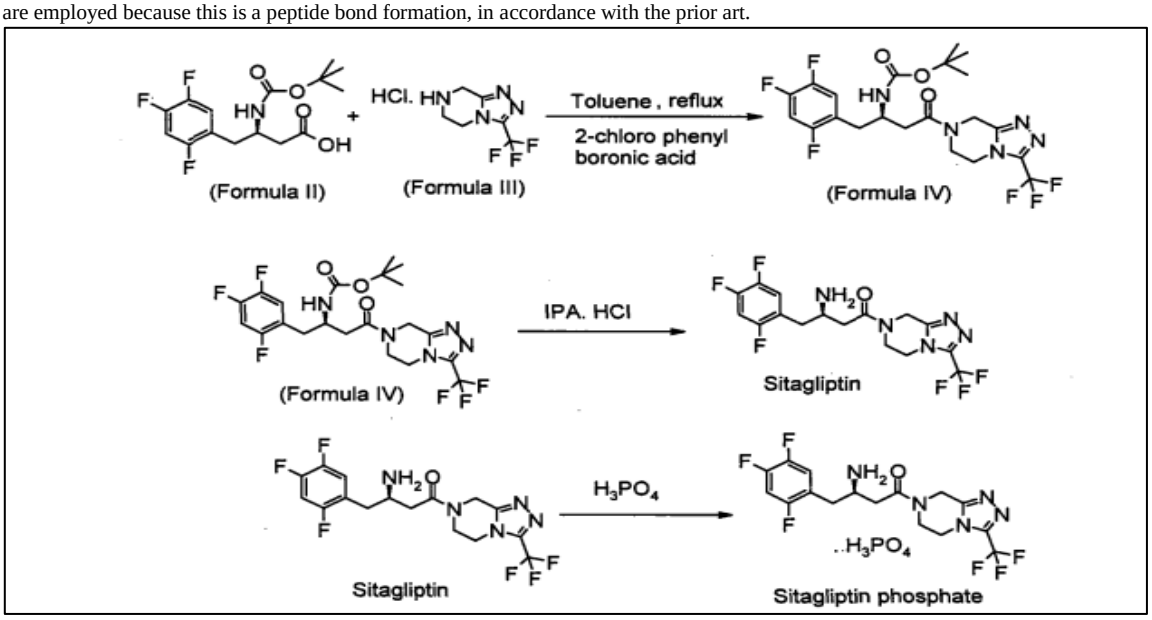
Sitagliptin: -



The first DPP4i to be approved for sale was sitagliptin. The drug sitagliptin has a renal clearance rate of 350 mL/min and an apparent terminal elimination half-life of 12.4 hours. After a single 100 mg dosage, sitagliptin is quickly absorbed orally in healthy adult volunteers, reaching peak plasma concentration 14 hours later. Sitagliptin's pharmacokinetic properties in people with type 2 diabetes are largely comparable to those of healthy

volunteers. Previous findings indicated that the majority of sitagliptin's excretion was via the kidneys, with the renal clearance rate accounting for roughly 70% of the drug's plasma clearance rate in healthy individuals. Food has no effect on the oral absorption of sitagliptin, which has an absolute bioavailability of 87%. Medications can be taken with or without food.

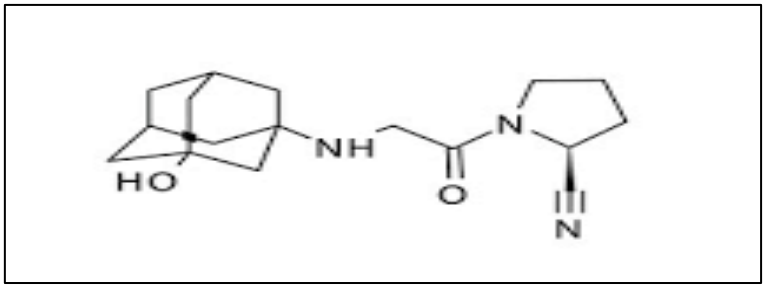
Synthesis: The condensation of an amino acid derivative with the triazolo pyrazine compound is a crucial step in the synthesis of sitagliptin. Standard peptide coupling conditions and reagents are employed because this is a peptide bond formation, in accordance with the prior art. The condensation of an amino acid derivative with the triazolo pyrazine compound is a crucial step in the synthesis of sitagliptin. Standard peptide coupling conditions and reagents are employed because this is a peptide bond formation, in accordance with the prior art.



Marketed formulations

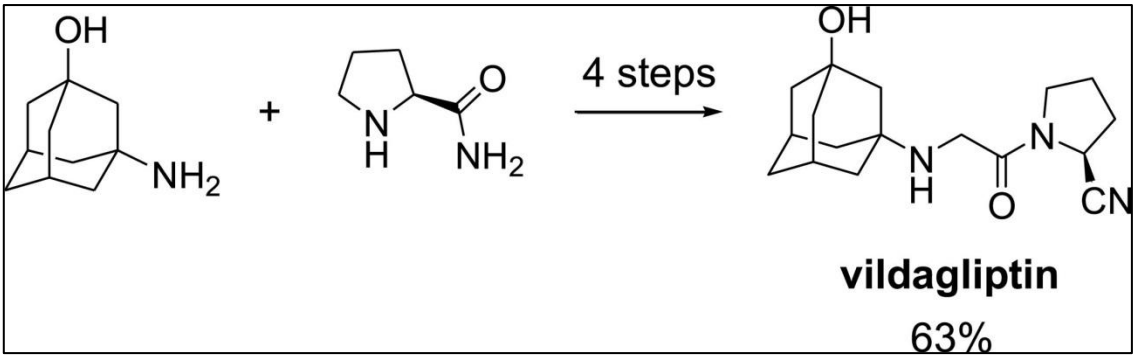
- Sitagliptin systemic
- Brand names: Januvia, Zituvio
- Metformin/sitagliptin systemic
- Brand names: Janumet, Janumet XR, Zituvimet
- Simvastatin/sitagliptin systemic
- Brand name: Juvisync

Vidagliptin: -

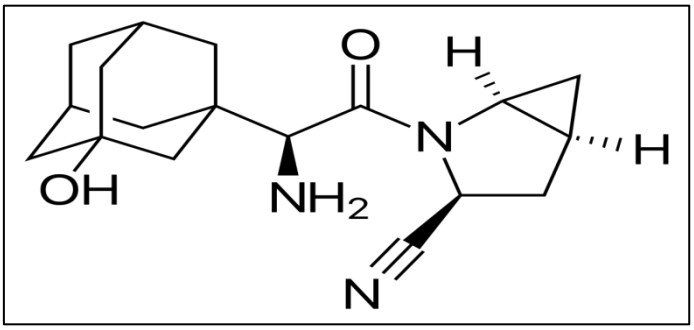


Vildagliptin was the second DPP4i that the European Union authorized. A significant amount of hydrolysis, about 57% of it, results in an inactive molecule (LAY151). The remaining 18% is used as a medication that is active. Because of this, it is taken twice daily and has a shorter half-life (~2 h) than sitagliptin). Maternal drugs are primarily eliminated through this metabolism; however, LAY151 is excreted by the kidney and is administered in a way that puts patients with impaired renal function at higher risk of exposure.

Synthesis: Vildagliptin was synthesized in four steps using 3-amino-1-adamantanol, glyoxylic acid, and L-prolinamide, requiring the isolation of just two intermediates. The process yields vildagliptin in an overall yield of 63%, making it competitive with current protocols.

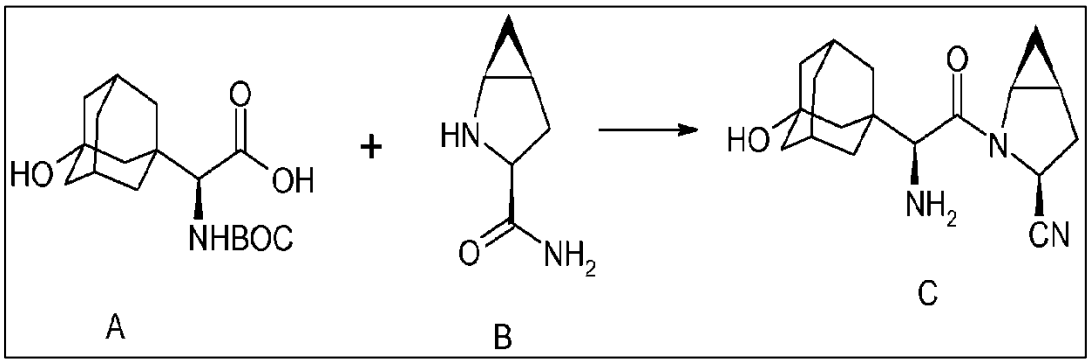


Saxagliptin: -



Saxagliptin is a potent anti-diabetic medication that increases the DPP4 enzyme's inhibitory effect and is metabolized by cytochrome P450 3A4/A5. With a short half-life (4–6 hours), saxagliptin must be dosed more than once daily due to its poor membrane permeability, solubility in water, and usage at a dose of 2.5 mg. The kidneys remove saxagliptin's metabolites, while the liver processes the drug's parent molecules. Since liver damage has little effect on drug exposure, the therapeutic dose does not need to be adjusted; however, in line with DPP4i's elimination in other kidneys, dose reductions are advised when renal function is reduced.

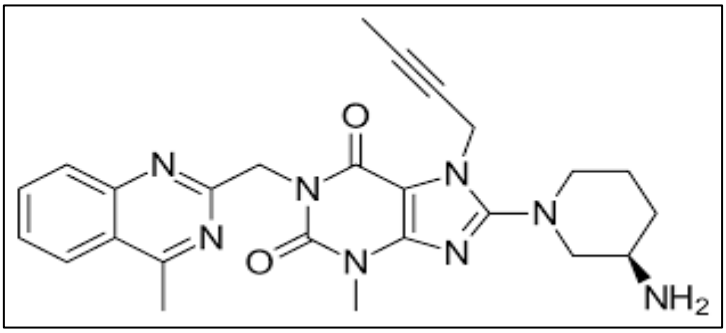
Synthesis:



Marketed formulations

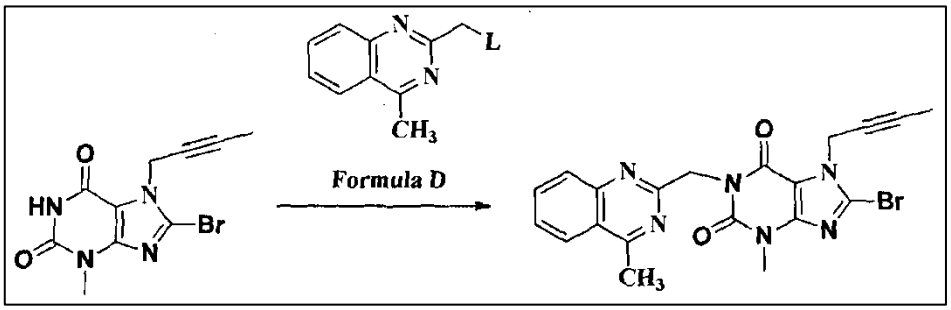
1. **Saxagliptin systemic**
   Brand name: Onglyza
2. **Dapagliflozin/metformin/saxagliptin systemic**
   Brand name: Qternmet XR
3. **Metformin/saxagliptin systemic**
   Brand name: Kombiglyze XR

Linagliptin: -



The most recent drug to enter the market is linagliptin, which is authorized for the glycemic control of type 2 diabetes. Linagliptin has a long half-life (effective half-life of approximately 12 hours, terminal decay of greater than or equal to 100 hours), and its metabolism is not readily apparent. However, in contrast to other DPP4i, the kidney has very little effect on the drug's clearance—less than 6% of the drug is cleared in the kidney; the majority is excreted into Molecules bile and subsequently eliminated in the stools. As a result, linagliptin is unaffected by variations in renal function, and its dosage is not modified in accordance with it. There is no clinically significant change in liver damage to either drug exposure or dose adjustment, despite the fact that it is eliminated by the biliary pathway. The most recent randomized trial found that linagliptin did not significantly increase the risk of major cardiovascular events (CV events) with a median follow-up of 2.2 years, when compared to placebo in patients with type 2 diabetes and high CV risk. In Asian T2DM patients, linagliptin is well tolerated and has a minimal chance of side effects.

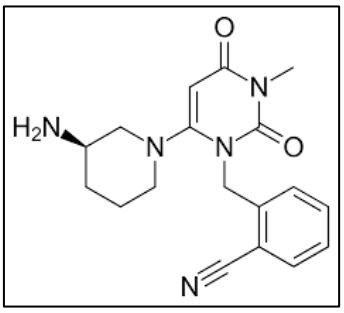
Synthesis:



Marketed formulation

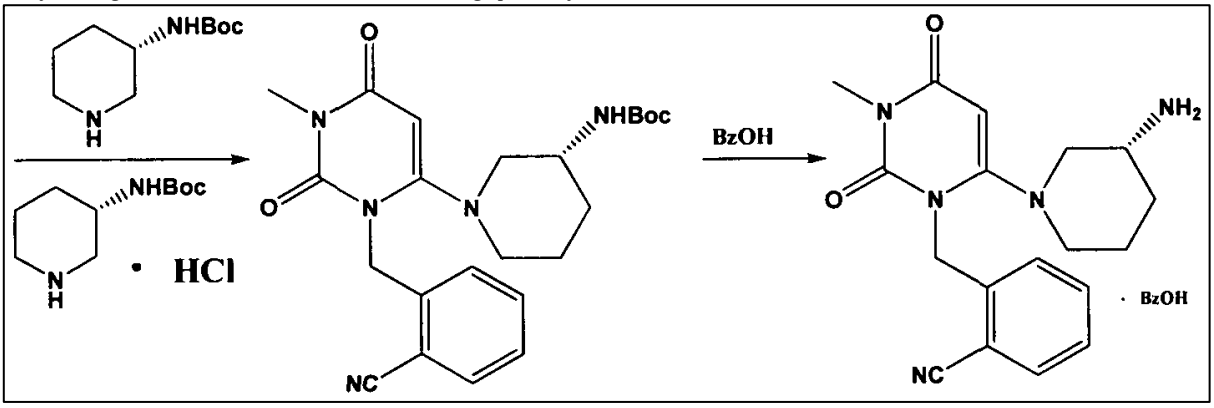
1) **Linagliptin systemic**
   Brand name: Tradjenta
2) **Empagliflozin/linagliptin systemic**
   Brand name: Glyxambi
3) **Empagliflozin/linagliptin/metformin systemic**
   Brand name: Trijardy XR
4) **Linagliptin/metformin systemic**
   Brand names: Jentadueto, Jentadueto XR

Alogliptin: -



Similar to sitagliptin, it has a half-life of roughly 12.4–21.4 hours and no discernible metabolism. Owing to its extended half-life, alogliptin is typically recommended once daily. Since the kidneys' glomerular filtration and active secretion processes are the main ways in which alogliptin is eliminated, it is advised that dosages be lowered in individuals with impaired renal function [74]. When compared to a placebo, alogliptin significantly improved glycemic control in adults or elderly T2DM, either by itself or in combination with metformin, pioglitazone, glyburide, or insulin. The main purpose of alogliptin is to prevent hypoglycemic episodes in elderly and congestive heart failure, kidney, and liver disease patients. Alogliptin is a promising pharmacological treatment for reducing lung toxicity because it protects against cyclophosphamide-induced lung toxicity by reducing oxidation, inflammation, and fibrosis.

Synthesis: This procedure yields the TV-benzyluracil derivative (2) in a 54% yield by alkylating 6-chlorouracil (1) with 2- (bromomethyl)benzonitrile in the presence of NaH and LiBr in a mixture of DMF-DMSO. Compound (2) undergoes additional alkylation in DMF/THF with iodomethane and NaH to yield 72% of the 1,3 disubstituted uracil (3). Alogliptin (4) is produced by replacing chlorouracil (IV) with 3(R)- aminopiperidine dihydrochloride in the presence of either NaHCO3 in heated methanol or K2CO3 in aqueous isopropanol. The corresponding benzoate salt is then isolated by treating ethanol with benzoic acid. This three-stage process yields a total of -20–25%.



Marketed formulations

1) Alogliptin systemic
Brand name: Nesina
2) Alogliptin/metformin systemic
Brand name: Kazano
3) Alogliptin/pioglitazone systemic
Brand name: Oseni

Pharmacological Interactions

Gliptins were frequently prescribed in clinical settings in conjunction with other antihypertensive, antihyperlipidemic, and antidiabetic medications. Consequently, determining whether potentially harmful interactions could exist is crucial. In the coadministration of metformin, glibenclamide, glitazones, and simvastatin, no adverse events (AEs) were reported. With a half maximal inhibitory concentration (IC50) of 18 nM, sitagliptin is the first DPP-4 inhibitor and is currently available as monotherapy or in a fixed dose combination with other antidiabetic agents. It is a competitive and fully reversible DPP-4 inhibitor. Due to the high selectivity, DPP-4 is guaranteed to be targeted, and any unfavorable side effects or potential toxicities from cross-inhibition of other DPP enzymes, like DPP8 or DPP9, are avoided. In healthy individuals, 50 mg of sitagliptin administered once daily reduces DPP-4 activity by about 80% at 12 hours, and 100 mg of sitagliptin administered once daily keeps inhibition at comparable levels for 24 hours. Furthermore, sitagliptin is well tolerated; even at doses six times higher than the suggested oral dose of 100 mg, these levels of inhibition are attained without any overt rise in adverse event reporting or hypoglycemic episodes. An oral glucose tolerance test revealed that a dose of 100 mg once daily achieved approximately 24 hours of mean DPP-4 inhibition of > 80% in T2DM patients. This led to a two-fold increase in active GLP-1 and gastric inhibitory polypeptide levels, which in turn caused a near-maximum drop in plasma glucose.

Pharmacokinetics: -

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

Absorption.

87% of the oral dose of sitagliptin was shown to be bioavailable in a study involving its administration via IV in healthy volunteers. When compared to fasting levels in the same study, eating a high-fat meal had no discernible effect on the agent's bioavailability, maximum plasma concentration (Cmax), or half-life. Studies comparing the plasma area-under-the-curve (AUC) concentrations of saxagliptin and sitagliptin in fed and fasted states have shown that taking the medications with a meal increases their concentrations by 20% and 27%, respectively.7,8 Both medications can be taken with or without

food because there isn't a statistically significant increase when taken with a high-fat meal.7,9 The 100 mg dose of sitagliptin reaches its peak plasma levels one to four hours after oral administration. After taking five milligrams, saxagliptin reaches its peak levels two hours later, while its active metabolite peaks four hours later. According to reviews of the pharmacokinetics of these agents at different dosages, there was a dose-proportional increase in the Cmax and AUC concentration.

1) **Distribution: -**

Saxagliptin and sitagliptin distribution is typically influenced by a number of variables, including plasma protein binding. Both medications exhibit minimal serum protein binding. Therefore, it is unlikely that disease states that may affect protein levels will result in significant differences in how these agents behave.

2) **Metabolism:**

The way that sitagliptin and saxagliptin alter their initial biochemical structures is different. Approximately 87% of the radiolabeled sitagliptin that was consumed was eliminated as unaltered medication.Low amounts of nine metabolites were found, but it is not anticipated that these would increase sitagliptin's DPP-4 inhibitory effect. However, there is a metabolite of saxagliptin that keeps half of the original compound's activity. Since the cyto-chrome P450 (CYP 450) 3A4/5 system is mainly responsible for mediated metabolism, saxagliptin concentrations are predicted to be impacted by inducers and inhibitors of this system.

3) **Excretion:**

Oral doses of saxagliptin and sitagliptin are eliminated through renal and hepatic pathways. Following oral carbon 14-labeled sitagliptin administration, roughly 13% and 87% of the drug was found in the urine and feces, respectively.9. Following the administration of saxa-gliptin labeled with carbon 14, the percentages of the drug excreted in the urine as active metabolites and unchanged drug were 36% and 24%, respectively.7. Twenty-two percent of the radioactivity that was administered was found in the feces as saxagliptin. The removal of both agents involves active tubular secretion. Sitagliptin's terminal half-life is roughly 12.4 hours, while saxagliptin's and its metabolite's half-lives are 2.5 and 3.1 hours, respectively.

4) **Renal and hepatic insufficiency:**

The impact of renal insufficiency on the pharmacokinetics of saxagliptin and sitagliptin was assessed through single-dose open-label studies.

5) **Renal impairment:**

Patients with mild (creatinine clearance [CrCl], 50–80 mL/minute), moderate (CrCl, 30-50 mL/minute), severe (CrCl, less than 30 mL/minute), and endstage renal disease were all evaluated for sitagliptin. Comparing patients with mild renal insufficiency to control patients with normal renal function, the difference in plasma AUC levels was less than twofold. Plasma AUC levels increased by about 2.3 to 4.5 times in patients with moderate and severe renal impairment, including those receiving hemodialysis. Along with severe renal impairment, this also correlated with an increased Cmax and an increased terminal half-life of up to 22.5 hours. Four hours after oral administration, during a three- to four-hour session of hemodialysis, 13.5% of sitagliptin was eliminated.

Drug-Drug Interaction: -

It is not anticipated that sitagliptin will cause clinically significant drug interactions due to its limited hepatic metabolism. However, CYP 450 isoenzymes 3A4/5 are involved in saxagliptin metabolism, which means that interactions with systemic inducers and inhibitors may occur. The pharmacokinetics of metformin, glyburide (DiaBeta, Sanofi-Aventis), pioglitazone (Actos, Takeda/Lilly), digoxin (Lanoxin, GlaxoSmithKline), simvastatin (Zocor, Merck), diltiazem (e.g., Cardizem, Abbott; Tiazac, Forest), and ketoconazole (Nizoral, Janssen) have been studied in vivo, and the results show that saxagliptin has no effect. Concurrent ketoconazole administration, a strong inhibitor of the CYP 450 3A4/5 and P-glycoprotein systems, was reviewed in relation to its effects on saxagliptin. causes saxagliptin's Cmax and AUC levels to rise, while its metabolite's Cmax and AUC levels correspondingly decrease. A moderate inhibitor of the CYP 450 3A4 system, diltiazem, has also been observed to have this effect. When using strong CYP 450 3A4/5 inhibitors with saxagliptin, a 50% dose reduction is advised. Using moderate inhibitors with saxagliptin may require further monitoring or the use of alternative medications.

Contraindication:

Severe hypersensitivity reactions, such as anaphylaxis, angioedema, and Stevens-Johnson syndrome, have been linked to sitagliptin. People who are allergic to sitagliptin or any of its constituents should not use this agent.Pancreatitis postmarketing reports have been linked to sitagliptin. People who have a history of pancreatitis should proceed with caution; if pancreatitis is suspected, sitagliptin should be stopped. It would be wise to stop taking saxagliptin as well if pancreatitis is suspected, even though there is currently no evidence to support that pancreatitis is a class effect of these medications.

Pharmacodynamics:

The percentages of DPP-4 inhibition and the rise in GLP-1 levels are frequently reported in assessments of the physiological effects of sitagliptin and saxagliptin. In two investigations, dose-dependent inhibition of DPP-4 activity was observed in healthy volunteers administered sitagliptin at varying doses. For 100 mg over the course of a 24-hour period, the difference in inhibition was greater than 80% when compared to the placebo. Additionally, sitagliptin significantly outperformed a placebo in terms of average postprandial active GLP-1 levels. Similar outcomes were observed in patients with type-2 diabetes, with up to a two-fold increase in GLP-1 levels and an 80% inhibition of plasma DPP-4 activity 24 hours after oral administration. Similarly, studies involving both healthy and diabetic patients showed that 2.5 mg of saxagliptin reduced plasma DPP-4 levels by 50%. GLP-1 levels after meals rose 1.5–3 times higher than those of a placebo.

Safety and adverse effect:

Upper respiratory tract infection, nasopharyngitis, headache with sitagliptin, upper respiratory tract infection, urinary tract infection, and headache with saxagliptin were the most frequent adverse reactions that happened in 5% of patients or more who received DPP-4 inhibitors. It has been reported that using insulin or saxagliptin with a sulfonylurea increases the incidence of hypoglycemia, while using saxagliptin with a sulfonylurea increases the risk.The co-administration of insulin and saxagliptin has not been studied, but it is likely to increase the risk of hypoglycemia. Dosage modifications are also required in patients with renal impairment in order to reduce the risk of hypoglycemia. Post-marketing reports of sitagliptin have also revealed other adverse events, such as severe allergic reactions involving anaphylaxis, edema, and Stevens-Johnson syndrome. Sitagliptin should not be administered to people who are allergic to any of the formulation's ingredients. Patients with a history of pancreatitis should use sitagliptin with caution. Acute pancreatitis associated with sitagliptin use has been reported; this includes hemorrhagic and non-fatal necrotizing pancreatitis. Patients with a history of pancreatitis have not been studied while taking sitagliptin. It is wise to stop sitagliptin if pancreatitis is suspected in patients and to keep an eye out for any signs or symptoms of the condition.

Conclusion:

While metformin or a sulfonylurea is generally required as a first-line treatment for significantly lowering blood glucose levels, recent data suggest that both sitagliptin and saxagliptin are approved as adjunctive therapies to diet and exercise in type-2 diabetes. DPP-4 inhibitors may have a neutral effect on weight, a favorable adverse-effect profile, and a complementary mechanism of action with other antidiabetic drugs. Sitagliptin and saxagliptin are useful for patients who are nearing their target HbA1c but who consistently have elevated glucose levels after meals because they have a low risk of hypoglycemia. What benefits come from choosing one DPP-4 inhibitor over another? There are no comparable clinical data available. The selection process will be guided by certain attributes of these agents (e.g., dose modifications for renal impairment, drug interactions), as well as by prospective clinical experience and trial results.

A cost-benefit analysis of DPP-4 therapy should take into account the potential for hypoglycemia, the drug class's modest treatment effect, and the patient's eligibility. There are currently other DDP-4 inhibitors being developed, such as alogliptin (Takeda) and vildagliptin (Galvus, Novartis).

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