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Review on Sitagliptin Phosphate as an Anti-Diabetic Drug

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ABSTRACT

A dipeptidyl-peptidase inhibitor (DPP-4) called sitagliptin was recently approved to treat type 2 diabetes. Like other DPP-4 inhibitors, it works by increasing levels of the incretin hormones glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Sitagliptin effectively lowers postprandial glucose, fasting blood sugar, and HbA1c when used alone or in combination with other oral antidiabetic drugs. Insulin secretion rises while glucagon secretion falls in the presence of hyperglycaemia. In clinical trials, it has no weight. This article provides an overview of the pharmacology, safety, clinical effectiveness, and mechanism of action of sitagliptin in the treatment of type 2 diabetes. The inhibition of DPP4 by sitagliptin has been found to be mediated by increasing levels of two DPP-4 substrates, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Sitagliptin is currently being investigated in the treatment of type II diabetes.

Keywords: Diabetic therapy, DPP-4 inhibitors, sitagliptin, and type 2 diabetes

INTRODUCTION

Among the obvious metabolic problems in people with Type 2 Diabetes Mellitus (T2DM) include obesity, insulin resistance, anomalies in both the quality and quantity of insulin secretion, dysregulated secretion of other islet hormones such glucagon and amylin, and elevated endogenous glucose generation. Moreover, there is a reduced incretin effect as a result of deficiencies in the secretion and function of the incretin hormones glucose-dependent insulinotropic peptide (GIP) and glucagon-like peptide-1 (GLP-1.)

The US Food and Drug Administration (US FDA) authorized Exenatide, a GLP-1 receptor analogue resistant to Dipeptidyl peptidase-4 (DPP-4) in April 2005, making it the first incretin mimetic. Degradation, as supplemental treatment for those with type 2 diabetes; nevertheless, the drug's parenteral mode of administration restricts its utilization. Consequently, a lot of work has gone into developing an oral hypoglycemic medication that targets the incretin pathway. Native incretins have a longer half-life when the enzyme DPP-4 is inhibited, which prolongs their physiological effects. The first oral incretin enhancer, Sitagliptin, a selective DPP-4 inhibitor, was licensed by the US FDA on October 17, 2006, and can be used either alone or in conjunction with thiazolidinediones or metformin.2. Sitagliptin (MK-O431) is authorized and sold as monotherapy in India under the brand Januvia-Merck is her name. Under the brand name Janumet-Merck, sitagliptin is marketed for clinical use in India as a combination therapy with metformin. Other medications in the DPP-4 inhibitor class include Alogliptin, Vildagliptin, and Saxagliptin in addition to Sitagliptin.

MAKING USE OF GLP-1'S THERAPEUTIC POTENTIAL IN TYPE 2

Diabetes Due to its extremely short biological half-life, glucagon-like peptide-1 (GLP-1) is not a practical treatment option for type 2 diabetes. Consequently, two main strategies have been developed to take advantage of the beneficial effects of GLP-1.

Incretin mimetics, also known as GLP-1 analogues, are long-acting, highly comparable to native GLP-1 peptides that are resistant to the dipeptidyl-peptidase inhibitor (DPP-4 inhibitor). One such peptide that was first discovered in the saliva of the gila monster is called exendin-4, or exenatide in its recombinant form. Exenatide is a GLP-1 receptor agonist that shares a high degree of amino acid sequence similarity with GLP-1. It is approved for use as a type 2 diabetes treatment for those with inadequate under the trade name Byetta® provides effective glucose control whether used in conjunction with metformin, sulfonylureas, or a combination of both Novo Nordisk Pharmaceuticals is developing ligarglutide, a GLP-1 analogue, and is currently undergoing phase III clinical studies to assess its efficacy and safety in type 2 diabetes.The direct suppression of DPP-4 by oral active agents is another method of utilizing GLP-1 effects in type 2 diabetes

A highly selective DPP-4 inhibitor called sitagliptin has been licensed for the treatment of type 2 diabetes.

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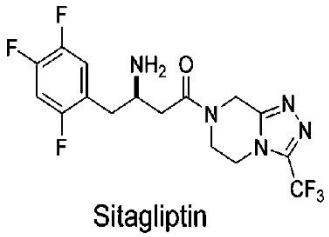
INHIBITION OF DPP-4 IN TYPE 2 DIABETES

With type 2 diabetes, the incretin impact is lessened. In patients with type 2 diabetes, increasing intact GLP-1 concentrations can reduce or even return plasma glucose levels to normal. DPP-4, an enzyme that is widely distributed in the endothelium and can also be tested in the circulation, rapidly breaks down GLP-1. Peptides with an N-terminal Proline or alanine amino acid residue are broken down by DPP-4 The two GLP-1 fragments produced by DPP-4 activity are both inert biologically; in fact, some research has even suggested that the fragment GLP-1 amide contains GLP-1 antagonistic characteristics. After a meal, intact GLP-1 plasma concentrations are raised by DPP-4 inhibition to levels seen in the stimulated state. Unlike GLP-1, which possesses a Several peptides with a very high affinity for DPP-4 as a substrate, including pituitary adenylate cyclase-activating polypeptide (PACAP), gastrin-releasing peptide (GRP), and glucose-dependent insulinotropic peptide (GIP) (see Table 1), are likewise inactivated by DPP-4 by enzymatic cleavage. An additional function of several of these peptides is in glucose homeostasis Additionally, expressed on T cells, DPP-4 has sometimes been referred to detrimental effects in this respect. Peptide hormones are broken down by additional dipeptidyl peptidases, such as DPP-8 or DPP-9, in addition to DPP-4. in the creation of inhibitors for DPP-4 Having a high specificity for DPP-4 and no inhibitory effect against the other DPPs was crucial.

THE SITAGLIPTIN PHARMACOLOGICAL PROFILE



Sitagliptin

Fig. 1: Stucture of Sitagliptin

Chemically, sitagliptin (MK-0431)
(2R)3-(trifluoromethyl)-5,6-dihydro [1,2,4] -4-Oxo-4-[triazolo [4,3-a] [pyrazin-7(8H)-yl]-1-(trifluoropropane-2,4,5) With an IC(50) of 18 nM, butan-2-amine exhibits a very high selectivity towards DPP-4. DPP-8 and DPP-9, two more DDP enzymes, are not favored. It is registered under the trade name and has been approved for the treatment of type 2 diabetes in the USA and Europe.
The tolerability of various doses administered once or twice daily is good in healthy volunteers and in patients with type 2 diabetes from diverse ethnic backgrounds. Following prolonged treatment, the primary pharmacokinetic parameters (Tmax, Cmax, and t1/2) assessed in the studies were comparable at baseline and in the steady state. After three days, sitaglitptin plasma concentrations attain their steady-state levels. Once According to the accumulation rate is low on a daily basis (AUC accumulation ratio [day 10/day 1] range, 1.05–1.29). The elimination and excretion is predominantly renal (75% of an oral dose is detected in the urine as unmodified drug), and the rest is processed via the cytochromes CYP 3A4 and CYP 2C8. Clinical trials on sitagliptin therapy did not reveal any drug-drug interactions; in particular, no such interactions were reported with other antihyperglycemic medications in individuals with type 2 diabetes. (14) Twelve to fourteen hours is the elimination half-time. Once-daily doses of 50–200 mg/d sitagliptin result in plasma levels of >100 nM and a ≥80% inhibition of DPP-4 over 24 hours. Consequently, the postprandial state causes a two- to three-fold increase in the level of physiologically active, intact GLP-1. Hypoglycemia episodes or other adverse events did not differ substantially from those found in the control groups in any of the conducted investigations, and the safety statistics are excellent. Sitagliptin did not result in hypoglycemia when used as a monotherapy or in studies looking at a combination with metformin or thiazolidinediones (TZDs).

STUDIES ON ANIMALS WITH SITAGLIPTIN

Investigations into sitagliptin's impact on beta- and alpha-cells in the pancreatic islets have been conducted on animals. Moreover, studies have looked into how sitagliptin affects islet cell mass. In the latter investigations, des-fluoro-sitagliptin was used in a mouse model of diabetes (mice fed with a high-fat diet [HFD] and streptozotocin-induced [STZ] diabetes). These mice showed improvements in their glycemic and lipid markers (HbA1c, fasting and postprandial glucose, triglycerides, and free fatty acids) after receiving therapy with the sitagliptin analogue for two to three months. At the conclusion of the trial, a histological assessment of the islets in the treated animals revealed a normalization of the beta-to-alpha-cell ratio and an increase in insulin-positive cells The separated islets' release of insulin from was considerably greater in sitagliptin-treated mice than in control animal islets treated with sulfonylurea, suggesting that the impact was not due to a reduction in glucose toxicity. Sitagliptin might increase beta-cell function and beta-cell mass in type 2 diabetes according to this animal data Studies on isolated islets from mice given vildagliptin for nine weeks demonstrate a significant increase in glucose-stimulated insulin production, supporting this theory. It is highly probable that GLP-1 mediates the protective impact of DDP-4 inhibition on beta-cells. When INS-1 cells from an insulinoma cell line are cultured with GLP-1 in vitro, the apoptosis that STZ causes in these cells is inhibited in a dose-dependent manner. DPP-4 inhibitors dramatically raised endogenous GLP-1 concentrations in vivo in animal experiments

along as beta-cell bulk and function have improved investigations on animals, particularly double receptor "knock-out" (DIRKO-mice) investigations, suggest that additional gut hormones such as GIP, GRP, and PACAP may potentially play a role in this action. Additional evidence for this comes from DPP-4/CD26-deficient mice (also known as CD26-/- or DPP-4 "knock-out" mice). These animals have increased circulating plasma concentrations of intact GLP-1 and other incretin hormones, and they are resistant to diabetes induced by (STZ) However, further research is required to fully understand how DPP-4 inhibitors affect islet cell mass, beta- and alpha-cell activity, and type 2 diabetes.

PREPARATION OF SITAGLIPTIN PHOSPHATE FLOATING TABLETS

By using the direct compression method, tablets containing 50 mg of sitagliptin were created in accordance with the design shown in Table I. Separately, the weighted amounts of each powder—the lactose diluent, sodium bicarbonate gas producing agent, release-modifying polymers HPMC K100M or HPM K4M, and the active component sitagliptin—were passed through sieve #16. For ten minutes, the powders were mixed in a mortar with a pestle. The combined powders were then supplemented with talc and magnesium stearate. Five more minutes of mixing were spent. In order to create the required tablets, 200 mg of the powdered mixture were finally roughly weighed and manually fed into the die of a multistation rotating tablet press (Rimek Mini Press II compression machine). The pills' hardness was changed at use a Monsanto hardness tester, 5 kg/cm^2.

SITAGLIPTIN IN TYPE 2 DIABETES CLINICAL TRIALS

Sitagliptin, administered once daily in doses of 100 mg and 200 mg, reduced the glycemic indices HbA1c, fasting glucose, and postprandial glucose in individuals with type 2 diabetes in clinical tests. The research lasted 24 weeks. Both fasting glucose levels (17.1 mg/dL and 21.3 mg/dL, respectively) and HbA1c were dose-dependently decreased by 0.79% (100 mg/d) and 0.94% (200 mg/d) In a standardized meal-tolerance test, the postprandial glucose was significantly lower (2 h postprandial glucose 46.7 mg/dL and 54.1 mg/dL, respectively). Beta-cell function as evaluated by HOMA-B, the postprandial insulin- and C-peptide responses, as well as the proinsulin/insulin ratio also improved in type 2 diabetic patients. In different Glycemic parameters improved in a similar way in monotherapy trials that lasted 12 or 18 weeks Sitagliptin was weight neutral in all monotherapy trials; in fact, the 200 mg/d doses caused the study participants' weight to drop by 1.1 kg. In the longer 18-week investigation by Rat. there was no discernible change in the potencies of 100 mg and 200 mg, despite the fact that the 200 mg dose was more potent than the 100 mg dose in the 24-week study by Ashner This could be brought about by the various study demographics and study periods. For sitagliptin, a daily intake of up to 100 mg is permitted. The medication sitagliptin was well tolerated, and the incidence of hypoglycemia or other adverse effects was not increased.

After 24 weeks, the addition of sitagliptin (100 mg/d) to metformin as a combination therapy added to the oral antidiabetic medication already in place resulted in a significant decrease in HbA1c (0.65%), fasting plasma glucose (25.4 mg/dL), and postprandial glucose (2 h) (50.6 mg/dL). The in this trial, the baseline HbA1c was 8.0%. The above-mentioned metrics measured beta-cell function, which improved as in the monotherapy experiments. Weight-neutrality was also achieved by adding sitagliptin to the continuing metformin medication. The combination therapy was well tolerated, and there was no increase in gastrointestinal side effects or hypoglycemia episodes

Similar outcomes were seen in a similar-designed study where sitagliptin was added to an already-existing pioglitazone medication. As in the metformin combo research, the glycemic indices HbA1c, and fasting and 2-h postprandial glucose improved. From a baseline HbA1c of 7.9%, a signtificantly larger percentage of patients obtained a target HbA1c <7.0% (45%) compared with the group staying on pioglitazone alone (23%). Once more, sitagliptin had no effect on body weight development in patients receiving pioglitazone medication. While the incidence of hypoglycemias was not different between the pioglitazone monotherapy and combination therapy groups, the incidence of adverse events was.

SITAGLIPTIN PHOSPHATE FLOATING TABLETS: FORMULATION & EVALUATION

Table 1 lists the ingredients of several sitagliptin phosphate formulations.

S.NO	**Ingredients**	**Purpose**	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8 (1:1)**	**F9 (1:2)**
1.	**Sitagliptin phosphate**	Model drug	50	50	**50**	50	50	50	50	50	50
2.	**Lactose monohydrate**	Diluents	86	66	**76**	61	51	41	31	76	86
3	**Poly ethylene glycol**	Plasticizer	8	8	**8**	8	8	8	8	8	8

4.	**HPMC (K4M)**	Release controlling polymer	-	-	-	30	40	50	60	10	10
5.	**HPMC(K100)**	Release controlling polymer	20	40	**30**	-	-	-	-	10	20
6.	**Sodium bicarbonate**	Gas generating agent	20	20	**20**	20	20	20	20	20	20
7.	**Carbomer**	Binder	-	-	-	16	16	16	16	-	-
8.	**Aerosil**	Glidant	6	6	**6**	10	10	10	10	6	6
9.	**Magnesium stearate**	lubricant	6	6	**6**	5	5	5	5	6	6
10.	**Talc**	Glidant	4	4	**4**	-	-	-	-	4	4
11.	**Tablet weight**	-	200	200	**200**	200	200	200	200	200	200

PERSPECTIVES

In the treatment of type 2 diabetes, sitagliptin has been demonstrated to be safe, well-tolerated, and effective when used alone or in conjunction with metformin or thiazolidinediones. It enhances beta-cell function and lowers the glycemic markers HbA1c, fasting, and postprandial glucose. The studies' findings showed that the HbA1c reduction was on par with that of other oral antihyperglycemic medications. It is important to highlight, however, that the effectiveness of oral medications in reducing type 2 diabetes HbA1c also depends on the initial HbA1c; studies with higher initial HbA1c values typically show greater HbA1c decreases.

Sitagliptin has no effect on weight and doesn't raise the risk of adverse events or hypoglycemia episodes. Longer studies will be released soon; the ones that have already been published include data from up to 24 weeks. Long-term information on the immunological effects of CD-26 in humans is still unclear, however neither clinical trials nor long-term animal research have found any changes in immune function.

In type 2 diabetes, sitagliptin and DPP-4 inhibitors as a whole target a novel multimodal principle of action. Under hyperglycemic circumstances, insulin secretion is stimulated and glucagon secretion is repressed due to the preservation of stimulated circulating plasma levels of incretin hormones. Therefore, this unique treatment principle covers unmet needs of type 2 diabetes therapy in addition to altering insulin production and insulin resistance, as did the previously utilized oral antihyperglycemic drugs.

Sitagliptin may also be helpful in the pre-diabetic and early stages of type 2 diabetes to slow or stop the disease's progression if the effects on beta-cell mass and function seen in preclinical research translate to human studies.

USES OF SITAGLIPTIN-

Sitagliptin is used to treat elevated levels of sugar alongside with a healthy diet, regular exercise, and maybe additional drugs. Individuals with diabetes of the type 2 variety use it. Keeping blood sugar levels under control can help avoid kidney damage, blindness, nerve damage, limb loss, and issues with reproductive health. Keeping your diabetes under management may also reduce your chance of having a coronary artery disease or accident. Sitagliptin is a medication for diabetes that functions by raising the body's natural levels of the incretins. Incretins stimulate the secretion of insulin, allowing the body to regulate glucose in the blood, especially after an entire meal. They also lessen your liver's manufacturing of sugar.

How to take sitagliptin tablet-

- Each time you receive a refill or before you begin taking sitagliptin, read the Medical Handbook that your pharmacist has gave them. See your physician or pharmacist if you have any queries.
- Administer this prescription drug orally, as advised by your physician, generally once a day, with or without meal.
- Your medical condition, kidney function, and reaction to treatment will all determine the dosage. Take it at the same time every day to aid in memory. Pay close attention to the food diet, exercise regimen, and pharmaceutical treatment plan that your doctor has prescribed.
- As advised by your physician, take regular readings of your blood sugar. Make a note of the findings and provide them to your physician.

SIDE EFFECTS

- Recall that your healthcare provider recommended this medication given that they believe it will benefit you more than it will cause adverse consequences. A lot of customers of this prescription medication report no significant adverse effects.
- While hypoglycemia, or low blood sugar, is uncommon when sitagliptin is used alone, it can happen when it is provided with other diabetic drugs. To find out if you need to reduce the dosage of your other diabetes medication(s), speak with your doctor or pharmacist.
- Sudden perspiration, trembling, a rapid heartbeat, hunger, impaired vision, lightheadedness, or tingling in the hands or feet are signs of low blood sugar. Keeping glucose gel or tablets on hand is a smart move for managing low blood sugar. In the event that you lack these dependable sources of glucose, quickly increase your blood sugar levels by consuming non-diet Coke or fruit juice, or by ingesting a quick source of sugar such table sugar, honey, or candies.
- If you are allergic to sitagliptin or have any other allergies, let your doctor or pharmacist know before starting to use it. For further information, consult your pharmacist.
- Inform your doctor or pharmacist about all of your medical history before using this drug, including any instances of kidney disease, heart failure, pancreatitis, or gallstones.
- Too high or too low blood sugar can cause tiredness, dizziness, and blurred vision. Wait until you are certain that you can accomplish tasks requiring alertness or clear vision safely before operating machinery, driving, or engaging in any other activity.

PREVENTIONS-

While using this medication, avoid drinking too much alcohol as it may raise your risk of low blood sugar. When your body is under stress (from a fever, infection, injury, or surgery, for example), it could be more difficult to regulate your blood sugar. Speak with your physician as heightened stress may necessitate alterations to your drug regimen, treatment strategy, or blood sugar monitoring. Inform your doctor or dentist about everything you use before surgery, including over-the-counter, prescription, and herbal products.

INTERACTION

Interactions between medications might alter the way your prescriptions function or raise the possibility of serious negative effects. Not every potential medication interaction is covered in this document. Make a list of everything you use, including over-the-counter and prescription medications as well as herbal remedies, and provide it to your pharmacist and physician. Before beginning, stopping, or altering the amount of any medication, get your doctor's approval.

TOXICITY

At characteristic doses, animal trials throughout gestation haven't shown any adverse consequences on the mother's reproductive system or offspring; however, these findings may not always translate to humans Label. Fetal irradiation is currently voluntarily registeredLabel,7. Studies on animals at 100 times the highest doses advised for humans showed a rise in rib malformations Label. Rat milking contains sitagliptin, however it's unclear if this substance would also be secreted within human breast milk Label. It is necessary to weigh the risks along with the advantages of prescription a medication carefully because numerous medications are synthesized in human breast milk. Data on both safety and effectiveness in youngsters are currently insufficient. Include a label on. However, there were no discernible variations in security and effectiveness between older and younger people.

FUNCTIONING & MECHANISM

The functioning of the mechanism

The breakdown of the incretins that include it and GIPLabel is slowed down by sitagliptin's binding to DPP-4. For the purpose of maintaining glucose homeostasis, the intestines are discharged around the day and increased in response to mealsLabel,4. Lower incretin levels blockade causes an increase in insulin production and a corresponding reduction in the production of glucagon that is dependent upon the volume of glucose supplied. Marc,1. Reduced prices in hemoglobin that has been glycosylated (HbA1c) Label,4, suggest these effects bring about an overall benefit in sugar metabolism.

Extended-Duration the DPP-4 Blockers

presently, the United States of America &/or Europeans have given approval to five DPP-4 inhibitors: Vildagliptin, sitagliptin, Alogliptin, Linagliptin, and Saxagliptin. Every single one of their ears, with exception of vildagliptin, which is taken on two separate occasions, are taken at breakfast & suppress enzyme DPP-4, which takes down GLP-1 and GIP, for a full day. Omarigliptin (MK Foods-3105; 25 mg), a once-weekly DPP-4 agent that was recently developed by Merck Significant & Dohme60, improved A1C through a placebo-adjusted 0.71% within a 12-per week.

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