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Recent Drug Advances in the Management of Diabetes Complications: An Overview

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***Abstract*:** A chronic metabolic disease known as diabetes mellitus (DM) is typified by elevated blood sugar (glucose) levels. It results from either insufficient insulin production or improper insulin use by the body. The hormone insulin facilitates the uptake of glucose into cells for energy production. Diabetes mellitus (DM) cannot be cured, but it can be controlled with medication, exercise, and a good diet. Individuals diagnosed with diabetes mellitus can lower their chance of long-term complications by managing their blood sugar levels. You can lower your chance of long-term complications and live a long and healthy life by managing your blood sugar levels and doing as your doctor advises. Around 250–300 BC, Apollonius of Memphis coined the term "diabetes." Mering and Minkowski identified the pancreas' function in the aetiology of diabetes in 1889. At the University of Toronto, Banting, Best, and Collip isolated the hormone insulin from cow pancreas in 1922, which made an efficient diabetes treatment possible. Diabetes has been the subject of amazing research over the years, leading to numerous discoveries and management techniques to address this expanding issue. Regretfully, diabetes remains one of the most prevalent chronic illnesses both domestically and globally. It continues to be the seventh most common cause of death in the US.

Key points: *Diabetes Mellitus, Blood sugar, diseases, glucose, complications*

Introduction

A class of metabolic diseases known as diabetes mellitus is defined by persistently high blood sugar levels over an extended period of time. Diabetes is brought on by either insufficient insulin production by the pancreas, improper insulin cellular response, or both. The primary hormone that controls how much glucose is absorbed by body cells from the blood, insulin is crucial for maintaining proper blood glucose levels in the body. The

pancreatic islets of Langerhans' beta cells secrete insulin into the blood.

Blood glucose level:-

- Fasting blood glucose level 90-130 mg/dl
- Blood glucose level after 2 hours of meal greater than or equal to 150 mg/dl
- Glycoxylated Hemoglobin Index Test (HbA1c) the normal range for the hemoglobinA1c level is between 4% and 5.6%. Hemoglobin A1c levels between 5.7% and 6.4%mean you have prediabetes and a higher chance of getting diabetes. Levels of 6.5% orhigher mean you have diabetes. [1]

A carbohydrate called sugar instructs the endocrine pancreas to release the hormone insulin. Most body tissue types, including the liver, muscles, and fat tissues, absorb and store sugar as a result of insulin. Diabetes cannot currently be cured, but long-term complications from the disease can be avoided by managing blood sugar levels with medication, exercise, and a healthy diet.

Long-term DM complications that can be experienced are:-

1) Eyes – cataracts and retinopathy (gradual damaging of the eye) that may lead toblindness
2) Kidneys – kidney disease and kidney failure (Nephropathy)
3) Nerves – neuropathy (gradual damaging of nerves)
4) Feet – ulcers, infections, gangrene, etc.
5) Cardiovascular system – hardening of arteries, heart disease and stroke [2]

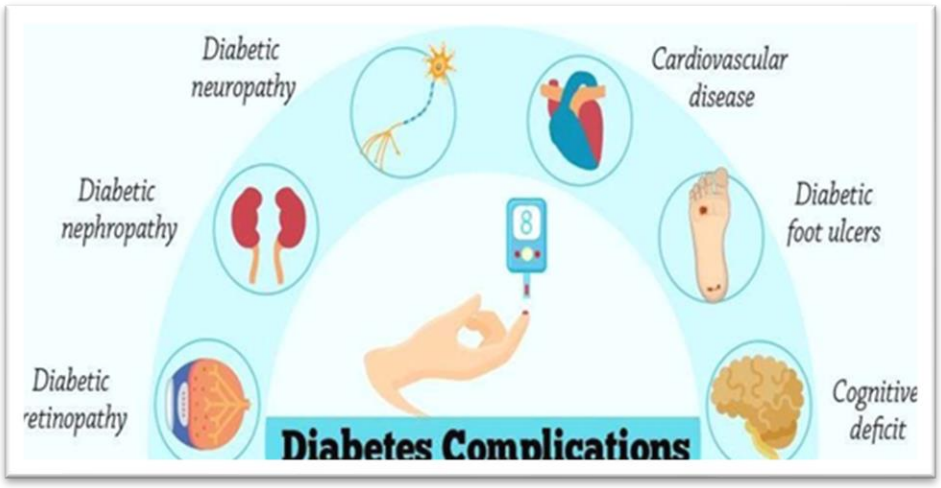


Fig: 1. Diabetes Complications

Diabetes mellitus is derived from the Latin word mellitus, which means sweet, and the Greek word diabetes, which means syphon, to pass through. According to historical accounts, Apollonius of Memphis coined the term "diabetes" approximately 250–300 BC. The term "Diabetes Mellitus" originated when ancient Greek, Indian, and Egyptian civilizations realized that the urine produced in this condition was sweet. In 1889, Mering and Minkowski made the discovery that the pancreas plays a part in the pathogenesis of diabetes. At the University of Toronto, Banting, Best, and Collip isolated the hormone insulin from cow pancreas in 1922, which made an efficient diabetes treatment available that year. Outstanding research has been conducted over the years, leading to numerous discoveries and the development of management techniques to address this expanding issue. Regretfully, diabetes remains one of the most prevalent chronic illnesses both domestically and globally. It continues to rank as the seventh most common cause of death in the US.[3]

Diabetes mellitus (DM) is a metabolic disease, involving in appropriately elevated blood glucose levels. DM has several categories including

TYPES:-

Type 1- Insulin Dependent Diabetes mellitus or Juvenile Onset Diabetes mellitus Type IA DM: Immune-mediated

Type IB DM: Idiopathic II

Type 2-Non-Insulin Dependent Diabetes mellitus or Adult onset DMType 3-Gestational Diabetes mellitus

Other Specific types of Diabetes mellitus

A. Genetic defect of B-cell function due to mutations in various enzymes (earlier called maturity-onset diabetes of the young or MODY) (e.g. hepatocyte nuclear transcription factor HNF, glucokinase)

B. Genetic defect in insulin action (e.g. type A insulin resistance)

C. Diseases of exocrine pancreas (e.g. chronic pancreatitis, pancreatic tumours, post- pancreatectomy)

D. Endocrinopathies (e.g. acromegaly, Cushing's syndrome, pheochromocytoma)

E. Drug- or chemical-induced (e.g. steroids, thyroid hormone, thiazides, B-blockers etc)

F. Infections (e.g. congenital rubella, cytomegalovirus)

G. Uncommon forms of immune-mediated DM (stiff man syndrome, anti-insulin receptor antibodies)

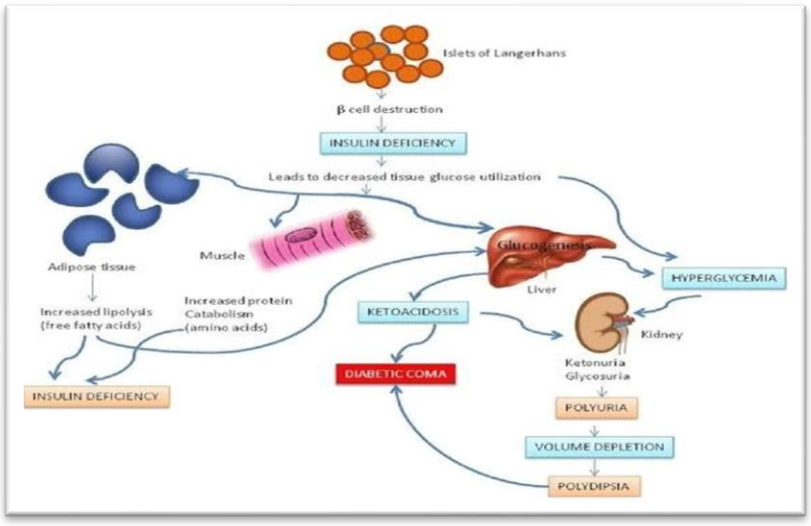
H. Other genetic syndromes (e.g. Down's syndrome, Klinefelter's syndrome, Turner's syndrome). [4]

TYPE 1 Diabetes Mellitus

Juvenile diabetes, also referred to as type 1 diabetes (T1D), is an autoimmune disease that starts when the immune system attacks beta cells, which are the cells that produce insulin. This kind of diabetes, which affects 5%–10% of people with the diagnosis, is brought on by the pancreatic β cells being destroyed. In children and adolescents, 80%–90% of cases of diabetes are caused by type 1 diabetes. The International Diabetes Federation (IDF) reports that 497100 children (0–14 years old) received a type 1 diabetes diagnosis globally in 2013 and 78900 new cases are diagnosed annually. Due to the high prevalence of type 1 diabetes in adolescents and adults over the age of 14, these numbers do not accurately reflect the overall number of patients with the disease.

Pathogenesis of DM TYPE1

Fig: 2. Pathogenesis of Diabetes Mellitus type I



The primary cause of type 1 diabetes is an autoimmune response that destroys the pancreatic β cells through humoral (B cell) and T-cell-mediated inflammation (insulitis). Type 1 diabetes is characterized by the presence of auto antibodies against pancreatic islet cells, though it is unclear how these antibodies contribute to the disease's aetiology. Islet cell autoantibody, insulin (IAA), glutamic acid decarboxylase (GAD, GAD65), protein tyrosine phosphatase (IA2 and IA2β), and zinc transporter protein [ZnT8A] are among these auto antibodies. These pancreatic auto antibodies, which are indicative of type 1 diabetes, may have been found in

the patients' serum months or even years before the condition manifested. Insulin secretion is absent in this autoimmune type 1 diabetes, which is more common in children and teenagers. A number of environmental factors have been linked to the aetiology of type 1 diabetes, in addition to the significance of genetic predisposition. These factors include low vitamin D levels, prenatal exposure to pollutants, improved living and hygiene conditions, early infant nutrition—such as using cow's milk formula instead of breast milk—and early childhood insulin resistance brought on by obesity or faster height growth velocity. [5]

TYPE 2 Diabetes Mellitus

This group includes more than 90%–95% of diabetic patients, the majority of whom are adults. In the United States, 0.46 per 1000 people under the age of 20 had type 2 diabetes in 2009; this group accounted for about 20% of all juvenile cases of the disease. The primary cause of the rise in type 2 diabetes cases among young people is the shift in children's lifestyles towards less nutritious diets and more sedentary lives. Type 2 diabetes is primarily caused by insulin resistance, which is primarily caused by obesity.

Pathogenesis of DM TYPE2

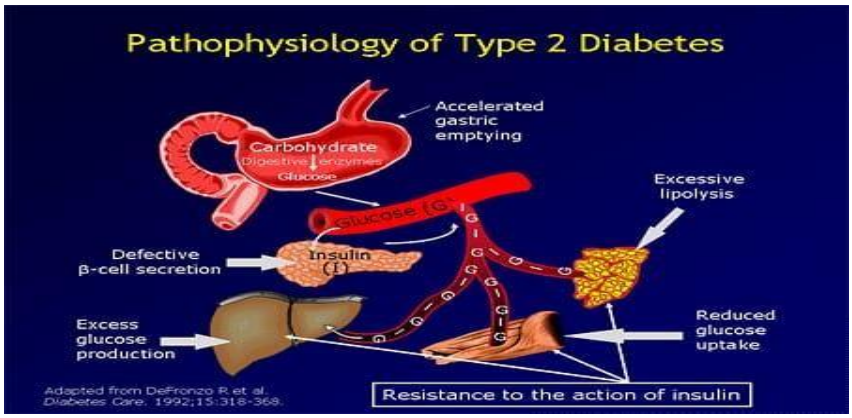


Fig: 3. Pathogenesis of Diabetes Mellitus type II

Patients with type 2 diabetes who are insulin resistant have higher insulin requirements in insulin-target tissues. In addition to insulin resistance, malfunctions in the function of the pancreatic β cells prevented them from meeting the increased demand for insulin. Conversely, as the body gradually loses its β cell supply, insulin secretion falls off in response to the rising insulin requirement, potentially making some type 2 diabetics insulin-dependent. As long as insulin is secreted continuously and insulin depletion is infrequent, the majority of type 2 diabetes patients do not require insulin. Dependence on insulin is one of the major differences from type 1 diabetes. Other differences include the absence of ketoacidosis in most patients of type 2 diabetes and autoimmune destruction of β cells does not occur. This delay in diagnosis could increase the incidence of long-term complications in type 2 diabetes patients since hyperglycemia is not treated during this undiagnosed period. In addition to diabetes, insulin resistance has many manifestations that include obesity, nephropathy, essential hypertension, dyslipidemia (hypertriglyceridemia, low HDL, decreased LDL particle diameter, enhanced postprandial lipemia and remnant lipoprotein accumulation), ovarian hyperandrogenism and premature adrenarche, non-

alcoholic fatty liver disease and systemic inflammation. The presence of type 2 diabetes in children and adolescence who are not obese, the occasional severe dehydration and the presence of ketoacidosis in some pediatric patients with type 2 diabetes.[5]

Gestational Diabetes

When diabetes is discovered for the first time during a pregnancy, it is known as gestational diabetes. Gestational diabetes affects how your cells use sugar, or glucose, just like other types of diabetes. High blood sugar levels brought on by gestational diabetes can harm both you and your unborn child during pregnancy. Gestational diabetes can be managed during pregnancy with a diet rich in whole foods, regular exercise, and, if needed, medication. Maintaining blood sugar control can help avoid a difficult delivery and keep both you and your child healthy. When you give birth, your blood sugar usually returns to normal if you had gestational diabetes during your pregnancy. However, your chance of developing type 2 diabetes is increased if you had gestational diabetes. More frequent blood sugar testing will be required.

Symptoms:-

1. Increased frequent urination.
2. Increased thirst.
3. Fatigue.
4. Nausea and vomiting.
5. Weight loss even with increased appetite.
6. Blurred vision.
7. Yeast infections.

Complications:-

If you have gestational diabetes, your baby may be at increased risk of:-

1. Excessive birth weight
2. Early birth(preterm)
3. Serious breathing difficulties
4. Low blood sugar (hypoglycemia)
5. Obesity and type 2 diabetes later in life
6. High blood pressure and preeclampsia
7. Having a surgical delivery (C-section).
8. Future diabetes [6]

Etiology of Diabetes Mellitus

1. **Etiological Factors**

a) Genetic defects of B-cell function.
b) Mutation in mitochondrial DNA
c) Genetic defects in insulin action

2. **Environmental Factors:**

a) Obesity associated with rising living standards
b) Steady urban migration
c) Lifestyle changes (including consumption of alcohol)
d) Lack of physical activity due to sedentary lifestyle.

3. **Factors within the Individual:**

a) Production of auto-antibodies that destruct B-cells in the pancreas

b) Deficiency in insulin synthesis and secretion
c) Insulin resistance (because the cells do not respond to the insulin produced)
d) Presence of diseases that may extensively damage the pancreas causing pancreatitis, trauma, infection, pancreatic carcinoma, and pancreatectomy
e) Excessive secretion of hormones (e.g., growth hormone, cortisol, glucagon, and epinephrine) that antagonize insulin action.
f) Impairment of insulin secretion resulting from the consumption of drugs, and
g) Infections caused by viruses that cause B-cell destruction.[7]

Symptoms of DM:-

The following symptoms are experienced by diabetic patients:

1) Ketoacidosis (presence of Ketones in urine)
2) Glycosuria (presence of glucose in urine)
3) Polydipsia (increased thirst)
4) Polyuria (increase in frequency of urination)
5) Polyphagia (extreme hunger)
6) Unexplained weight loss
7) Fatigue and headache
8) Imitability and Blurred vision
9) Frequent infections with retarded healing of cuts and wounds.[7]

Fig: 4. Symptoms of Diabetes Mellitus

Table: 1. Drugs used in Diabetic Nephropathy

Sr.no.	Present drug	New drug
1	Tolazamide	Empagliflozin
2	Glimepride	Sitagliptin
3	Glipizide	Alogliptin

Table: 2. Drugs used in Diabetic Neuropathy

Sr.no.	Present drug	New drug
1.	Voglibose	Teneligliptin
2.	Pioglitazone	Canagliflozin
3.	Metformin	Saxagliptin

Table: 3. Drugs used in Diabetic Cardiovascular Diseases

Sr.no.	Present drug	New drug
1.	Albiglutide	Bexagliflozin
2.	Acarbose	Dapagliflozin
3.	Pramlintide	Liraglutide

Table: 4. Drugs used in Diabetic Retinopathy

Sr.no.	Present drug	New drug
1.	Glibenclamide	Linagliptin
2.	Tolbutamide	Vildagliptin
3.	Repaglinide	Saroglitazar

Drugs used in Diabetic Nephropathy:-

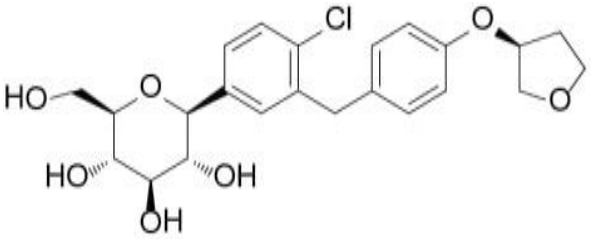
1. Empagliflozin

Introduction:-

Empagliflozin, a selective inhibitor of sodium-glucose cotransporter 2, decreases hyperglycemia in individuals with type 2 diabetes by decreasing glucose reabsorption in the kidneys and raising glucose excretion in the urine. Empagliflozin use has been linked to reductions in weight and blood pressure without elevations in heart rate, as well as a lowering of glycated haemoglobin levels in patients with type 2 diabetes, including those with stage 2 or 3 chronic kidney disease. In patients with type 1 diabetes, empagliflozin has been demonstrated to lower intraglomerular pressure and enhance hyper filtration; it has been hypothesized that these benefits could translate into better renal outcomes. Nonetheless, there is worry that the sodium-glucose cotransporter.[8]

Chemistry:-

Empagliflozin is a non-hygroscopic, white to yellowish powder. It is practically insoluble in toluene, very slightly soluble in 50% Acetonitrile/water, sparingly soluble in methanol, slightly soluble in ethanol and Acetonitrile, and barely soluble in water. Its molecular weight is 450.91 and its formula is C23H27ClO7.
The structural formula is:



The chemical name of empagliflozin is **D-Glucitol,1,5-anhydro-1-C-[4-chloro-3-[[4-[[(3S)- tetrahydro-3furanyl]oxy]phenyl]methyl]phenyl]-, (1S).**

Mechanism of Action:-

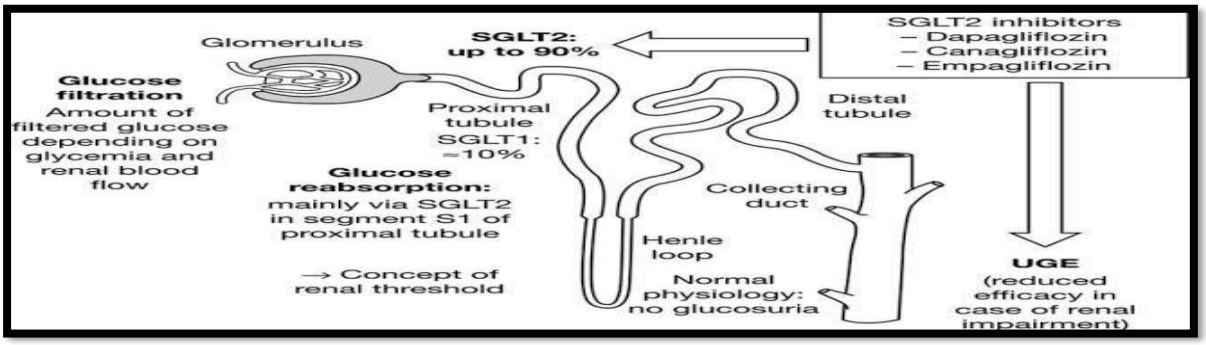


Fig: 5. Mechanism of Action of Empagliflozin

The mechanism of action of empagliflozin involves blocking the sodium-glucose co-transporter-2 (SGLT-2) present in the kidney's proximal tubules. Empagliflozin decreases renal reabsorption of glucose and raises urinary excretion of glucose by inhibiting SGLT2. Insulin has no effect on the drug's ability to lower glucose. Urinary glucose excretion rose by roughly 64 grammes per day with 10 mg of empagliflozin and 78 grammes per day with 25 mg in patients with type 2 diabetes. Empagliflozin's diuretic and natriuretic effects cause intravascular contraction by lowering sodium and volume load. Weight loss and blood pressure drops without raising heart rate are linked to empagliflozin.[9]

Dosage of Empagliflozin :-

Prior to Initiation Of Treatment Assess renal function before initiating Empagliflozin and as clinically indicated [see WARNINGS AND PRECAUTIONS]. In patients with volume depletion, correct this condition before initiating Empagliflozin.

Fig: 6. Dosage of marketed Empagliflozin tablets

Empagliflozin 10 mg once daily in the morning, with or without food, is the recommended dosage. In patients tolerating JARDIANCE, the dose may be increased to 25 mg for additional glycemic control. It is not advised to use for glycemic control in patients whose eGFR is less than 30 mL/min/1.73 m2.who have heart failure with an

eGFR less than 20 mL/min/1.73 m2 or who have type 2 diabetes and established cardiovascular disease with an eGFR less than 30 mL/min/1.73 m2.

Drug Interaction of Empagliflozin:-

1. Empagliflozin may increase the diuretic activities of Canrenoic acid.
2. The risk or severity of renal failure, hypotension, and hyperkalemia can be increased when Empagliflozin is combined with Captopril.
3. The risk or severity of adverse effects can be increased when Carbetocin is combined with Empagliflozin.

Side Effects:-

1. Bladder pain.
2. Bloody or cloudy urine.
3. Change in the color, amount, or odor of vaginal discharge.
4. Difficult burning or painful urination.
5. Frequent urge to urinate.
6. Itching, stinging, or redness of the vaginal area.
7. pain during sexual intercourse

Contraindications:-

1. History of a severe allergic reaction to empagliflozin
2. End-stage kidney disease those patient on dialysis
3. Diabetic ketoacidosis patient
4. In instances of severe renal impairment, defined as GFR less than 30 mL/min/1.73m^2, empagliflozin is contraindicated. The use of empagliflozin is not recommended if GFR is less than 45 mL/min or during the second and third trimesters of pregnancy.

Adverse drug reaction:-

1. Hypotension
2. Ketoacidosis
3. Acute kidney injury
4. Genital mycotic infections
5. Hypoglycemia when used with insulin
6. Dyslipidemia
7. Fournier gangrene, and pyelonephritis.[10]

Uses:-

1. Empagliflozin is used in the diabetic induced nephropathy and chronic kidney disorder.
2. Used in diabetic induced cardiovascular disorder such heart attack , ischemia andMayocardial infaction.

2. Sitagliptin

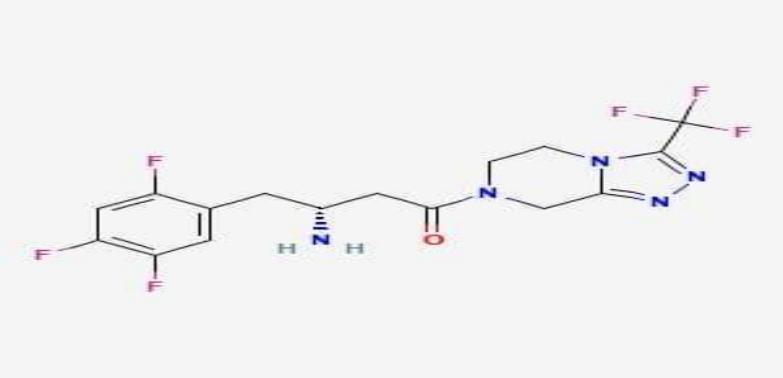
Introduction:

Sitagliptin belongs to a class of oral dipeptidyl peptidase-4 (DPP-4) inhibitors, which are used to treat type 2 diabetes. These consist of vildagliptin, linagliptin, teneligliptin, saxagliptin, and sitagliptin. Since its approval in 2006 for patients with type 2 diabetes, sitagliptin—the first DPP-4 inhibitor to hit the market—has been used extensively to treat both types of the disease. Angiotensin II type 1 receptor blockade combined with DPP-4 inhibition increased the renoprotective effects in patients with DN, according to a recent study. According to a study, sitagliptin lowers albuminuria, which is reliant on adequate blood sugar regulation. Some groups, on the

other hand, dispute the existence of a meaningful correlation between the change in the UACR and HbA1c and assert that sitagliptin lowers blood pressure by raising sodium levels. Sitagliptin raises the amount of the hormone glucagon-like polypeptide (GLP)-1. GLP-1 inhibits the Na+/H+ exchange at the proximal tubular cells, which reduces salt intake and increases salt excretion in the urine. It functions by raising the concentrations of some organic compounds, like insulin, which lowers elevated blood sugar. It's been demonstrated that sitagliptin reduces HbA1c levels by roughly 0.7%. Taken alone, it is marginally less efficacious than metformin. Sitagliptin is advised as a backup medication (in conjunction with other medications) in case metformin and diet/exercise don't work together.[11]

Chemistry:-
Sitagliptin is a triazolepyrazine that has a PH-dependent aqueous solubility, hypoglycemic action, and a white to off powder appearance. It dissolves in water and N,N-dimethyl formamide; it is insoluble in isopropanol and isopropyl acetate, but soluble in ethanol, acetone, and acetonotrile; it is also slightly soluble in methanol. Its molecular weight is 407.31 and its formula is C16H15F6N5O.

The structural formula of Sitagliptin is



The chemical name of Sitagliptin is
7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-[3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate

Mechanism of Action:-

Dipeptidyl peptidase 4 (DPP-4) is competitively inhibited by sitagliptin. The digestive hormones known as incretins, or GLP-1 and GIP, are released after a meal and are broken down by this enzyme. They are able to suppress the release of glucagon by the pancreatic alpha cells and enhance the secretion of insulin by blocking the breakdown of GLP-1 and GIP. Blood glucose levels move closer to normal as a result. The amounts of insulin released and glucagon suppressed decrease as blood glucose levels get closer to normal, helping to avoid the "overshoot" and subsequent low blood sugar (hypoglycemia) that can occur with some other oral hypoglycemic medications.[9]

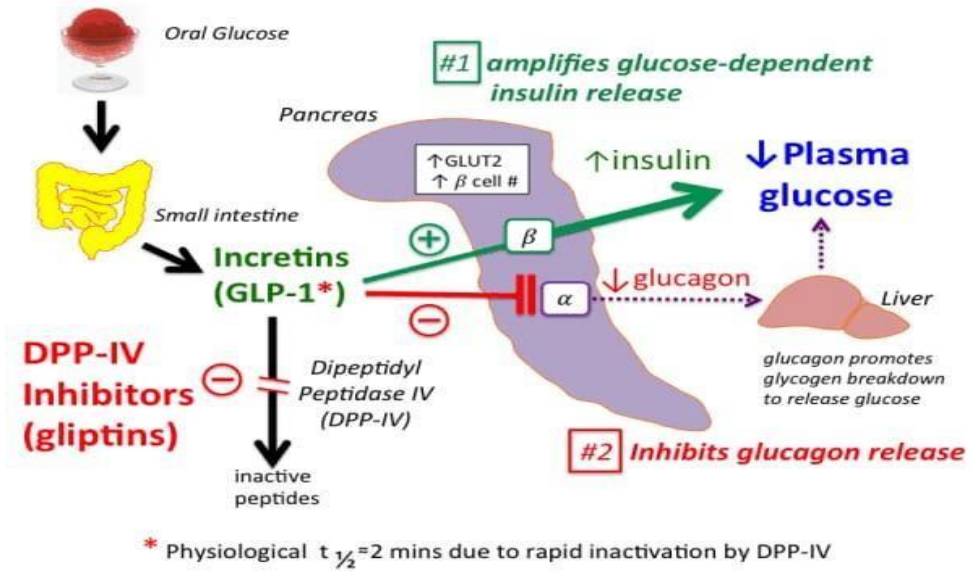


Fig: 7. Mechanism of action of Sitagliptin

Dosage of Sitagliptin:-

1. **For patients taking metformin alone:**
   Grownups—First, a daily dose of 100 mg of sitagliptin in addition to the previously prescribed dosage of metformin. Until your blood sugar is under control, your doctor might progressively raise your dosage. You can begin by taking two 50 mg sitagliptin tablets and 1000 mg of metformin once daily if you are currently taking 850 or 1000 mg of immediate-release metformin twice a day.
   Children:—Use and dose must be determined by your doctor
2. **For patients taking sitagliptin alone**
   Adults—At first, 100 milligrams (mg) of sitagliptin and 1000 mg of metformin once a day. Your doctor may gradually increase your dose until your blood sugar is controlled. However, the dose is usually not more than 100 mg of sitagliptin and 2000 mg of metformin once a day.
   Children—Use and dose must be determined by your doctor.

Drug Interaction of Sitagliptin:-

Sitagliptin has no known severe interactions with other drugs. Serious interactions ofsitagliptin include:

1. Ethanol
2. Ivacafto

Side Effects:-

1. Feeling hungry
2. Trembling or shaking
3. Sweating
4. Confusion
5. Difficulty concentrating

Contraindications:-

1. Sitagliptin is contraindicated in patients with a known sitagliptin hypersensitivity, suchas anaphylaxis, urticaria, angioedema, exfoliative dermatitis or other serious skin conditions (serious rash), including Stevens-Johnson syndrome.
2. Chronic heart failure
3. Chronic inflammation of the pancreas
4. kidney disease with likely reduction in kidney function

Adverse drug reaction:-

1. Nausea.
2. Gastrointestinal disturbance, including diarrhea and constipation.
3. Abdominal pain.
4. Allergic skin reactions.
5. Liver inflammation.

Uses:-

1. Sitagliptin is used in the diabetic induced nephropathy chronic and acute kidneydisorder.
2. It is used in diabetic induced cardiovascular disorder such heart attack, ischemia.
3. It is used in diabetic induced eye disorder such as retinopathy.

Drugs used in Diabetic Neuropathy:-

1. Teneligliptin

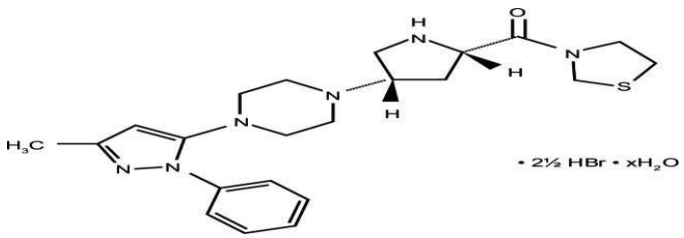
Introduction:-

Teneligliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor, a class of medication used to treat type 2 diabetes in people whose blood sugar levels are not controlled by diet and exercise alone. It functions by preventing DPP-4 from acting, an enzyme that breaks down the hormone "Incretin." When not needed, the enzyme "Incretins" lowers the liver's blood sugar level and aids in the production of more insulin when needed. Patients with type 1 diabetes and those treating diabetic ketoacidosis shouldn't use TENELIGLIPTIN. As a result, TENELIGLIPTIN is essential for regulating blood sugar levels and preventing major consequences associated with diabetes, such as retinopathy, nephropathy, diabetic foot ulcers, and delayed wound healing.[12]

Chemistry:-

Teneligliptin is an oral bioavailable pyrrolidone antidiabetic agent that has a long-acting effect. It has a white colour and is easily soluble in water, methanol, and Acetonitrile. It is only weakly soluble in ethanol (99.5) and insoluble in ethanol.

The structural formula of Teneligliptin is:-



The chemical name of Teneligliptin is:- {(2S,4S)-4-[4-(3-Methyl-1-phenyl-1H-pyrazol-5-yl)-1-piperazinyl]-2-pyrrolidinyl}(1,3-thiazolidin-3-yl)methanone

Mechanism of Action:-

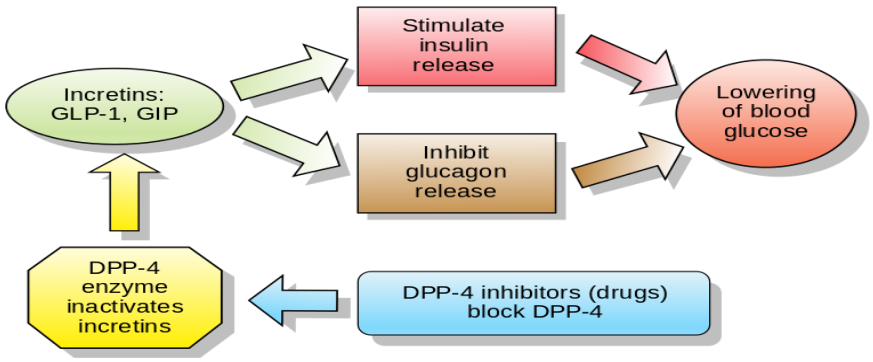


Fig: 8. Mechanism of Action of Teneligliptin

Teneligliptin slows down the fast breakdown of incretin by blocking the activity of DPP-4 enzymes. Additionally, it causes the pancreas to produce more insulin and lowers glucagon levels, which act as an insulin counter-hormone and lower blood sugar levels. After a meal, the alimentary canal secretes glucagon-like peptide-1 (GLP-1), which in turn stimulates the pancreas to secrete insulin and controls glucagon secretion to control blood sugar levels. Teneligliptin has a hypoglycemic effect by preventing GLP-1 from being broken down by dipeptidyl peptidase-4 (DPP-4) activity inhibition, which raises the amount of active GLP-1 in the blood.

Dosage of Teneligliptin:-

Teneligliptin is given orally to adults at a dose of 20 mg once daily, with a maximum of 40 mg per day. Patients with renal impairment do not require a dose adjustment because the drug's metabolites are excreted by the liver and kidneys.

Drug Interaction of Teneligliptin:-

Drug-Drug Interaction: TENELIGLIPTIN interacts with antidepressants (bupropion, selegiline, isocarboxide, phenelzine), diabetes medications (glipizide, gliclazide, glimepiride), high blood pressure medications (atenolol, bisoprolol, metoprolol, nadolol, propranolol), and painkillers (aspirin).

Drug-Food Interaction: Drinking too much alcohol can raise your risk of developing the potentially fatal illness known as lactic acidosis. Thus, abstain from alcohol consumption while taking TENELIGLIPTIN.

Side Effects

1. Dizziness
2. Headache
3. Diarrhoea
4. Increased body temperature
5. Upper respiratory tract infection
6. Nasopharyngitis (infection of nose and throat with common cold)

Contraindications

Teneligliptin tablets should not be used by people who are allergic to the medication or any of its ingredients. Severe ketosis, diabetic coma, diabetic pre-coma, and type 1 diabetes that requires immediate attention severe injuries, both before and after surgery, and situations in which insulin injections are required to control blood glucose.[13]

Adverse drug reaction

1. Headache
2. Nasopharyngitis
3. Intestinal Obstruction (0.1%)
4. Liver dysfunction (unknown frequency)
5. Interstitial pneumonia (frequency unknown)

Uses:-

1. Teneligliptin is used in the diabetic induced neuropathy to treat the hyperglycemia.
2. It is used in Diabetic induced cardiovascular disorder such as ischemia.

2. Canagliflozin

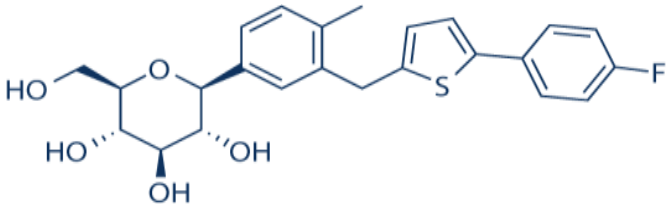
Introduction:-

When treating type 2 diabetes, canagliflozin is used in addition to diet, exercise, and occasionally other medications to lower blood sugar levels (condition in which blood sugar is too high because the body does not produce or use insulin normally). An inhibitor of sodium-glucose cotransporter-2 (SGLT2) is canagliflozin. It functions by raising the amount of glucose lost through urination.

Chemistry:-

Canagliflozin Anhydrous is the anhydrous form of canagliflozin, a thiophene-ringed C-glucoside that has antihyperglycemic properties and is available as an oral inhibitor of sodium-glucose transporter 2 (SGLT2). Canagliflozin has a low risk of hypoglycemia and can also help reduce body weight.

The structural formula of Canagliflozin is:

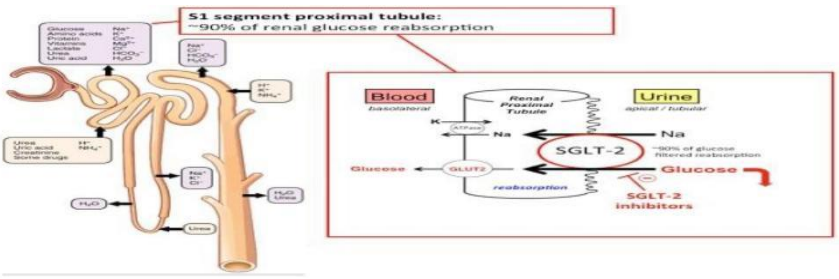


The chemical name of canagliflozin is: **(2S,3R,4R,5S,6R)-2-{3-[5-[4-Fluoro-phenyl)- thiophen-2-ylmethyl]-4-methyl-phenyl}-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol**

Mechanism of action:-

At least 90% of renal glucose reabsorption is accomplished by subtype 2 sodium-glucose transport proteins (SGLT2), which is inhibited by canagliflozin (SGLT1 accounts for the remaining 10%). Up to 119 grammes of blood glucose, or 476 kilocalories, can be eliminated through the urine each day when this transporter is blocked. Osmotic diuresis causes the body to rid itself of extra water, which lowers blood pressure. When compared to other anti-diabetic medication types like insulin and sulfonylurea derivatives, this mechanism is linked to a lower risk of hypoglycemia, or too low blood glucose.[15]

Fig: 9. Mechanism of Action of Canagliflozin



Dosage:-

Tablet 100mg, 300mg

Type 2 Diabetes Mellitus Initially 100 mg per day Orally taken before the first meal of the dayMay increase dose to 300 mg q Day if 100 mg/day tolerated in patients who have eGFR ≥60 mL/min/1.73 m² and require additional glycemic control.

Drug interaction:-

When used with diuretics, the medication may make dehydration more likely. Treatment with canagliflozin prevents renal reabsorption of 1,5-anhydroglucitol by increasing renal excretion of glucose, which causes artifactual decreases in serum 1,5-anhydroglucitol. Consequently, using serum 1,5-anhydroglucitol as a gauge of postprandial glucose levels may be hampered by canagliflozin.

Side effects:-

1. Common side effects include vaginal yeast infections, nausea, constipation, and urinarytract infections
2. Serious side effects may include low blood sugar, Fournier's gangrene, leg amputation, kidney problems, high blood potassium, and low blood pressure
3. Diabetic ketoacidosis may occur despite nearly normal blood sugar levels.[14]

Contraindication:-

1. Type 1 diabetes Diabetic ketoacidosis
2. Severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m2)
3. end-stage renal disease Patients on dialysis.

Adverse Drug Reaction:-

1. volume depletion (body fluid decreased) followed by genital infection,
2. polyuria/pollakiuria (increased urination)
3. urinary tract infection.

Uses:-

1. Canagliflozin is used in the diabetic induced neuropathy and chronic kidney disorder.
2. Canagliflozin is used in diabetic induced Retinopathy and Nephropathy.

Drugs used in Diabetic Cardiovascular Diseases:-

1. Bexagliflozin

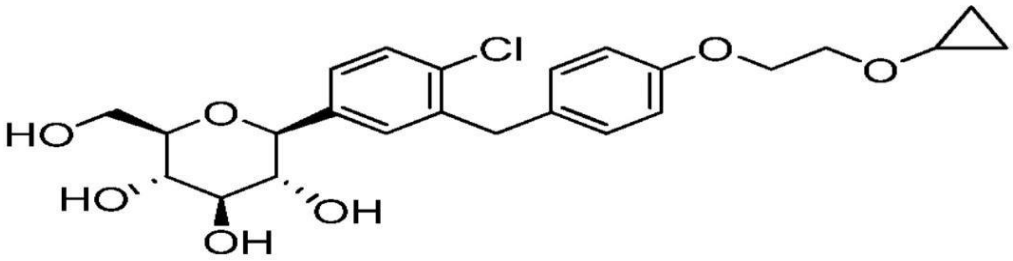
Introduction:-

As an addition to diet and exercise, adults with type 2 diabetes can improve their glycemic control by taking bexagliflozin, also marketed under the brand name Brenzavvy. This medication is an oral sodium-glucose cotransporter 2 (SGLT2) inhibitor. A class of oral antidiabetic drugs known as sodium-glucose cotransporter 2 (SGLT2) inhibitors lowers hyperglycemia by reducing renal proximal tubular reabsorption of glucose and causing glucosuria. This class of agents lowers blood pressure, body eight, haemoglobin A1c, and some have even been shown to improve kidney and cardiovascular outcomes. In the multinational BEST trial, which was placebo-controlled, bexagliflozin, an SGLT2 inhibitor, decreased HbA1c in patients who were at high risk of cardiovascular (CV) events and improved blood pressure and weight. The effectiveness and safety of bexagliflozin in managing blood pressure, weight, and hyperglycemia were investigated in patients with established cardiovascular disease (CVD) or multiple CV risk factors in addition to type 2 diabetes mellitus (T2DM).[16]

Chemistry :-

The powder form of bexagliflozin is white, off-white, to pale yellow. It dissolves readily in methanol, acetone, ethylene glycol, and propylene glycol but only very slightly in water. It dissolves somewhat in toluene,

cyclohexane, and heptane. Bexagliflozin in crystal form is not hygroscopic. C24H29ClO7 is the molecular formula, and 464.94 g/mol is the molecular weight. The structural formula is:



The Chemical name of bexagliflozin is :
(2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-(2-cyclopropoxyethoxy)benzyl)phenyl)-6- (hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

Mechanism of Action :-

The sodium-glucose co-transporter 2 (SGLT2), which is primarily in charge of reabsorbing glucose from the renal glomerular filtrate into the renal proximal tubule, is inhibited by bexagliflozin. By blocking SGLT2, bexagliflozin lowers the renal threshold for glucose and decreases renal reabsorption of filtered glucose, increasing urine glucose excretion independently of insulin sensitivity. Several hypotheses have been put forth to account for the advantageous effects of SGLT2 inhibitors. These include beneficial effects of SGLT2 inhibition on the following:

1) blood pressure lowering
2) increasing diuresis/natriuresis
3) improving cardiac energy metabolism
4) improving glucose control
5) inhibiting the sympathetic nervous system
6) preventing adverse cardiac remodeling
7) preventing ischemia/reperfusion injury
8) inhibiting the cardiac Na+/H+ exchanger
9) decreasing epicardial fat mass
10) increasing erythropoietin (EPO) levels
11) increasing circulating provascular progenitor cells
12) decreasing oxidative stress 13)improving vascular function. [17]

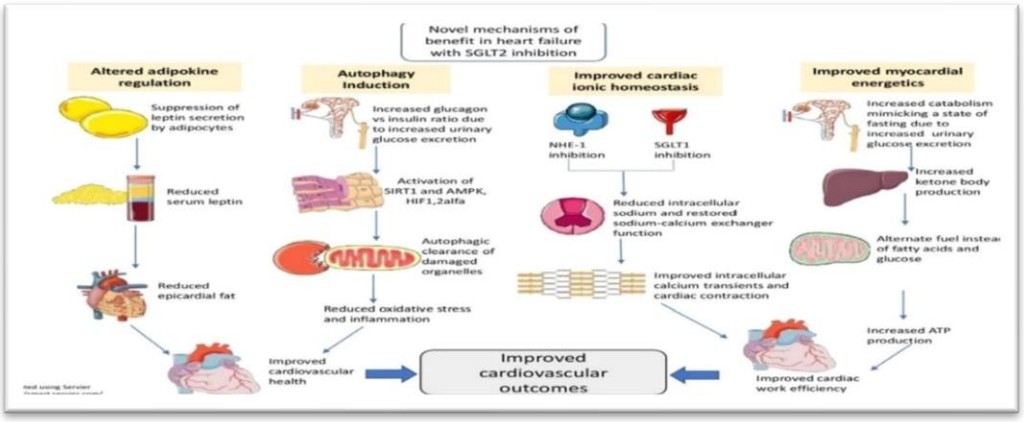


Fig: 9. Mechanism of Action of Bexagliflozin

Dosage of Bexagliflozin :-

20 mg of BRENZAVVY taken orally once daily in the morning, with or without food, is the recommended dosage. The tablets contain the dosage form, which is 20 mg. They are blue, caplet-shaped, biconvex, bevel-edged, and have an inverted "2" and a debossed "2" on one side..

Drug Interaction of Bexagliflozin :-

1] UGT Enzyme Inducers may significantly reduce exposure to BRENZAVVY and lead to decreased efficacy.

2] The risk of hypoglycemia is increased when BRENZAVVY is used in combination withinsulin and/or an insulin secretagogue.

3] Concomitant use with SGLT2 inhibitors such as BRENZAVVY may decrease serum lithium concentrations.

Side Effects:-

1. signs of a bladder infection
2. Increased urination
3. Low blood sugar
4. Fever
5. Pain in your pelvis or back
6. Dehydration

Contraindications:-

1] History of severe allergic reaction to bexagliflozin2] On dialysis
3] Not recommended in patients with an eGFR less than 30 mL/min/1.73 m2.

Adverse Drug Reaction:-

1) Ketoacidosis
2) Lower Limb Amputation
3) Acute kidney injury
4) Hypotension
5) Urosepsis and Pyelonephritis
6) Necrotizing Fasciitis of the Perineum
7) Genital Mycotic Infections
8) Hypoglycemia with Concomitant Use with Insulin and Insulin Secretagogues.[18]

Uses:-

1] Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

2] It is used in diabetes induced cardiovascular diseases.

Drugs used in Diabetic Retinopathy:-

1. **Linagliptin**

Introduction:

For patients with type 2 diabetes, linagliptin is used in conjunction with diet, exercise, and other medications as needed to lower blood sugar levels (condition in which blood sugar is too high because the body does not produce or use insulin normally). Linagliptin is a member of the dipeptidyl peptidase-4 (DPP-4) inhibitors drug class. It functions by raising the concentrations of specific organic compounds that, when elevated in the blood,

lower blood sugar. Linagliptin is not used to treat diabetic ketoacidosis, a dangerous condition that can arise if high blood sugar is not treated, or type 1 diabetes, a condition in which the body does not produce insulin and cannot control the amount of sugar in the blood.

Chemistry: -

It is described as a crystalline solid and is white to yellow in colour. Very slightly soluble in isopropanol, alcohol, and methanol; sparingly soluble in ethanol 3.33 mg/L in water at 25 °C If kept as instructed and kept away from strong oxidising agents, stable. Toxic gases like carbon monoxide, carbon dioxide, and nitrogen oxides can be produced during thermal decomposition.

Melting Point: 190-196 °C

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

Mechanism of action :-

A reversible, competitive DPP-4 inhibitor is linagliptin. The breakdown of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) is slowed when this enzyme is inhibited3,5. While glucagon release from pancreatic beta cells is inhibited, GLP-1 and GIP stimulate the release of insulin from these cells5. When combined, these effects lessen the liver's breakdown of glycogen and enhance the release of insulin in response to glucose.[19]

Dosage :-

Each patient will require a different dosage of this medication. Observe the label's instructions or the advice of your physician. Only the average dosages for this medication are listed below. If your dosage is different, don't adjust it unless your physician instructs you to. The strength of the medication determines how much of it you take. The medical condition for which you are taking the medication also affects how many doses you take daily, how long you can wait between doses, and how long you take the medication for.

1) For oral dosage form (tablets):For type 2 diabetes:
2) Adults—5 milligrams (mg) once a day.
3) Children—Use and dose must be determined by your doctor.

Missed Dose

If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do not double doses.

Drug interaction:-

Rifampin is a product that might interact with this medication.

Metoprolol, propranolol, and timolol glaucoma eye drops are examples of beta-blocker medications that may help avoid hypoglycemia, the fast or pounding heartbeat that occurs when blood sugar levels fall too low. These medications have no effect on other signs of low blood sugar, such as sweating, hunger, or dizziness.

Blood sugar control becomes more challenging when using drugs that alter blood sugar levels. Consult your doctor or chemist about any medication's potential effects on blood sugar before beginning, stopping, or altering your regimen. As advised by your physician, take regular readings of your blood sugar. Inform your physician of the findings as well as any signs of elevated or lowered blood sugar. Your diabetic medication, exercise regimen, or diet may need to be modified by your physician.

Side Effects:-

1. fast heart beat
2. Drowsiness sweating
3. weakness

4. feeling jittery
5. Dizziness
6. confusion
7. stuffy or runny nose and sore throat

Precautions /Contraindication:-

Alcohol—drinking alcohol may cause severe low blood sugar. Discuss this with your health care team.

Other medicines— Take no more medications without first talking to your doctor about them. This covers over-the-counter medications like aspirin in particular, as well as medications for sinus issues, hay fever, colds, cough, asthma, and appetite control.

Counseling— It is necessary for other family members to get knowledge on how to stop side effects or provide assistance when they do occur. Additionally, individuals with diabetes may require additional counselling regarding possible adjustments to the dosage of their diabetes medication due to dietary or exercise modifications.

Travel—Carry your medical history and a current prescription with you. As with any other emergency, be ready for anything. Keep your meal times as close to your regular meal times as possible and allow for time zone changes.[20]

Adverse drug reaction:-

1. Severe stomach pains.
2. the whites of eyes turn yellow
3. Skin turns yellow although this may be less obvious on brown or black skin – this can be a sign of liver problems.
4. If you take linagliptine with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher.

Uses:-

1. Linagliptin is used in diabetic induced retinopathy and nephropathy.
2. It is also used in diabetic induced neuropathy and cvs disorder.

2. Vildagliptin

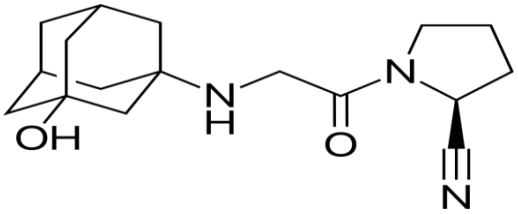
Introduction:-

Vildagliptin is a novel dipeptidyl peptidase-4 (DPP-4) inhibitor class oral anti-hyperglycemic (anti-diabetic) drug. The drug acts by stopping gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) from being inactivated by DPP-4. In the islets of Langerhans of the pancreas, this inhibitory activity results in a dual action where GLP-1 and GIP enhance insulin secretion by beta cells while inhibiting glucagon secretion by alpha cells.

Chemistry:-

Vildagliptin is an oral bioavailable inhibitor of dipeptidyl peptidase 4 (DPP-4) with hypoglycemic action that is based on cyanopyrrolidines. Vildagliptin is a crystalline powder that ranges in colour from white to slightly yellowish to slightly greyish. No polymorphs or solvates have yet to be discovered. Vildagliptin is readily soluble in water and non-hygroscopic.

The structural formula is:



The chemical name of vildagliptin is:
(S)-1-[2-(3-Hydroxyadamantan-1-ylamino) acetyl]pyrrolidine-2-carbonitrile

- **Mechanism of action:-**

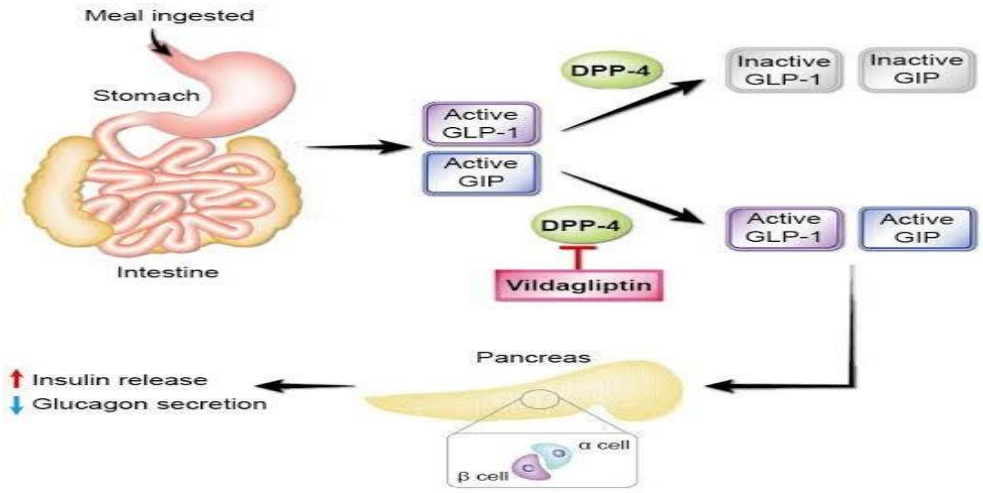


Fig: 10. Mechanism of Action of Vildagliptin

By specifically blocking dipeptidyl peptidase-4 (DPP-4), an enzyme that quickly truncates and inactivates GLP-1 and GIP upon their release from intestinal cells, vildagliptin lowers blood glucose levels. Vildagliptin lowers HbA1c, prandial glucose, and fasting glucose. It increases glucose-dependent insulin secretion and the sensitivity of alpha and beta cells to glucose. Postprandial lipid and lipoprotein metabolism is enhanced, and fasting and postprandial glucose levels are reduced. When an oral glucose challenge is given, over 70% of the insulin response is attributed to GLP-1 and GIP activity. Through G-protein-coupled GIP and GLP-1 receptor signalling, they induce insulin secretion in a glucose-dependent manner. GLP-1 has effects on insulin secretion, but it also promotes islet neogenesis and differentiation and reduces beta-cell apoptosis in the pancreas.[21]

Dosage:-

Vildagliptin is prescribed at a dose of 50 mg once daily in the morning, with or without food. In patients who are able to tolerate vildagliptin, the dose may be increased to 500 mg for additional glycemic control. Vildagliptin is administered in combination with metformin to provide extra glycemic control.

Drug Interaction:-

VILDAGLIPTIN interacts with antacids (cimetidine), thyroid hormones (thyroxine), high blood pressure medications (nifedipine, captopril, enalapril, and lisinopril), and pain relievers (aspirin, ibuprofen, and celecoxib).[22]

Side effects:-

Some of the common and major side effects of Vildagliptin are:

1. Headache
2. Cough
3. Constipation
4. Sweating
5. Hypoglycaemia
6. Weakness

7. Excessive sweating
8. Heartburn
9. Swelling of face, lips and eyelids

Contraindications:-

Type 1 diabetes, diabetic ketoacidosis, and severe liver impairment during pregnancy and breastfeeding.

Adverse drug reaction:-

1. Nasopharyngitis
2. Urinary tract infection
3. Skin lesions
4. Dizziness
5. Hepatotoxicity[23]

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