**REVIEW ARTICLE**

# Compilation of Scientific Data for Newly CDSCO-Approved Antidiabetic Drugs in Last Five Years: A Review

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**ABSTRACT**

Diabetes is a substantial medical problem that is increasing globally due to a rise in sedentary lifestyles, unhealthy eating habits, and obesity rates. There is a tight relationship between diabetes with obesity. Several epidemiological studies suggested that 80% of T2D patients are obese or overweight. Indeed, the immune system assaults the pancreatic beta cells that produce insulin in T1D, an autoimmune disease. High blood sugar levels occur when the body generates very little insulin. is frequently linked to unhealthy habits, including not getting enough exercise, eating poorly, and being overweight. Heart disease, diabetic neuropathy, kidney problems, ketoacidosis, and nerve damage are only some of the many health consequences that are more common with both types. Antidiabetic drugs like metformin can be used to lower the blood glucose level. Sulfonylureas, glinides, and thiazolidinediones are some most common oral antidiabetics (OADs), and for newly analyzed type 2 diabetes, glucosidase inhibitors are cost-effective strategies to improve glycaemic control. As a second line of defense against T2D, you may be prescribed an enzyme inhibitor (DPP-4i), an inhibitor of renal SGLT-2i, or an agonist for glucagon-like peptide-1 receptor. Poor adherence to oral antidiabetic medication regimens is associated with therapy failure and other consequences in patients with type 2 diabetes, which is a collective medical problem. Acarbose, miglitol, alogliptin, sitagliptin, sitagliptin-metformin, tirzepatide, liraglutide, nateglinide, rapeglinide, dopagliflozin, empagliflozin-metformin, glipizide-metformin, glimepiride-pioglitazone, glipizide, rosiglitazone, pioglitazone-alogliptin, and pioglitazone-metformin, among other antidiabetic medications, have been approved for use in India by CDSCO. All across the world, regulatory bodies are in charge of making sure that pharmaceuticals are safe, effective, and up to par at every stage of the drug lifecycle, from development to manufacture to marketing. Their job is to keep the public healthy.

**Keywords:** Antidiabetic drugs, CDSCO, OADs, Combinational therapy.

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## INTRODUCTION

Elevated blood glucose levels and an inadequate or inefficient response to insulin secretion are the hallmarks of diabetes, a metabolic disorder that affects the body over time. Although certain people may be more likely to develop diabetes due to their genes, environmental and lifestyle variables are much more important in setting the stage for the illness to begin and worsen.[1] The composition of the microbiome (the bacteria that live in your gut) and epigenetics are two more potential variables that impact the development and risk of diabetes. Insufficiency of insulin production by the pancreas causes an increase in blood sugar levels.

Understanding the underlying pathophysiology and potential complications of diabetes is crucial for developing effective strategies to manage and improve the condition.[2,3] Autoimmune lysis of pancreatic beta cells causes insulin deficiency in T1D. T2D is characterized by a decline in insulin production by the pancreatic beta cells. The effects of chronic diabetes on several bodily systems and organs are real. Diabetic foot ulcers, peripheral artery disease, nephropathy, retinopathy, peripheral neuropathy, and other sequelae are among these.[4] According to the International Diabetes Federation (IDF), diabetes is a big public health concern since it affects a substantial percentage of the global population. In 2021, 537 million adults (ranging in age from 20–79) were living with diabetes.[5] This figure is anticipated to climb to 783 million by 2045, according to the IDF, suggesting a substantial upsurge in the incidence of diabetes in decades to come.[6] It is estimated that by 2025, the figure of individuals suffering from diabetes in India will increase by 57.2 million.[7] For all these complications,

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the financial burden of diabetes and high morbidity, there is a strong emphasis on research across various domains to advance our understanding and develop new therapeutics. These initiatives encompass basic, applied, and clinical research aimed at addressing several key areas like new therapeutics for diabetes (insulin therapies, oral antidiabetic agents, beta-cell regeneration and preservation, gene therapy, and stem cell research), complications research (diabetic neuropathy and nephropathy, retinopathy and eye health, cardiovascular complications, etc.) and pharmacology of antidiabetic drugs (drug combination and personalized medicine, mechanism of action). Apart from these complications, diabetes leads to mental, physical, and societal issues for the patients.

Metformin and other antidiabetic medications can help bring blood glucose levels down. Oral antidiabetics such as glinides, thiazolidinediones, and sulfonylureas are among the most popular options. One cost-effective strategy for improving blood sugar regulation in newly diagnosed type 2 diabetics is the use of glucosidase inhibitors. Glucagon-like peptide-1 receptor agonists, inhibitors of dipeptidyl peptidase-4 enzyme (DPP-4i), and renal sodium-glucose co-transporter-2 are among the drugs used as a secondary defense against type 2 diabetes. Treatment failure and other complications might occur in type 2 diabetes individuals if they do not adhere to taking their oral antidiabetic medicine as prescribed. Chronic hyperglycemia, comorbidities, and hospitalizations are more common in type 2 diabetics (T2D) who do not adhere to their medication regimens, making it imperative that efforts be made to increase adherence to oral antidiabetic medications (OADs) among T2D patients.[9] Although oral drugs are being administered, there are issues with them, such as frequent dosage, adverse effects, and non-compliance from patients. The injectable method of administering insulin presents additional challenges. When these medications' dosages are missed, blood glucose levels fluctuate, which has serious negative consequences. In recent years, there have been significant progressions in the pharmacological management of diabetes, particularly in the development of new drug combinations and alternative therapies. Metformin with SGLT2 Inhibitors and DPP4 Inhibitors combination has gained popularity due to its synergistic effects in managing blood glucose levels. SGLT2 inhibitors reduce renal glucose reabsorption, while DPP4 inhibitors prevent the breakdown of incretin hormones, leading to improved glycemic control. In addition to insulin and metformin, CDSCO has authorized a number of interesting alternatives for the management of diabetes, such as the novel thiazolidinedione lobe glitazone, efpeglenatide, and tirzepatide, all of which were undergoing clinical trials in 2022.[10]

Patients by T2D who do not tolerate metformin are given fixed-dose combinations of several oral antidiabetic medications; strict glycemic control is a key component of their treatment. Sulfonylureas, GLP-1 receptor agonists, thiazolidinediones, SGLT-2 and DPP-4 inhibitors are common components of such combos. Tolerance, comorbidities, renal function, and target glycemic levels are some of the variables that go into choosing a combination. An integral part of managing type 2 diabetes is the utilization of fixed-dose combinations (FDCs), which help with patient adherence, cost reduction, and successful glycemic control. Changes to one's way of life, a single-agent oral antidiabetic drug (OAD), and eventually combination therapy are the standard steps in the management of T2D. Consider initiating insulin or glucagon-like peptide one agonist, adding a third oral medication, a DPP-4 inhibitor, an SGLT2 inhibitor, or TZDs if glucose objectives are not achieved with two medicines. Sulfonylureas or human insulin may be administered to patients with T2D if metformin alone does not bring about glycemic control. In the treatment of T2D, metformin is the active ingredient most often found in FDCs. With their combination of metformin, SU, and either voglibose or pioglitazone, triple FDCs have possible to recover glycemic control, decrease pill burden, and increase compliance. Metformin-alogliptin, metformin-repaglinide, sitagliptin-metformin, empagliflozin-metformin, glipizide-metformin, and pioglitazone- -metformin, etc. are some common fixed dose combination antidiabetics in which metformin is common for all the antidiabetic drugs[11,12]

Even though there are some classes of antidiabetic drugs on the market, research is being done to find new, safer antihyperglycemic drugs that are more potent and more tolerable.[13]

Due to their delayed drug release feature and avoidance of first-pass metabolism with oral antidiabetics, a variety of transdermal systems are being used in conjunction with many techniques and approaches (iontophoresis, nanoformulations, electroporation, and microneedles) to control diabetes. These transdermal methods have a higher bioavailability than oral delivery.[14] The complexity and protracted nature of diabetes cause micro- and macrovascular issues that are frequent in its patients. Globally, the increasing occurrence and frequency of diabetes pose a significant risk to public health. Inadequate prolongitivity of action, site specificity, restricted bioavailability, and dose-related side effects are approximately difficulties with presently accessible antidiabetic drugs, which attract the researcher's interest towards the discovery of new antidiabetics with good bioavailability and low side effects.[15]

For the management of diabetes, thousands of new antidiabetic drugs are synthesized each year, but it is really difficult to get rid of this disease.

The "drug regulatory authority" typically refers to an organization or government agency responsible for overseeing the regulation, approval, manufacturing standards, marketing, and safety of pharmaceutical drugs and medical devices within a particular country or region. It is imperative that these agencies guarantee that all pharmaceuticals and medical supplies are up to par in terms of safety, quality, and effectiveness before they are sold to the general population. Indeed, regulatory bodies are vital in making sure that pharmaceutical goods are safe, effective, and of high quality and that drug information is accurate and suitable. Pharmaceutical research and development, licensing, registration, production, advertising,

**Table 1:** List of antidiabetic drugs with improved dosage and dosage forms approved in the last five years

| *S. No.* | *Drug* | *Year of approval* | *Approving authority* |
|---|---|---|---|
| 1 | Injectable solutions of tirzepatide in prefilled pens containing 2.5, 5, 7.5, 10, 12.5, and 15 mg of drug per mL. | 19-01-2024 | CDSCO |
| 2 | Imeglimin hydrochloride tablet 500/1000 mg and bulk | 6-10- 2023 | |
| 3 | Lobeglitazone sulfate 0.5 mg + Glimepiride 1-mg tablets | 23-5-2023 | |
| 4 | Sitagliptin fentanil phaohate tablet 35, 70 mg, 140 g | 29-11-2022 | |
| 5 | Imeglimin hydrochloride tablet 1000 mg and bulk drug | 18-11-2022 | |
| 6 | Lobeglitazone sulfate tablet 0.5 mg and lobeglitazone sulfate bulk | 16-09-2022 | |
| 7 | Lobeglitazone sulfate tablet 0.5 mg + Metformin HCL extended release 500 mg tablet and lobeglitazone sulfate tablet 0.5 mg + Metformin HCL extended release 1000 mg | 30-12-2022 | |
| 8 | The film-coated tablets of 100 mg remogliflozin etabonate and the bulk form of this medicine | 26-04-2019 | |

and labeling are all matters that fall under the purview of individual regulatory bodies. Several international organizations ensure consistency in drug regulation, including the following: MHRA in the United Kingdom, USFDA in the United States, TGA in Australia, CDSCO in India, ANVISA in Brazil, MCC in South Africa, HEALTH CANADA in Canada, EMEA in the European Union, SFDA in China, NAFDAC in Nigeria, MHLW in Japan, MEDSAFE in New Zealand, MCAZ in Zimbabwe, KFDA in Korea, SWISSMEDIC in Switzerland, and MoH in Sri Lanka. These regulatory authorities work tirelessly to ensure that pharmaceutical products meet rigorous standards for safety, efficacy, and quality, ultimately protecting public health and ensuring access to safe and effective treatments.[16,17]

The list of antidiabetic drugs with improved dosage forms is mentioned in Table 1. The list is specifically designed using the data of the last five years.

**Tirzepatide (2024)**

Tirzepatide is a novel approved drug by CDSCO, which FDA already approved in May 2022 for treating type 2 diabetes.[18] It is also used off-label for treating obesity and is a once-a-week subcutaneous injectable medication with incremental dose increases. The doses approved in the year 2024 are 2.5,5, 7.5, 10,12.5, and 15 mg/0.5 mL solution, which are filled in the pen as an injection.

Tirzepatide is a synthetic peptide that stimulates insulin release from the pancreas and reduces hyperglycemia. It also increases the levels of adiponectin and lowers the user's appetite. With the exception of T2D, tirzepatide is a GLP-1 and GIP receptor agonist that has been licensed for use by FDA. The reason being, both hormones work to decrease blood sugar levels. While blood sugar levels are extraordinary, the hormone GLP-1 enhances insulin production, and when food is consumed, another hormone, GIP, boosts insulin secretion. Tirzepatide advances insulin response to meals by activating GIP receptors, which in turn increases insulin release from pancreatic beta cells.[19] In type 2 diabetes, it aids weight loss and better glycemic control.[18] Since tirzepatide is still a relatively young medication, there is a lack of data on this front. [20] When taken in conjunction with a well diet and consistent exercise, tirzepatide can help people with T2D keep their blood sugar levels more under control. At the GIP receptor, tirzepatide acts similarly to natural GIP, but at the GLP-1 receptor, it favors cAMP production over β-arrestin recruitment and has a reduced capacity to promote GLP-1 receptor internalization compared to GLP-1.[21]

*Pharmacokinetics*

There is a predictable pattern to the distribution and elimination of tirzepatide in the body, as its pharmacokinetics are well-characterized *via* a two-compartment model through first-order absorption and elimination. It takes approximately 5 days for half of the drug to be eliminated from the body. This extended half-life is significant because it allows for sustained exposure to tirzepatide with once-weekly subcutaneous dosing.[22] Tirzepatide has an approximate bioavailability of 80%, meaning that about 80% of the administered dose reaches the bloodstream and is available to produce a pharmacological effect.[18]

**Imeglimin Hydrochloride (2023)**

Imeglimin is a promising new antidiabetic medication that works by targeting the mitochondrial oxidative phosphorylation process. It's being developed as an add-on treatment for combination therapy in T2D patients to improve insulin secretion and sensitivity. Imeglimin works by phosphorylation of Akt leads to its activation, which in turn promotes glucose uptake and metabolism. Imeglimin's ability to increase Akt phosphorylation can enhance insulin sensitivity. Imeglimin's modulation of insulin receptor substrate phosphorylation may contribute to improved insulin sensitivity in diabetic conditions.[13]

*Structure*

The structural formula is given in Figure 1.

*Chemistry of imeglimin hydrochloride*

It has molecular formula $C_6H_{14}ClN_5$. imeglimin is a novel tetrahydrotriazene compound.[23] Imeglimin contains a glimin core structure, which is characterized by a cyclic guanidine group that is responsible for antidiabetic activity. Modification in this guanidine group alters the potency of the drug. EWG or EDG on its chemical structure, can influence the drug's physicochemical properties. Structural modifications involving substituents or side chains attached to the glimin core may enhance imeglimin's selectivity, metabolic stability, and target specificity.[24]

*Pharmacological profile*

Imeglimin has a dual action: first, it increases the amount of GSIS, which preserves β-cell mass. Secondly, it improves insulin action, which includes increasing insulin signaling in skeletal muscle and the liver and limiting the outflow of glucose from the liver. [25]

*Pharmacokinetic*

The organic cation transporters OCT1, OCT2, and MATE1 are all regulated by imeglimin, which also inhibits MATE1 and MATE2. Due to its low metabolism and passive and active absorption mechanisms, imideglimin is a promising new drug candidate. In addition to inhibiting the OCT1, OCT2, and MATE1 transporters, it is a substrate of the MATE2-K transporter. [26] Suboptimal oral absorption and gastrointestinal discomfort are some drawbacks of imeglimin. Therefore imeglimin nanofibers are designed to have good solubility and improved bioavailability. Imeglimin is excreted unchanged from the urine.[27]Among healthy volunteers, imeglimin has a half-life of 10 to 20 hours. After oral administration of imeglimin, the bioavailability typically falls between 50 and 20%, albeit it does decrease with increasing dosage.[28,29]

*Manufacturing companies*

Imeglimin hydrochloride is produced by a number of different businesses, including Arene Lifesciences, Ami Lifesciences Private Limited, Metrochem API Private Limited, Kimia Biosciences, Synaptics Labs, Viruj Pharmaceuticals Pvt Ltd, Harman Finochem, Morepen Laboratories, and other more. Simson Pharma provides the best quality imeglimin hydrochloride.

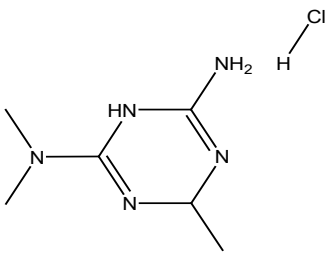


**Figure 1:** 3,6-dihydro-N2,N2,6-trimethyl-1,3,5-triazine-2,4-diamine hydrochloride

**Imeglimin Hydrochloride Tablet 1000 mg (2023)**

Imeglyn 1000 tablet is a medication belonging to the DPP-4 inhibitor class used to manage diabetes. The way it works to help control blood glucose levels by cumulative insulin production and preventing excessive glucose release is crucial in preventing complications associated with diabetes. It's good advice to maintain a routine of taking the medication, following a healthy diet, and engaging in exercise to manage the condition effectively and reduce the risk of complications.

**Lobeglitazone Sulfate Tablet 0.5 mg and Lobeglitazone Sulfate Bulk (2022)**

Lobeglitazone is a newer oral hypoglycaemic that belongs to the thiazolidinedione class (Table 2). *In-vitro* and *in-vivo* studies confirmed that it exhibits much more antidiabetic activity than other TZDs like pioglitazone and rosiglitazone.[30] Due to adverse effects, including cardiac issues, risk of bladder cancer, and edema associated with pioglitazone and rosiglitazone, their use has declined. Some Asian countries and India have approved the use of lobeglitazone as powerful TZDs.[31,32]

*Chemistry of lobeglitazone sulphate*

It has molecular formula$C_{24}H_{24}N_4O_5S$.

Lobeglitazone exhibits a 12-fold greater affinity for PPARγ than pioglitazone and rosiglitazone due to its structural alteration of rosiglitazone structure to include a p-methoxy phenoxy group at 4-position of pyrimidine moiety.[33] By interacting with the hydrophobic pocket, the extended p-methoxy phenol moiety of lobeglitazone increases its binding affinity and may have an impression on PPAR-γ phosphorylation in ser245 mediated by cyclin-dependent kinase 5 (Cdk5).[34] Thiazolidinedione ring responsible for antidiabetic activity, alkyl substitution at various positions of thiazolidinedione ring influence the selectivity and potency of the lobeglitzone. EWG or EDG, by affecting electronic properties, affects its interaction with the PRARγ receptor. The aromatic ring and side chains in lebeglitazone play an important role in receptor binding, selectivity and therapeutic efficacy any modification in the aromatic ring or side chain may alter these properties.[35,36]

*Pharmacological profile*

A fat cell insulin sensitizer, lobeglitazone sulfate, works by attaching to and activating peroxisome proliferator-activated receptor gamma. Research shows that lobeglitazone improves lipid and liver profiles, lowers blood glucose and hemoglobin A1C levels, and encourages insulin binding at fat cells.[37] Overexpression of protein tyrosine phosphatase (PTP) 1B leads to insulin resistance, T2D, and obesity because it negatively regulates the insulin and leptin signaling pathways. Lobeglitazone is one of several thiazolidinediones that inhibit PTP1B *in-vitro* and may also do the same *in-vivo*.[38]

*Pharmacokinetic*

The pharmacokinetic properties of lobeglitazone, as described in the study by Lee et al. in rats are, showed high oral bioavailability with an absolute bioavailability of 95%. This suggests that the drug is well-absorbed from the gastrointestinal

tract after oral administration. When lobeglitazone was administered intravenously in rats, its pharmacokinetics were linear between 0.2 and 2 mg/kg. The study noted that the excretion of lobeglitazone was minimal in rats, with less than 10% of the dose excreted in urine, bile, feces, and intestine.[39] The mean (standard deviation) values of AUCor the lobeglitazone formulations were found as 367.49 (157.92) ng×h/mL. For the lobeglitazone formulations, the mean (standard deviation) $C_{max}$ values were 50.35 (6.94) ng/mL. 40. If up to 4 mg of lobeglitazone were taken orally one day, it was well-tolerated since lobeglitazone's pharmacokinetic characteristics were shown to be linearly dose proportionate for dosages of 1 to 4 mg.[41]

*Manufacturing companies*

Glenmark Pharmaceuticals Limited has become the first to launch thiazolidinedione lobeglitazone in India, which is marketed under the brand name LOBG and contains 0.5 mg lobeglitazone.[42] Akums Drugs and Pharmaceutical Limited, India's top contract drug manufacturing company [CDMO], has made a significant contribution to the treatment of T2D by launching novel antidiabetic drug "Lobeglitazone."

This is an appropriate treatment for managing individuals with adult-onset T2D. Firstly, this lobeglitazone is used as monotherapy for those who are not getting enough exercise and dietary control and for whom metformin is contraindicated or not suitable due to allergies. Other options can be considered. If glycaemic control in individuals is incompetently controlled by diet and exercise and taking metformin despite a maximally tolerated dose of metformin monotherapy and who are inadequately controlled by diet and exercise and taking a sulphonylurea at the maximally tolerated dose of sulphonylurea monotherapy in which metformin is unsuitable as of contraindications or intolerance dual therapy in combination is suggested. In the years 2022 and 2023, lobeglitazone again appeared in a list of approved drugs but in combination with metformin and glimepiride, respectively.

**Lobeglitazone Sulfate Tablet 0.5 mg and Metformin HCL Extended Release 500 mg Tablet (2022)-**

This fixed dose combination includes two insulin sensitizers: Metformin, which belongs to the biguanide category and a lobeglitazone from TZD. If metformin alone is unable to bring blood glucose levels down to a healthy range, further antidiabetic medications should be added to the regimen,

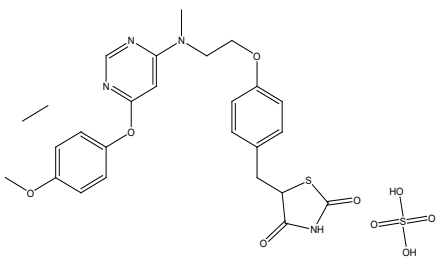

**Figure 2:** 5-[[4-[2-[[6-(4-methoxyphenoxy)pyrimidin-4-yl]-methylamino] ethoxy]phenyl]methyl]-1,3-thiazolidine-2,4-dione;sulfuric acid

according to the American Association's recommendations. The combination of metformin and TZD lowers glycated hemoglobin (HbA1c), and it may have an additive or synergistic effect on insulin resistance. In addition to making changes to their diet and level of physical activity, patients who are not well controlled with metformin alone at the maximum tolerated dose or who are already taking combination therapy may find that adding 0.5 mg of lobeglitazone sulfate tablet to 500 mg of metformin HCL extended-release tablet helps. The results showed that AUC was higher in the fed condition compared to the fasted condition, and the trials with the combination of lobeglitazone 0.5 mg and metformin 1000 mg likewise showed that Tmax of metformin was delayed when given orally with a high-fat meal in a single dosage.[43,44]

*Manufacturing companies*

Glenmark Pharmaceuticals gets the approval to manufacture and market this combination.

**Lobeglitazone Sulfate 0.5 mg + Glimepiride 1-mg (2023)**

One medication that helps with T2D glycemic control is glimepiride, a second-generation sulfonylurea that was initially launched in 1995. Given that they are thought to exert effects beyond the pancreas, like increasing the absorption of glucose by the peripheral insulin-mediated cells, in addition to their action of stimulating the beta-cell production of insulin.[45,46] If a person with T2D is already taking thiazolidinedione and sulphonylurea, or if they are not controlling their blood sugar well enough with those medications alone, they may benefit from adding this lobeglitazone sulfate and glimepiride combination to their diet and exercise routine. The binding affinity of glimepiride to plasma proteins is above 99.5%.[47] Glimepiride has an elimination $t_{1/2}$ of up to 9 hours after 5 to 8 hours of dosing.[46] As an insulin sensitizer, lobeglitazone sulfate increases fat cell sensitivity to insulin by binding to PRAR receptors. In contrast, glimepiride lowers blood sugar levels by exciting the pancreas to create insulin, and it also helps the body make better use of insulin.[48,49]

In 2023, the combination of lobeglitazone sulfate 0.5 mg and glimepiride 1-mg was approved for the treatment of T2D. It is prescribed to patients who are already taking thiazolidinedione or sulphonylurea or who are not controlling their blood sugar levels adequately with those medications alone. Nutrition and exercise are also endorsed to help progress glycemic control. This fixed dose combination works by different mechanisms to improve insulin secretion and reduce blood sugar levels.[50]

*Manufacturing companies*

Glenmark Pharmaceutical manufactures the combination salt of lobeglitazone sulfate 0.5 mg+glimepiride 1-mg. Functional committee SEC under CDSCO gives the green signal to Akum Pharmaceuticals to manufacture and market the fixed-dose combination of glimepiride and lobeglitazone sulfate tablets for the management of diabetes.

**Sitagliptin Fentanil Phaohate (2022)**

Use this antidiabetic medication in conjunction with strong

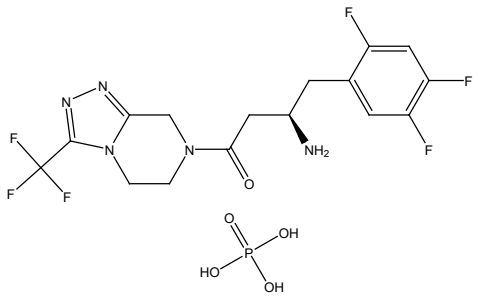

**Figure 3:** 3-amino-1-(3-trifluoromethyl)-6,8-dihydro-5H-(1,2,4) triazolo[4,3-a] pyrazin-7-yl- 4-(2,4,5-trifluorophenyl) butane-1-phosphoric acid hydrate

diet and regular workout to support retain blood sugar levels in check, for people who have T2D.

*Structure*

The structure of the same is depicted in Figure 3.

*Chemistry of sitagliptin fentanil phosphate*

It having molecular formula $C_{16}H_{15}F_6N_5O$. Fluorine present in the structure shows superlative properties similar to high lipophilicity, electronegativity, and electrostatic interaction. Fluorine also can improve the pharmacological efficacy, pharmacokinetic, membrane permeability, and metabolic stability.[51]

*Pharmacological profile*

As a dipeptidyl peptidase-4 (DPP-4) inhibitor, sitagliptin is an effective tool in the fight against T2D. One way it does its job is by raising the body's levels of incretion hormones like GLP-1 and GIP. [52] *Via* enhancing glycemic control, these hormones assist in regulating blood sugar levels by increasing insulin secretion and decreasing glucagon secretion. [53]

*Pharmacokinetic*

Sitagliptin is taken with or without food, has 87% bioavailability and reaches the maximum plasma concentration in 2 hours. About three-quarters of it goes straight to the kidneys in its unmetabolized form since it is not metabolized.[54] According to some research, sitagliptin has a half-life of 8 to 14 hours and a clearance of 350 mL/min.[55] Patients with T2D are advised to use sitagliptin in conjunction with healthy nutrition and consistent exercise in order to better regulate their blood sugar levels. People who have T1D or a history of pancreatitis should not take it.[56]

*Manufacturing companies*

Glenmark followed that up with the launch of sitagliptin (Sitazit®) and its FDCs in 2022.

**Remogliflozin Etabonate Bulk and Film-Coated Tablets 100 mg (2019)**

The oral prodrug of remogliflozin, remogliflozin etabonate, is an inhibitor of renal SGLT2 that has an antihyperglycemic effect. The inert prodrug, remogliflozin, becomes active upon administration and absorption and targets SGLT2. Suppose a patient is already on metformin and either mono-component of a fixed-dose combination of remogliflozin etabonate and teneligliptin is not producing the desired glycaemic control. In that case, the patient may be prescribed remogliflozin etabonate as an alternative. Used to help people with T2D better manage their blood sugar levels, this medication is only for adults (18 and over). When glycemic control is not achieved adequately with diet and exercise alone, monotherapy may be considered. If diet and exercise alone do not bring about sufficient glycemic control, add metformin to the treatment regimen.

*Structure*

The structure is given in Figure 4.

*Chemistry of remogliflozinetabonate*

It has molecular formula $C_{26}H_{38}N_2O_9$, remogliflozin etabonate contains aromatic rings and side chains that contribute to its three-dimensional structure and interactions with the SGLT2 transporter. Alterations or substitutions in these aromatic rings and side chains can influence the drug's potency, selectivity, and metabolic pathways.

*Pharmacological profile*

Like other drugs in its class, remogliflozin etabonate (RE) acts by blocking the enzyme SGLT2. One way RE works is by blocking SGLT2 in the kidneys. This means less glucose is reabsorbed into the bloodstream from urine.[57] Chemically, remogliflozin is an O-glucoside, and it is an inhibitor of SGLT2 enzymes. Enzymatic breakage of the β-glycosidic bond in remogliflozin can occur in the GI tract by β-glucosidases.

This cleavage would render remogliflozin inactive or less effective as a drug.

*Pharmacokinetic*

Remogliflozin etabonate (RE) seems to have a straightforward pathway of activation in the body, being converted from its prodrug form to an active state by esterases in the gastrointestinal tract. It's interesting that its absorption is rapid and almost complete, especially considering its quick availability in the plasma within just 10 minutes of administration with a $T_{max}$ of 0.5 to 1 hour. $T_{max}$ by around half an hour to an hour and a half (hrs) postponed marginally by the implementation of conventional breakfast. Neither the $C_{max}$ nor the area under the curve (AUC) differed significantly from the fasting state. Therefore, it is not necessary to have food when administering RE. The fact that remogliflozin has

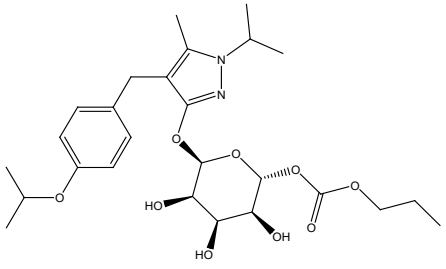

**Figure 4:** ethyl [(2R,3S,4S,5R,6S)-3,4,5-trihydroxy-6-[5-methyl-1-propan-2-yl-4-[(4-propan-2-yloxyphenyl)methyl]pyrazol-3-yl]oxyoxan-2-yl]methyl carbonate

a plasma protein binding of approximately 65% suggests that a significant portion of the drug circulates in a bound form in the bloodstream. The extensive metabolism of remogliflozin in systemic circulation involves several pathways, including N-dealkylation, O-dealkylation, oxidation, loss of glucose, and glucuronidation.[58] The common adverse effects associated with remogliflozin etabonate are similar to those seen with other SGLT2 inhibitors. These can include genital mycotic infections, urinary tract infections (UTIs), dizziness, etc.[57,59]

*Manufacturing companies*

Glenmark Pharmaceuticals later introduced remogliflozin (Remozen™and Remo®), a novel SGLT-2 inhibitor, in 2019 and, subsequently, its combinations.

## CONCLUSION

Over the last five years, several new antidiabetics have been approved, offering improved treatment options for patients with diabetes. These newly approved alternative medications, like tirzepatide, lobeglitazone, and imeglimin, often aim to provide better glycemic control while minimizing side effects commonly associated with older antidiabetic drugs. GIP and GLP-1 receptor agonist drugs like tirzepatide have appeared as a new class offering enhanced glycemic control and weight reduction. Binding and activating peroxisome proliferator-activated receptor (PPAR) have provided effective glycaemic control with a favorable safety profile. And the combination of drugs like lobeglitazone+glimepiride for patients who do not achieve appropriate glycaemic control with thiazolidinedione and sulfonylureas. Subcutaneous injections of tirzepatide once a week give a higher safety against side effects like kidney, cardiovascular disorders, etc. As per the International Diabetes Federation (IDF), in 2021, approx 537 million adults [age 18–79] were living with diabetes. The IDF projects that by 2045, this number is predictable to rise to 783 million. This problem needs more research and advancements in treatment options.

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