

An Overview of Dapagliflozin-Vildagliptin Combination: Their Drug Profiling and Applications as a Dual-Therapy Approach for Type-2 Diabetes

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Abstract—Managing Type 2 diabetes (T2D) often requires using more than one medication to keep blood sugar levels under control. A promising treatment option combines two drugs: dapagliflozin, an SGLT2 inhibitor, and vildagliptin, a DPP-4 inhibitor. This combination works in different ways to help manage diabetes. Dapagliflozin lowers blood sugar by helping the kidneys remove extra glucose through urine, while vildagliptin increases insulin release by blocking an enzyme that normally reduces the effect of certain helpful hormones. Working together, these medications help improve blood sugar control, make the body more sensitive to insulin, and lower the risk of heart problems linked to diabetes. They are also considered safe to use, with a low risk of causing low blood sugar (hypoglycemia) or weight gain. Studies show that this combination not only helps manage diabetes more effectively but may also support better kidney health, heart function, and overall quality of life. This summary explains how the combination works, its benefits, and any possible drawbacks, showing why it can be a useful and well-tolerated option for people with Type 2 diabetes.

I. INTRODUCTION

Type 2 diabetes mellitus (T2D) is a common long-term condition that affects how the body processes blood sugar. It happens when the body becomes resistant to insulin and the pancreas gradually loses its ability to produce enough of it, leading to high blood sugar levels. T2D can lead to serious health problems, such as heart disease, kidney damage, and stroke, so managing it properly is very important. The main goal in treating T2D is to keep blood sugar levels within a healthy range and to prevent or delay complications. This usually involves a mix of healthy lifestyle changes, like diet and exercise, along with medications. Although there are many oral medicines available, choosing the best treatment can be tricky because doctors must consider the complex nature of the disease and try to avoid side effects like low blood sugar and weight gain. In managing type 2 diabetes, using a combination of Dapagliflozin and Vildagliptin has shown promise as an effective treatment option. These two medications, sold under the brand names Forxiga® (Dapagliflozin) and Galvus® (Vildagliptin), work in different but complementary ways to help control blood sugar levels more effectively.

Dapagliflozin belongs to a class of drugs called SGLT2 inhibitors. It works by preventing the kidneys from reabsorbing glucose, which causes the excess sugar to be passed out of the body through urine. This not only helps lower blood sugar but may also protect the heart and kidneys by reducing the risk of heart failure and kidney problems.

Vildagliptin is a DPP-4 inhibitor that helps the body increase the levels of certain natural hormones (GLP-1 and GIP) that boost insulin production after eating and reduce the release of glucagon, a hormone that raises blood sugar.

By combining these two drugs, patients benefit from both improved insulin response and increased removal of excess

sugar from the body, making this dual-therapy approach a well-rounded way to manage type 2 diabetes.

Using Dapagliflozin and Vildagliptin together as a dual-therapy for type 2 diabetes offers several key benefits. This combination helps control blood sugar more effectively, with a lower risk of causing low blood sugar (hypoglycemia). It can also help patients lose weight and may protect the heart and kidneys, which is especially important for people at higher risk of complications related to these organs.

The combination is generally well-tolerated and considered safe for long-term use, making it a good option for ongoing diabetes management. Research from clinical trials has shown that this therapy can significantly improve HbA1c levels (a marker of long-term blood sugar control), reduce weight, and improve other health markers linked to diabetes.

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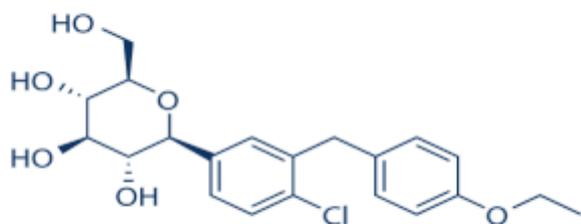
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Drug Profile:

Dapagliflozin is a type of medication used to help manage type 2 diabetes. When combined with a balanced diet and regular exercise, it works best. Dapagliflozin lowers blood sugar levels by stopping the kidneys from reabsorbing

glucose, so more sugar is removed from the body through urine. It was approved for use by the FDA on January 8, 2014.

Structure Of Dapagliflozin



Properties of : Dapagliflozin

Synonym:	(2s,3r,4r,5s,6r)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2h-pyran-3,4,5-triol Dapagliflozin Dapagliflozina
Cas number	461432-26-8
Iupac name	(2s,3r,4r,5s,6r)-2-(4-chloro-3-[(4-ethoxyphenyl)methyl]phenyl)-6-(hydroxymethyl)oxane-3,4,5-triol
Trade names	Farxiga
Therapeutic category	Sodium-glucose co-transporter 2 (sglt2) inhibitors
Molecular weight:	408.873

Indication: In adults with type 2 diabetes mellitus, dapagliflozin is prescribed to help regulate blood sugar levels in conjunction with diet and exercise

Absorption: When patients have been fasting, oral dapagliflozin achieves its peak concentration within one hour of administration. The time to maximum concentration increases to two hours and the maximum concentration lowers by half when patients have eaten a high-fat meal, but no dosage change is necessary. Oral dapagliflozin is 78% bioavailable

Metabolism: Dapagliflozin is mainly broken down in the body by a process called glucuronidation, turning about 60.7% of it into an inactive form known as the 3-O-glucuronide metabolite. It also forms a smaller amount (5.4%) of another glucuronidated version and less than 5% is changed into a de-ethylated metabolite.

Elimination: About 75.2% of dapagliflozin is removed from the body through urine, but only 1.6% of it leaves the body in its original form. Around 21% is passed out in the feces, with 15% of that being unchanged by metabolism.

Pharmacodynamics: Dapagliflozin works by blocking a protein called SGLT2, which is mostly found in the first part of the kidneys where blood is filtered. Normally, SGLT2 helps the kidneys take back about 90% of the sugar (glucose) into

the body. By blocking this protein, dapagliflozin lets more sugar pass out through urine. This helps lower blood sugar levels and can also lead to weight loss in people with type 2 diabetes.

Vildagliptin is a medicine taken once a day that belongs to a group called DPP-4 inhibitors. It's used to help control blood sugar levels in people with type 2 diabetes.

IUPAC name: (2S)-1-[2-[(3-hydroxy-1-adamanty)amino]acetyl]pyrrolidine-2-carbonitrile

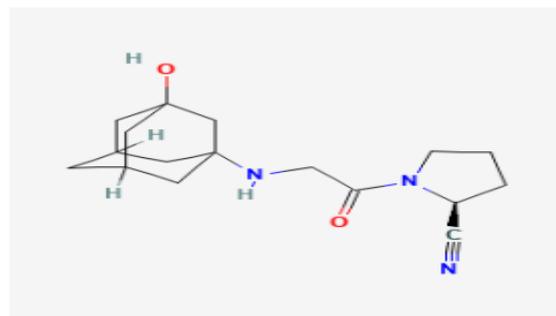
Synonyms: Vildagliptin, Vildagliptina

Molecular formula: C17H25N3O2

Molecular weight: 303.3993

Monoisotopic: 303.194677059

Structure of Vildagliptin



Brand names: Galvus, Jalra, Xiliarx

Melting point: 149-155°C

Category: oral anti-diabetic agent.

Storage: Store it at room temperature (25 to 30°C).

Stability: In acidic, alkaline, and oxidative environments, vildagliptin almost completely disintegrates at 70 °C.

Indication: Vildagliptin is a medicine used to treat type 2 diabetes in adults. It can be taken on its own by people who can't control their blood sugar with just diet and exercise and who can't take metformin because of side effects or health reasons. It can also be used along with other diabetes medications—like metformin, sulphonylureas, or thiazolidinediones—if one medicine alone isn't enough to control blood sugar. Vildagliptin is also available in a single tablet combined with metformin, which is helpful for adults whose diabetes isn't well managed by either drug alone. This combination can also be added to sulphonylureas or insulin (called triple therapy) for people who still have trouble controlling their blood sugar with one or two medicines, even when following a healthy diet and exercise plan.

Vildagliptin helps manage blood sugar in people with type 2 diabetes by making the pancreas's beta cells respond better to glucose. This means insulin is released only when it's needed, like after eating. It also boosts the levels of natural hormones called incretins, which help keep a healthy balance between insulin and glucagon—the two main hormones that control blood sugar. Because of this, the liver makes less glucose both between meals and after eating.

Vildagliptin doesn't affect how fast the stomach empties and doesn't change insulin or blood sugar levels in people without diabetes. In clinical studies, taking 50–100 mg of vildagliptin each day improved how beta cells work, reduced

levels of inactive insulin (proinsulin), and helped the body handle food better. It also lowered HbA1c (a marker of long-term blood sugar control) and fasting blood sugar levels.

Mechanism of action: GLP-1 and GIP are special hormones called incretins that help control blood sugar levels and keep them balanced. Together, they are responsible for over 70% of the insulin the body releases after eating sugar. These hormones work by attaching to receptors on cells and helping the pancreas release insulin only when blood sugar is high. GLP-1 also helps the pancreas grow new insulin-producing cells and protects them from damage. Besides their effects on the pancreas, incretin hormones can also affect fat storage and heart function.

In people with type 2 diabetes, the body doesn't make enough GLP-1, and GIP doesn't work as well as it should. Vildagliptin helps by blocking an enzyme called DPP-4, which normally breaks down GLP-1 and GIP shortly after they're released. By stopping this enzyme, vildagliptin keeps these helpful hormones active for longer, which boosts insulin release and lowers blood sugar. The effects of vildagliptin last longer when higher doses are used. It helps lower both fasting and after-meal blood sugar, reduces HbA1c (a long-term blood sugar marker), and improves how well fat and cholesterol are processed after meals.

Absorption: When taken by mouth on an empty stomach, vildagliptin is quickly absorbed into the body, with the highest level in the blood reached about 1.7 hours after taking it. As the dose increases, the amount of the drug in the blood increases in a similar way. Eating food slows down the time it takes to reach peak levels to about 2.5 hours and lowers the peak concentration by 19%. However, food doesn't change the total amount of drug the body absorbs. About 85% of the drug actually enters the bloodstream, which means it has high bioavailability.

Metabolism: About 69% of vildagliptin taken by mouth is broken down in the body through processes that don't involve cytochrome P450 enzymes. Studies in rats suggest that the DPP-4 enzyme plays a small role in breaking it down. In the kidneys, vildagliptin is mainly turned into inactive forms: a cyano product (57%) and an amide product (4%). The main active breakdown product is called LAY151 (also known as M20.7), which is a type of carboxylic acid formed from the cyano group. It makes up 57% of the total dose. Other breakdown products found in the blood include an N-glucuronide (M20.2), an amide product (M15.3), and two oxidized forms called M21.6 and M20.9.

Route of elimination: Vildagliptin is mainly removed from the body through metabolism. After taking it by mouth, about 85% of the drug is passed out in the urine, and around 15% is found in the feces. Of the amount that comes out in the urine, about 23% is the original, unchanged drug.

Half-life: On average, when vildagliptin is given through a vein (IV), it takes about two hours for half of the drug to leave the body. When taken by mouth, it takes around three hours for half of it to be eliminated.

Toxicity: The lowest harmful oral dose of vildagliptin is 0.3 mg/kg in rats and 1 mg/kg in mice. There isn't much detailed information about what happens if a person takes too much of

this drug. In one study, people who took 400 mg experienced mild side effects like muscle pain, tingling sensations, fever, swelling, and a temporary rise in a digestive enzyme called lipase. At a higher dose of 600 mg, one person had more serious symptoms, including swelling in the hands and feet and increased levels of certain body chemicals that suggest muscle or liver stress (like CPK, AST, CRP, and myoglobin).

If someone overdoses on vildagliptin, doctors treat the symptoms because there's no special cure or antidote. Also, the drug and its main breakdown product can't be removed from the body using dialysis.

Adverse effect: • Nasopharyngitis: 9% • Headache: 7% • Dizziness: 6% • Back pain: 6% • Diarrhoea: 6%

Applications as Dual-Therapy Approach for Type-2 Diabetes

Using dapagliflozin and vildagliptin together as a treatment for Type 2 diabetes (T2D) has shown promising results. These medications, sold as Forxiga® (dapagliflozin) and Galvus® (vildagliptin), work in different ways to help control blood sugar levels. When used together, they offer a stronger and more balanced way to manage T2D. This combination helps improve blood sugar control, leads to better overall health outcomes for patients, and reduces the chances of developing complications related to diabetes. Below are the main uses and advantages of this dual-therapy approach.

1. Improved Glycaemic Control

One of the primary goals in managing T2D is to achieve optimal blood glucose levels and reduce HbA1c, a long-term marker of glucose control. The combination of Dapagliflozin and Vildagliptin effectively lowers HbA1c levels by targeting different pathways in glucose metabolism. Dapagliflozin works by inhibiting the SGLT2 transporter in the kidneys, reducing glucose reabsorption and increasing glucose excretion in the urine. This leads to a decrease in blood glucose levels. Meanwhile, Vildagliptin increases the levels of endogenous incretin hormones (GLP-1 and GIP), which enhance insulin secretion in response to meals and inhibit glucagon release, improving insulin sensitivity. The combination of these two mechanisms provides more effective glycaemic control compared to monotherapy, particularly in patients whose blood glucose levels are not adequately controlled with a single agent.

2. Weight Loss and Reduced Risk of Weight Gain

Obesity is a significant risk factor in the development and progression of T2D. Many antidiabetic medications can lead to weight gain, which is undesirable for T2D patients who may already be overweight or obese. Dapagliflozin, an SGLT2 inhibitor, has been shown to induce weight loss by promoting the excretion of glucose, which results in a loss of calories. On the other hand, Vildagliptin does not contribute to weight gain and may, in some cases, even assist in weight reduction. When used together, these drugs offer a dual benefit of helping patients manage their weight, an important factor in improving overall metabolic health and reducing the burden of T2D.

3. Reduced Risk of Hypoglycemia

Low blood sugar, also known as hypoglycemia, is a common side effect of many diabetes medications, especially insulin and drugs like sulfonylureas. However, one major

benefit of using Dapagliflozin and Vildagliptin together is that they have a very low risk of causing hypoglycemia.

Dapagliflozin lowers blood sugar without relying on insulin, which helps avoid sudden drops in blood sugar. Vildagliptin, on the other hand, increases insulin release only when you eat, so it doesn't cause extra insulin to be released when it's not needed. This helps keep blood sugar levels stable.

Because of this, the Dapagliflozin-Vildagliptin combo is a safer option for people who are more likely to experience hypoglycemia, such as older adults or those with different levels of kidney function.

4. Cardiovascular Protection

Patients with T2D are at a significantly higher risk of developing cardiovascular diseases (CVD), including heart failure, stroke, and coronary artery disease. Both Dapagliflozin and Vildagliptin offer benefits beyond glucose control, particularly in cardiovascular protection. Dapagliflozin, an SGLT2 inhibitor, has been shown to reduce the risk of hospitalization due to heart failure and improve cardiovascular outcomes, as demonstrated in trials like the *DAPA-HF* study. Vildagliptin, while not primarily focused on cardiovascular effects, may offer indirect benefits through its effects on glycemic control and potential improvements in insulin sensitivity, which contribute to overall cardiovascular health. The dual combination therefore not only controls blood glucose but also helps to mitigate the risk of cardiovascular complications, making it an ideal therapy for patients with T2D who also have or are at risk for CVD.

5. Renal Protection

Chronic kidney disease (CKD) is another common complication of T2D. Both Dapagliflozin and Vildagliptin offer potential renal benefits, making this combination especially beneficial for patients with or at risk of kidney damage. Dapagliflozin has shown evidence of slowing the progression of kidney disease in patients with T2D, as it helps reduce albuminuria (a marker of kidney damage) and preserves renal function. Vildagliptin also contributes indirectly to renal protection by improving glycaemic control, which is a key factor in reducing the risk of diabetic nephropathy. As a dual therapy, the combination offers a comprehensive approach to preventing or delaying the onset of diabetic kidney disease, a critical concern in the long-term management of T2D.

6. Convenience and Adherence

Using combination therapies like Forxiga® and Galvus® can make diabetes treatment easier to follow, which may help patients stick to their medication plans. Many people with type 2 diabetes (T2D) take several different drugs to manage their blood sugar, but juggling multiple pills can be confusing and lead to missed doses. A fixed-dose combination of Dapagliflozin and Vildagliptin puts both medicines into one tablet, making it more convenient and reducing the number of pills a patient has to take. When patients follow their treatment more consistently, they usually have better blood sugar control

and are less likely to develop serious diabetes-related health problems over time.

7. Safety and Tolerability

The combination of Dapagliflozin and Vildagliptin is usually safe and well-tolerated. Because dapagliflozin helps the body remove extra sugar through urine, it can sometimes lead to urinary tract infections or yeast infections, but these side effects are usually mild and can be managed. Vildagliptin generally has few side effects, with some people experiencing mild stomach issues, which often go away on their own. One of the big advantages of this combination is that it has a low risk of causing low blood sugar (hypoglycemia) or weight gain, which makes it a good choice for long-term treatment in people with type 2 diabetes.

II. CONCLUSION

The combination of Dapagliflozin and Vildagliptin is a promising treatment option for people with type 2 diabetes (T2D). These two medications work in different but complementary ways to help lower blood sugar levels more effectively. Together, they not only improve blood sugar control but also help reduce the risk of low blood sugar (hypoglycemia) and may support weight loss. This combination also offers extra benefits, such as helping to protect the heart and kidneys, which are often affected in people with T2D. Dapagliflozin helps the body get rid of excess sugar through urine, while Vildagliptin helps the body make more insulin and less glucose by supporting incretin hormones. Taking both medicines in a single pill (a fixed-dose combination) makes it easier for patients to stick to their treatment, which is important for managing the disease over time. This combination is generally well-tolerated and backed by strong clinical research, making it a valuable option—especially for patients who have a higher risk of heart problems or kidney disease. As more people develop T2D, treatments like this can play a key role in improving health outcomes and quality of life.

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