Diabetes & Antidiabetic drugs

Under supervision

Prof. Dr / Shahinda Elmesary

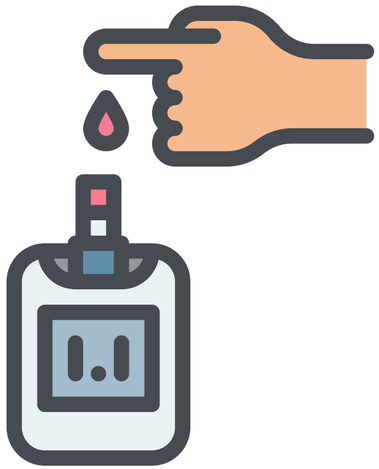
Definition of the disease

Pathophysiology (insulin & MOA)

Types of disease

Symptoms & Complications

Anti diabetic drugs



Definition :

Diabetes Mellitus

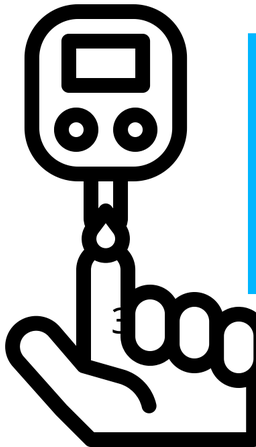
Is a disease state that results in an inappropriately high blood glucose levels over a prolonged period

There are 3 types:

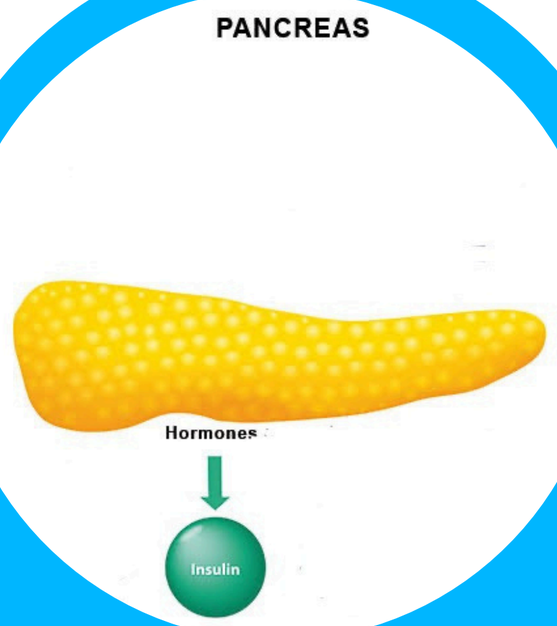
-type 1 & types 2

-Gestational diabetes ;

Occurs when pregnant women without a previous history of diabetes develop high blood sugar levels



1- INSULIN SECRETION



pancreatic tissue :

A) PANCREATIC ACINI : Exocrine part

B) PANCREATIC ISLETS : Endocrine part

Alpa cells & Beta cells & Delta cells & Epsilon cells

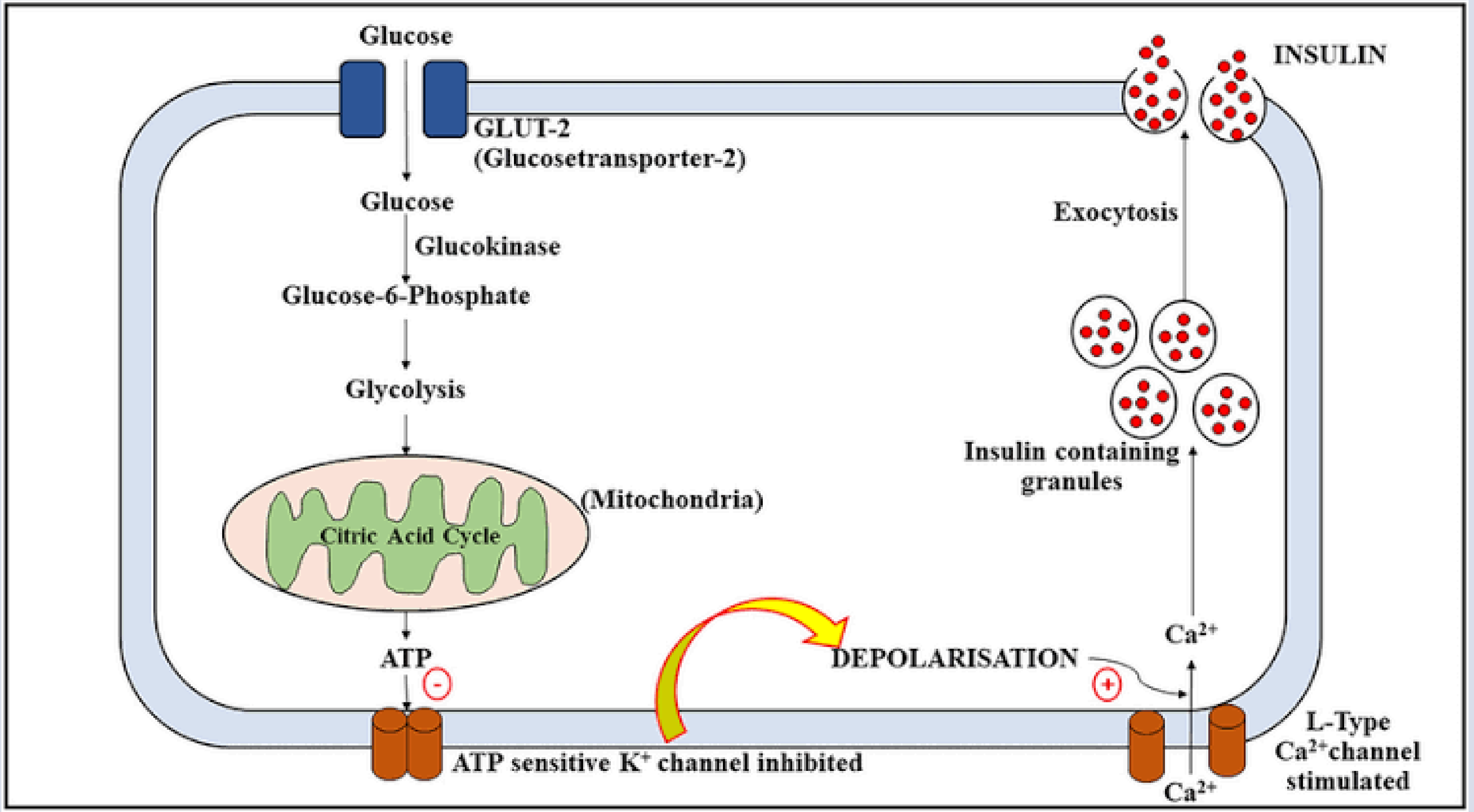
Beta cells is responsible for release of insulin

Mechanism of Insulin release & secretion ;

- Glucose is the primary stimuli for insulin release .
- Glucose enter the B - cells through the glucose transporters lead to depolarization .
- Upon depolarization, voltage-glated Calcium channels open .
- An increased intercellular Ca leading to increase insulin secretion

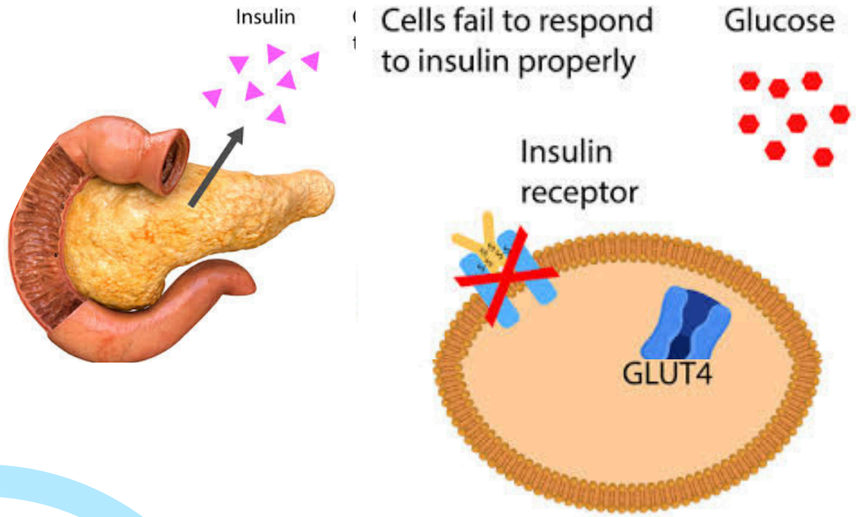
PATHOPHYSIOLOGY :

- Insulin secretion
- Insulin resistance


Glucose
GLUT-2
(Glucosetransporter-2)
Glucose
Glucokinase
Glucose-6-Phosphate
Glycolysis
(Mitochondria)
Citric Acid Cycle
ATP
ATP sensitive K+ channel inhibited
DEPOLARISATION
Ca2+
Ca2+
L-Type
Ca2+channel
stimulated
Exocytosis
Insulin containing
granules
INSULIN

INSULIN RESISTANCE :

Reduced biolological response to insulin



Causes :

1- pre-receptor;

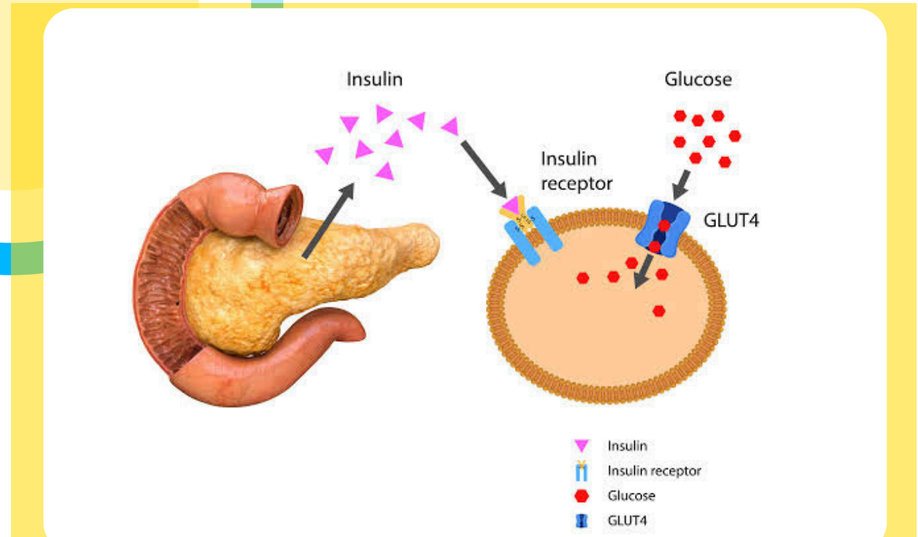
- insulin Abnormal
- Anti-insulin antibodies

2- Receptors ;

- Decreaced number of receptors
- reduced binding of insulin
- insulin receptors mutations
- insulin receptor - blocking antibodies

3- post-receptor

- defective signal transduction
- mutations of GLUT4



TYPES OF DIABETES

Type 1

Causes:

- Autoimmune destruction of insulin Producting beta cells of pancreas .
- Most common type in children .

Risk factors:

1- Genetics 2-Dietary factors

3 - viral infections 4- cytotoxic drugs

Type 2

Causes :

- Defective responsiveness of body tissue to insulin
- common type in adult

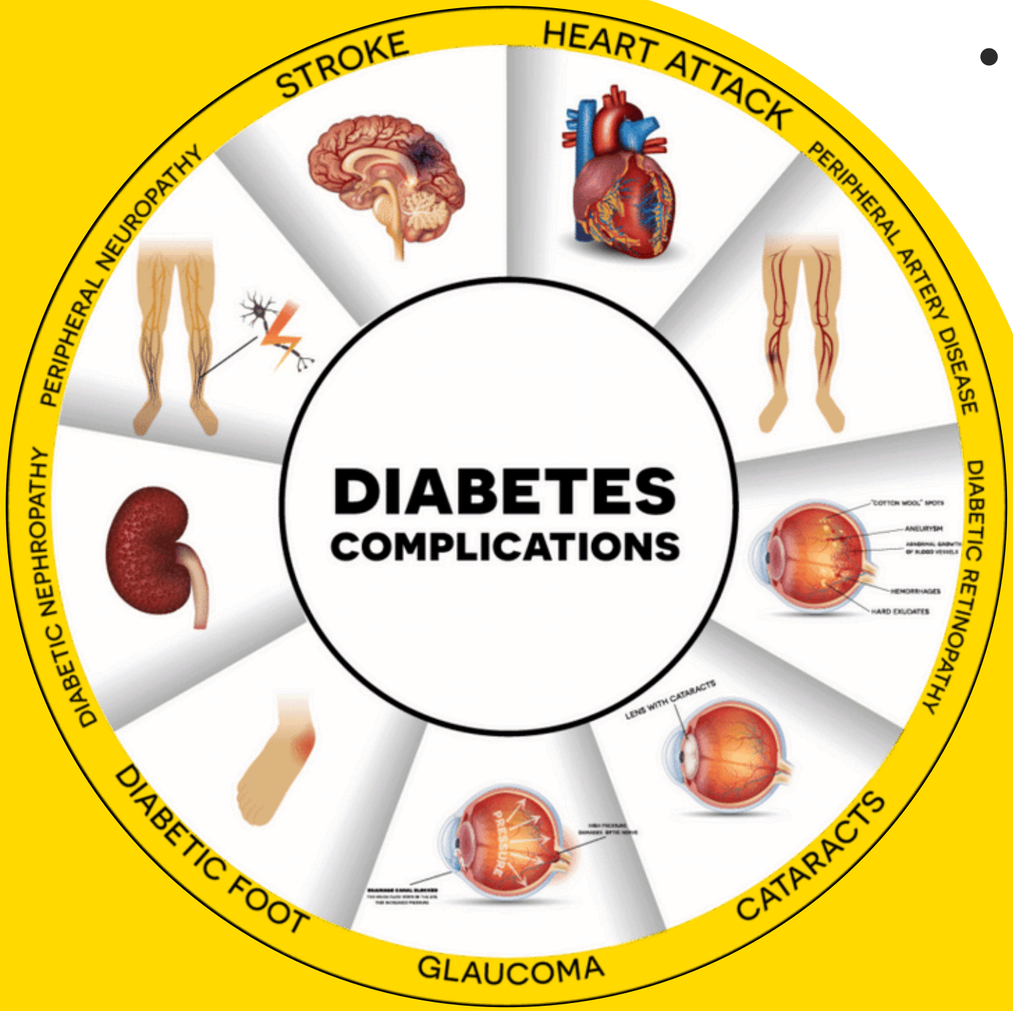
Risk factors:

1- family history 2- Age greater than 45

3- over weight. 4- polycystic ovarian syndrome

5- History of gestational diabetes

6- Hypertension or dyslipidemia



- If blood sugar levels well_controlled , the complications of diabetes are far less common and less severe .

ACUTE COMPLICATIONS ;

1- HYPOGLYCEMIA
2- DIABETIC KETOACIDOSIS
3- DIABETIC COMA
4- HYPERGLYCEMIA HYPEROSMOLAR STATE

CHRONIC COMPLICATIONS ;

Macrovascular Disease

1-Coronary artery disease
2-peripheral vascular disease
3-Diabetic foot

Microangiopathy

1- Diabetic Nephropathy
2- Diabetic Neuropathy
3- Diabetic Retinopathy

Immune Dysfunction

Infections & autoimmune diseases

DIABETIC COMPLICATIONS;

Acute complications **&** **Chronic complications**

Treatment of diabetes

1- LIFE STYLE MODIFICATIONS

_ Weight management
_ Alcohol consumption
_ Nutration therapy
_ physical activity

2 - MEDICATIONS ;_

_ Insulin for type 1&2

_ Metaformin & Incretin mimetic and oral Antibiotic for type 2

ANTIDIABETIC DRUDS

Insulin

Regular insulin
(Actirapid)

Insulin Aspart
(NovoRapid)

Insulin NPH
(Mixtard)

Insulin Glargine
(Lantau)

Insulin secretagogues

Sulfonylureas

- First generation
- second generation

Glimepiride
(Amaryl)

Meglitinides

Repaglinide
(NovoNorm)

Insulin-sensitizers

Biguanides

Metformin
(Glucophage)

Thiazolidinediones

Pioglitazone
(Actos)

Gliptin

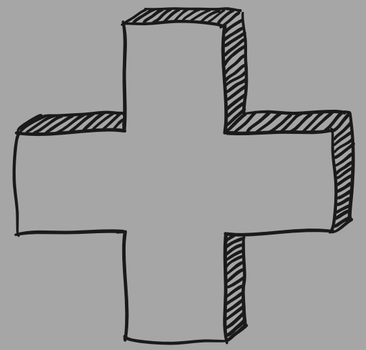
Sitagliptin (Januvia")

Vildagliptin (Galvus*)

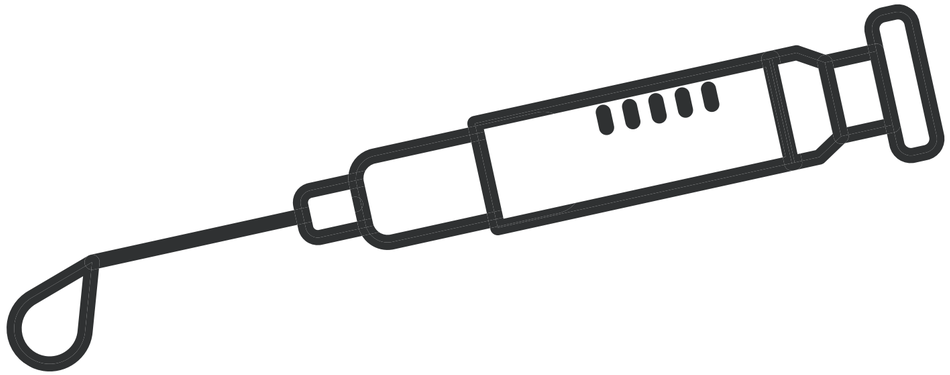
Saxagliptin (Onglyza*)

Linagliptin (Tradjenta")

Alogliptin (Nesina*)



Insulin Pens



Short-acting Insulin	Regular insulin (Actirapid)
Rapid-acting Insulin	Insulin Aspart (NovoRapid)
Intermediate acting Insulin	Insulin NPH (Mixtard)
Long-acting Insulin	Insulin Glargine (Lantau)

Short acting insulin

Regular insulin (Actirapid)

Uses :

Used to control the Postprandial Hyperglycemia (Bolus ONLY).

- Regular insulin can be use as lY m emergeney.

Time of Administrations

- 30:60 minutes before meal .

- Patient must eat (to avoid hypoglycemia .

Pharmacokinetics

Onset: 30-60 minutes.

Peak ; 2 - 4 hours

Duration: 4-8 hours

Rapid-acting Insulin

Insulin Aspart (NovoRapid)

-They are preferred to Regular Insulin because of faster onset and shorter duration, better mimicking physiological need during postprandial period.

---

uses :

-Used to control the Postprandial Hyperglycemia (Bolus ONLY).

-nsulin Aspart can be used as IV in emergency.

Time of Administrations

-5:15 minutes before meal; just before or with a meal.

-Patient must eat (Act very quickly hypoglycemia occur if not eat).

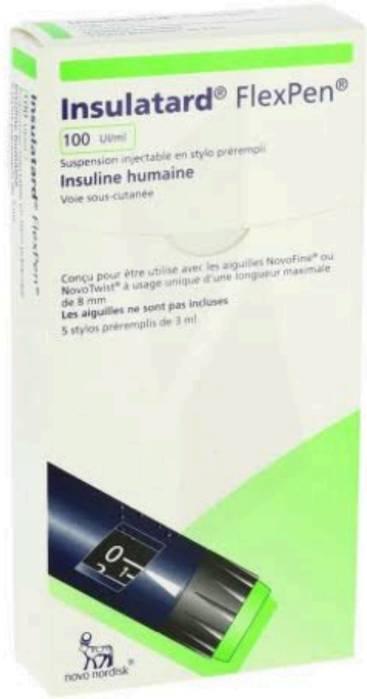
Pharmacokinetics

- Onset; 5-15 minutes. - Peak; 1-2 hours. - Duration; 3-5 hours.

Intermediate acting Insulin

Insulin NPH (insulatard)

Neutral Protamine Hagedorn (NPH)



- is a suspension (Cloudy/milky) of crystalline Zinc

Insulin combined with the positively charged polypeptide

Protamine; less soluble, resulting in delayed absorption and a longer duration of action.

Pharmacokinetics

Onset; 1-2 hours. - Peak; 5-10 hours. - Duration; 10-16 hours.

Long-acting Insulin

Insulin Glargine(Lantaus)

Pharmacokinetics

Onset; 2 hours, - Peak; (max. effect after 2-4 hours)

Duration; 10 - 16

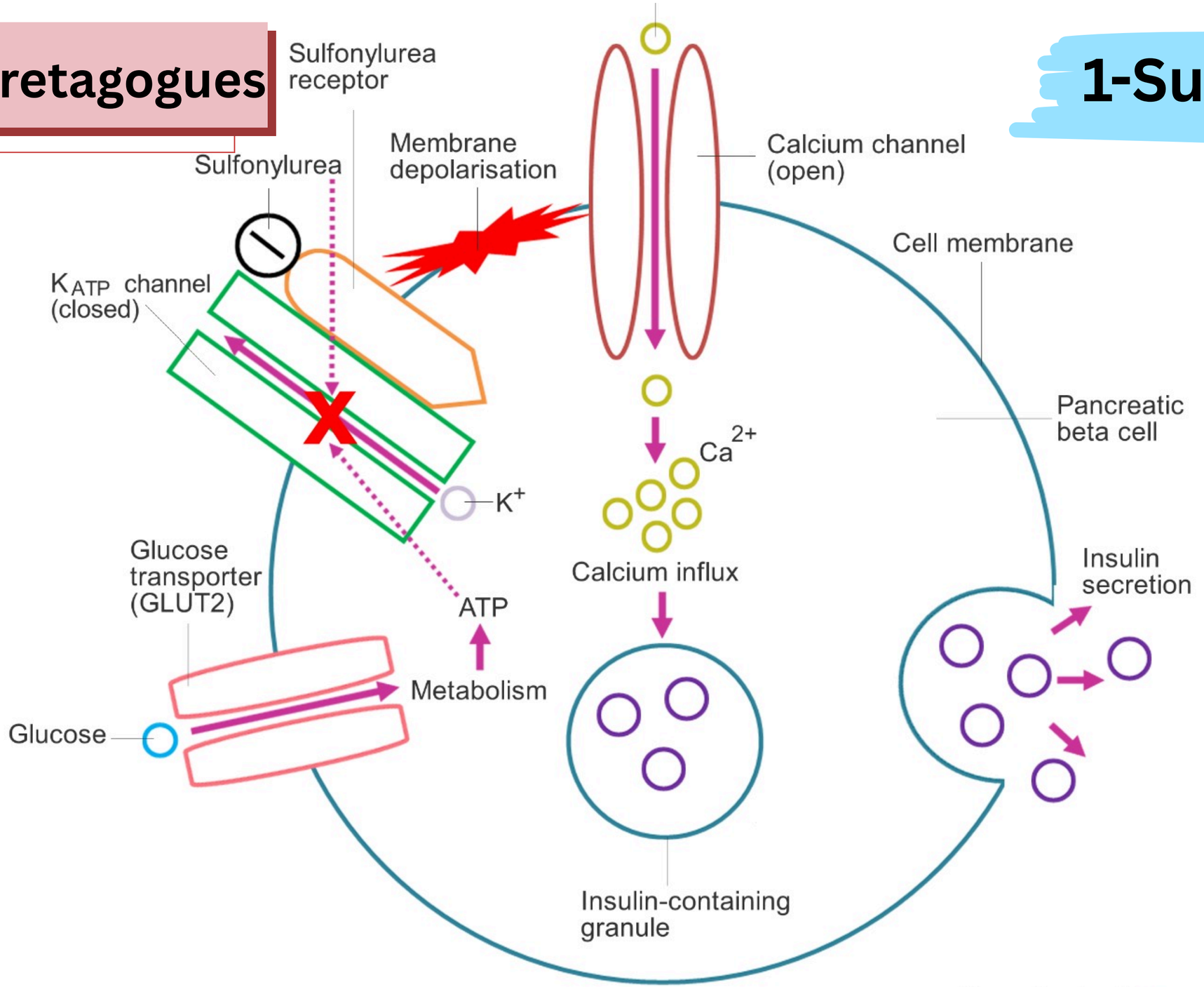
- To maintain solubility the formation is acidic (PH=4)
- Glargine is usually given once daily

Injection site reaction

(e.g. , edema , itching, pain , stinging) ; because acidic formulation ,

Insulin secretagogues

1-Sulfonylurea



Insulin secretagogues

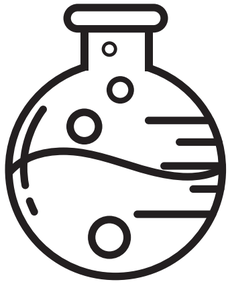
1-Sulfonylurea

- These agents are classified as insulin secretagogues, because they promote insulin realse from B-cells of Pancreas .

-The sulfonyllures current use is second generation .

- **Major side effect :**

Weight gain, hyperinsulinemia and hypoglycemia.



- **Drug interaction**

Drugs that decrease Sulfonylureas effects :

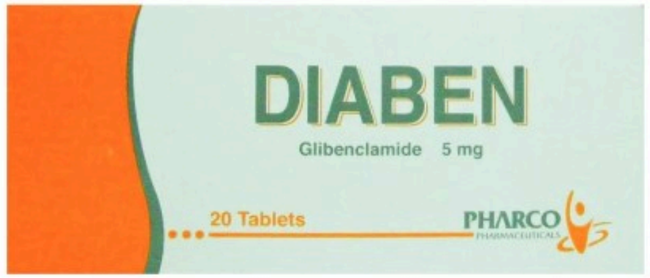
Corticosteroids, Diuretics, Niacin, Phenothiazines and Sympathomimetics.

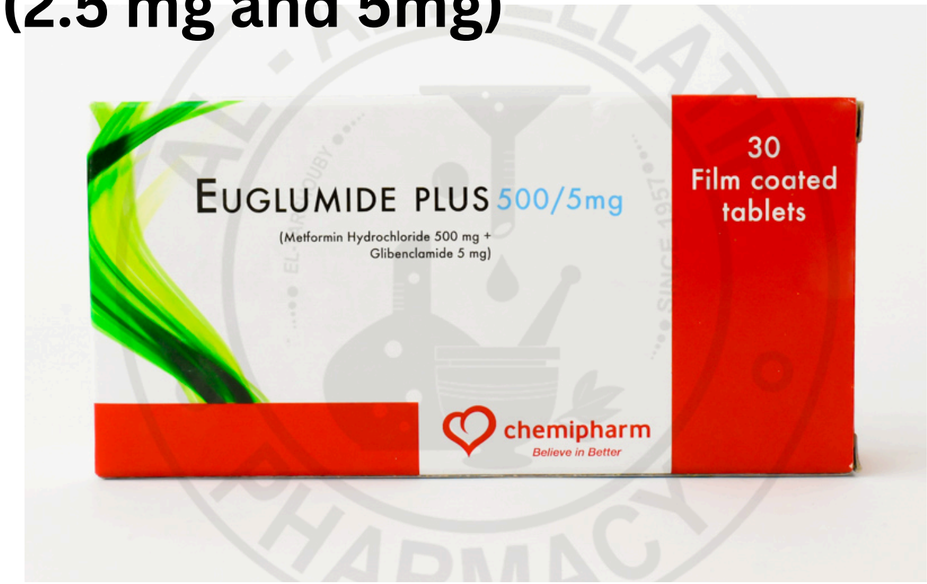
Drugs that ↑ Sulfonylureas effects; Azole antifungals, B-blockers & warfarin .

Insulin secretagogues

1-Sulfonylurea

- **Glibenclamide** : available as tablets : (2.5 mg and 5mg)





DIABEN

EUGLUMIDE
EUGLUMIDE PLUS

Insulin secretagogues

1-Sulfonylurea

- **GLIPIZIDE** : available as tablets(5mg) and Modified Release

MINIDIAB

DIAMICRON

Insulin secretagogues

1-Sulfonylurea

- **Glimepride**

available as tablets :
(1,2,3,4and6mg,)

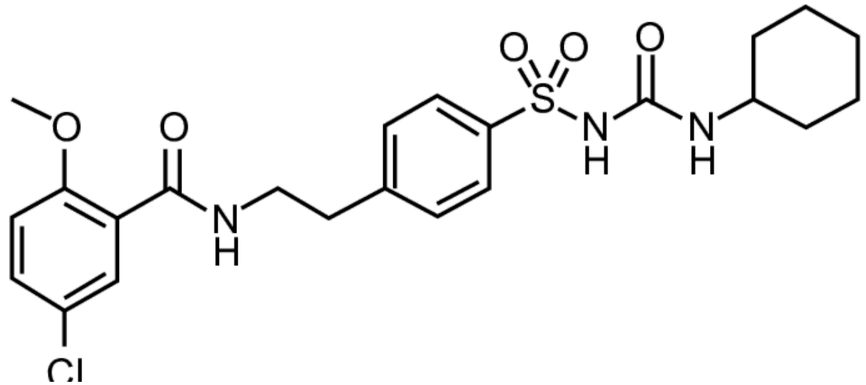
Amaryl
(monotherapy)

Amaryl M
(compination +metformin)

-Glimepride is approved for once-daily use as monotherapy or combination with insulin.

- second generation are usually combined with metaformin

• GLIBENCLAMIDE

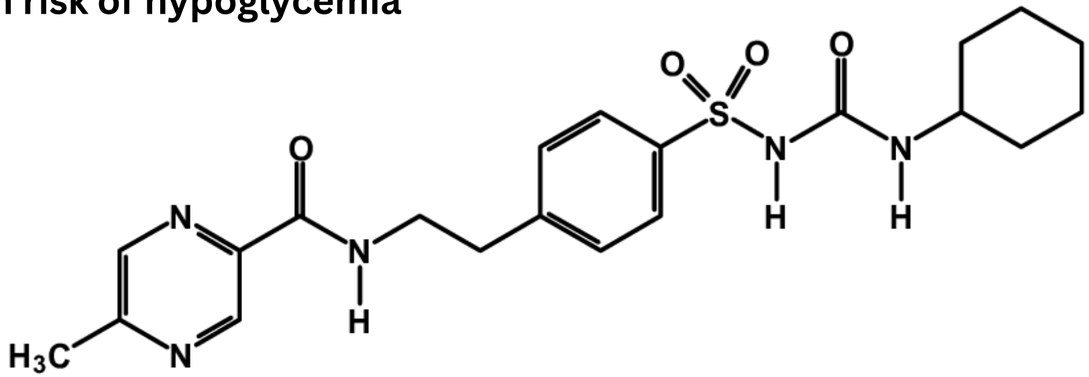


highly lipophilic and bulky.

Effect: strong and prolonged binding

to SUR1 → very potent insulin release and long duration. ⟶ high risk of hypoglycemia

• GLIPIZIDE

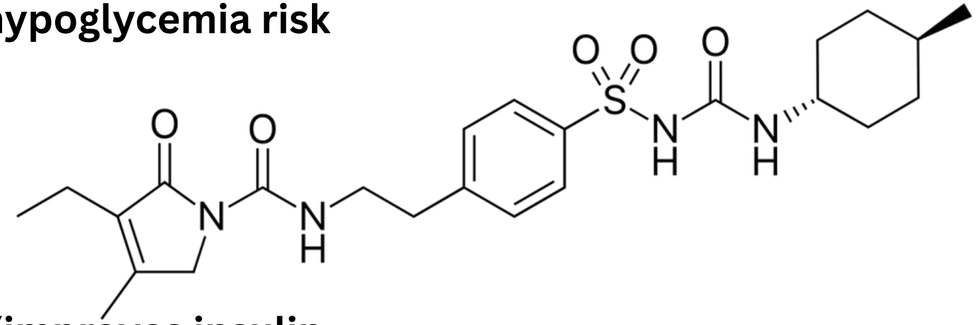


less lipophilic and smaller than glibenclamide.

Effect: absorbed quickly, shorter half-life, less tissue accumulation.

Clinical: faster onset, shorter duration compared with glyburide → lower hypoglycemia risk

• Glimepride



modification allows slightly different binding geometry at SUR1.

Effect: triggers insulin release more gently, and also has extra-pancreatic effects (improves insulin sensitivity in peripheral tissues).

Clinical: effective with once-daily dosing, lower hypoglycemia risk than glyburide.

2- Meglitinides

MOA ;

-meglitinides act on the same B-cell receptor as Sulfonylureas (Same mechanism) but have a diferent chemical structure with rapid onset and a short duration of action

Repaglinide

_NovoNorm® available as tablets (white: 0.5 mg; yellow: 1 mg; panc: 2 mg), dose; 15 minutes before each main meal; max, daily dose: 16 mg per day .

_Risk of hypoglycemia if meal is delayed or skipped or inadequate carbohydrata .

Major side effects:

1) Weight gain

2) Hypoglycemia

2- Meglitinides

- **MITIGLINIDE**

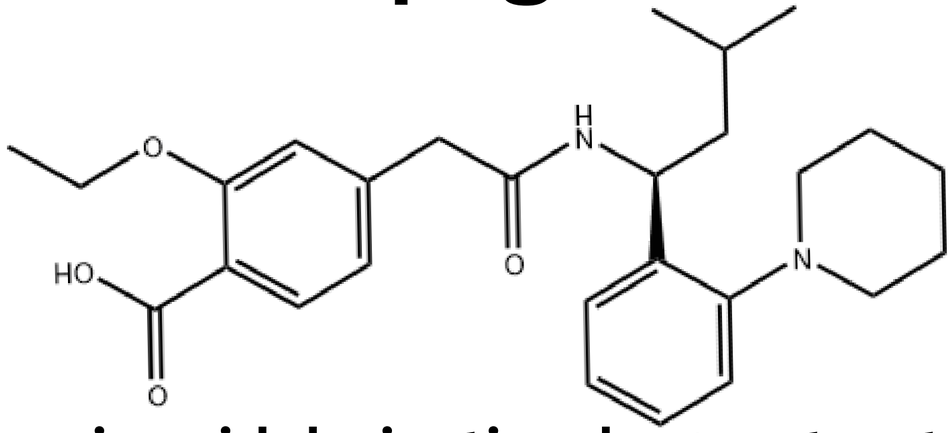
  available as tablets

  (5mg and 10mg)

MEGY-ONE

MEGLITINIDES

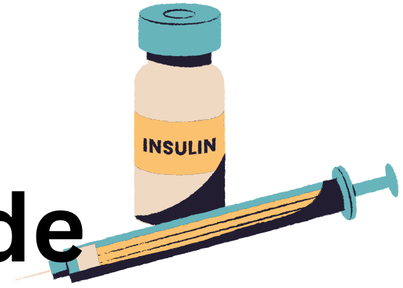
repaglinide

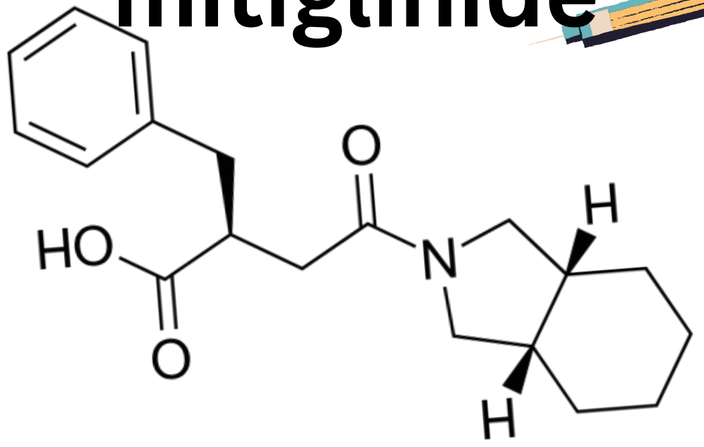


A benzoic acid derivative, larger structure, fast onset but longer duration (4–6 hours). It is metabolized mainly by CYP3A4 and CYP2C8, so it has many drug–drug interactions. Useful for postprandial glucose control, but requires caution in patients with liver impairment or polypharmacy

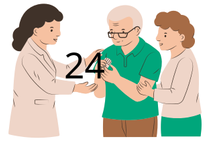
structure

mitiglinide





A simpler phenylalanine-like derivative, with a very rapid onset and shorter duration (2–3 hours). It has fewer CYP-mediated interactions, but its half-life may be prolonged in renal impairment, so caution is needed in kidney disease.



INSULIN SECRETAGOGUES

Sulfonylurea

Slower onset.

- Long duration (12–24 hours, depending on the drug).
- Usually taken once or twice daily.
- Higher risk of hypoglycemia (especially in elderly or renal impairment).
- Cause weight gain

Traditional, inexpensive, effective for fasting control, but safety concerns (hypoglycemia, weight).

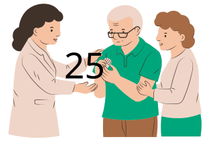
MEGLITINIDES

- Very rapid onset (within 15–30 minutes).

Short duration (2–6 hours).

- Must be taken with each meal.
- Lower risk of hypoglycemia
- Weight gain possible but generally less than sulfonylureas.

for patients with irregular meals, safer in renal impairment, and useful for postprandial hyperglycemia.



Insulin-Sensitizers

1) Biguanides

Metformin

_ The Insulin-Sensitizers are class of drugs that enhance the Insulin sensitivity in peripheral tissues (muscle, fat and liver); decrease insulin resistance and increases glucose uptake.

MOA

Metformin act by decrease insulin resistance;

* Suppressing liver Glucose production (decrease hepatic gluconeogenesis).
• Decreasing intestinal absorption of Glucose.

* Improving Insulin sensitivity by increasing peripheral Glucose uptake and utilization.

Uses;

Type 2 Diabetes (first line therapy; all patients).

Off-Label Uses; [Decrease Insulin Resistance];

- **Prediabetes; decrease their chances of diabetes.**

- **Gestational Diabetes**

- **Polycystic Ovary Syndrome (PCOS) and Female Infertility.**

- **Prevention of weight gain caused by antipsychotic medications.**

Dose

500 mg , 800 mg , 1000 mg (Available as immediate-release and extended-release tablets)

Side effects;

- **Gastrointestinal Upset** (including diarrhea, cramps, nausea and vomiting)
- **Lactic Acidosis** (rare, but potentially severe)
- **Long-term use may interfere with Vitamin B12 absorption.**

Examples ;

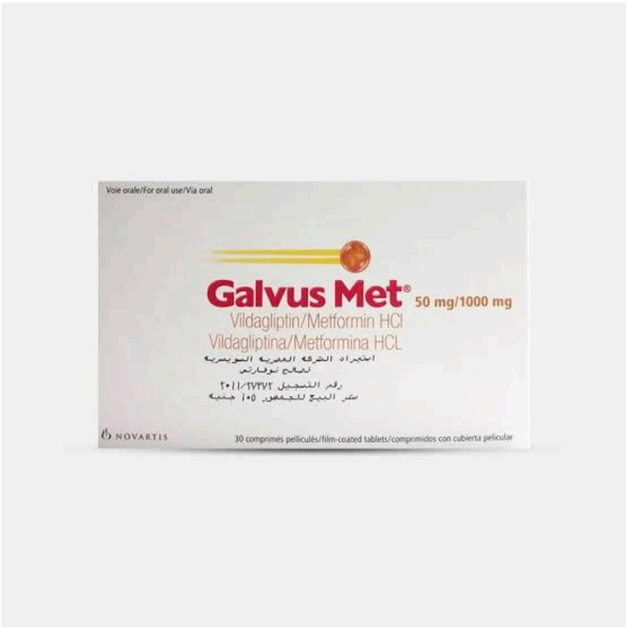
Cidophage

Glucophage

Combinations

+Sitagliptin

+Glimepride



+Vidagliptin

2-Thiazolidinediones

Thiazolidinediones are a class of oral antidiabetic agents used in the management of type 2 diabetes mellitus. They work by improving insulin sensitivity in peripheral tissues (muscle, adipose tissue) and the liver

MOA :

-TZDs are peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists.

-They bind to PPAR-γ nuclear receptors in adipose tissue, muscle, and liver.

-Increased glucose uptake in muscle and adipose tissue.

Examples:

-Pioglitazone

-Rosiglitazone (withdrawn)

Side effects:

-Weight gain (due to fluid retention and fat redistribution)

-Edema

-Heart failure risk

Gliptin

Definition

Gliptins are a class of antidiabetic drugs known as Dipeptidyl Peptidase-4 (DPP-4) inhibitors.

They are used in the management of Type 2 Diabetes Mellitus by prolonging the activity of incretin hormones.

MOA :

1. The enzyme DPP-4 normally degrades incretin hormones (GLP-1 and GIP).
2. By inhibiting DPP-4 → incretins remain active for a longer time.
3. This leads to:

Increased insulin secretion in a glucose-dependent manner.

Decreased glucagon secretion.

Better control of postprandial (after-meal) glucose levels.

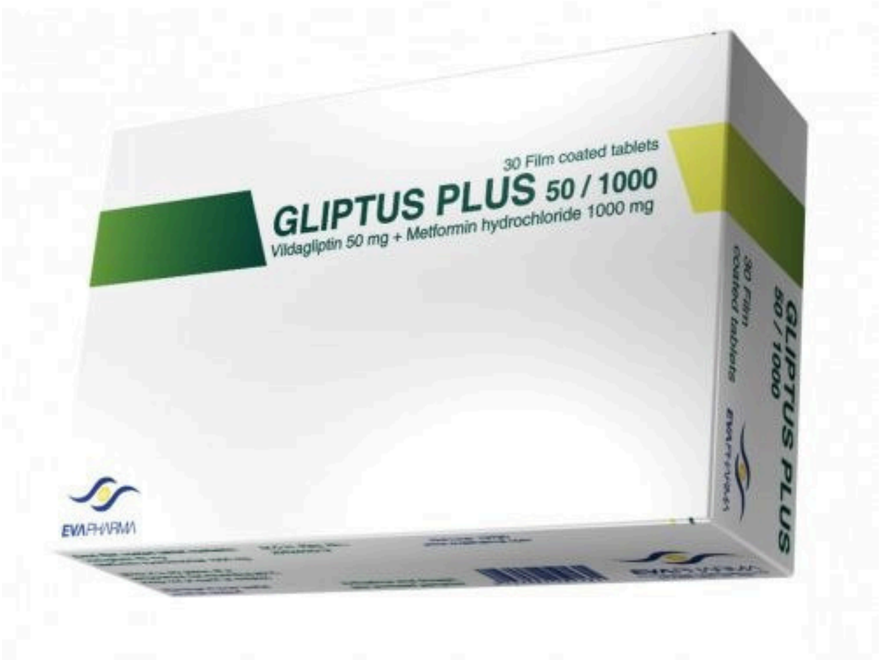
Examples :

-Sitagliptin

-Vildagliptin

-linagliptin

- saxagliptin



Combination Therapy :

-Gliptins can be used alone or in combination with other diabetes medications, such as metformin

Side effects:

Common:

-Headache

-Upper respiratory tract infections (URTI, nasopharyngitis)

-Mild gastrointestinal symptoms (nausea, diarrhea)

Thank You

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