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REVIEW ARTICLE

Review on Sitagliptin

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ABSTRACT

Sitagliptin is also known as Januvia which contains the active substance sitagliptin which is a member of a class of medicines called as dipeptidyl-peptidase-4 inhibitors (DPP-4) that lowers blood sugar levels in adult patients with type 2 diabetes mellitus. Sitagliptin is the first dipeptidyl-peptidase-4 inhibitor which is used in the treatment of diabetes mellitus. It is very useful in improving β-cell function and reducing sugar level in the blood and also used in the special circumstances like chronic kidney diseases with appropriate dose adjustment. It is one of the most effective dipeptidyl-peptidase-4 inhibitor involved in reducing glycosylated hemoglobin (HbA1c), fasting as well as postprandial blood sugar levels when used as monotherapy or in combination with other oral hypoglycemic agents. In this review article we have summarized all the previous studies relevant to sitagliptin use in the clinical practice.

KEYWORDS

Sitagliptin, Dipeptidyl-Peptidase-4 Inhibitors, Type 2 Diabetes Mellitus, Glycosylated Hemoglobin

INTRODUCTION

Molecular Formula: $C_{16}H_{15}F_6N_5O$

Molecular mass: 407.314 g/mol

Monoisotopic mass: 407.118073 Da

Sitagliptin is a newly introduced oral hypoglycemic agent. It is dipeptidyl-peptidase-4 inhibitor (DPP-4) that has been recently approved for the treatment of type-2 diabetes mellitus. Like other DPP-4 inhibitors its action is mediated by increasing levels of the incretin hormones such as glucagon-like peptide-1(GLP-1) and gastric inhibitory peptide (GIP).

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In October 2006, sitagliptin was approved by the FDA for the treatment of type 2 diabetes mellitus. After reporting of spontaneous adverse events such as anaphylaxis, angioedema, serious skin reactions, sitagliptin was updated in October 2007 and most of these events reported were occurred within the first 3 months of initiation of the therapy.[2]

Drug Properties

sitagliptin is an orally-bioavailable selective DPP-4 inhibitor that was discovered by the optimization of a class of β-amino-acid-derived DPP-4 inhibitors and also it lowers DPP-4 activity in a sustained manner after once daily administration, preserve the circulating levels of intact GIP and GLP-1 after having meals in both acute and chronic research studies. Finally it

reduces blood sugar level without significant causing hypoglycaemia.[3]

Chemically, sitagliptin is (2R)-4-oxo-4-[3-(trifluoromethyl)-5,6-ihydro[1,2,4]triazol[4,3]pyrazin-7(8H)-yl]-1-(2,4,5-trifluorophenyl)butan-2-amine, and is also having very high selectivity towards DPP-4. It has no affinity towards other dipeptidyl-peptidase enzymes like dipeptidyl-peptidase-8(DPP-8) and dipeptidyl-peptidase-9(DPP-9). After administration of sitagliptin, it takes minimum 3 days to reach the steady state plasma concentration in our body.

DPP-4 inhibitor makes slowing down the degradation and inactivation of the incretins, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide. DPP-4 inhibitors primarily inhibits glucagon secretion by acting on islets where it stimulates secretion of insulin there by promotes β-cell proliferation.[4]

Mechanism of Action

Sitagliptin inhibits gastrointestinal mediated dipeptidyl-peptidase-4 (DPP-4) which is responsible for inactivation and degradation of incretin hormones. The increased action of incretin stimulates insulin release and decreases glucagon secretion, resulting in lower glycosylated hemoglobin (HbA1c), lower fasting and postprandial blood sugar level. This action simultaneously increases the body's response to food while minimizing hypoglycemia.

Sitagliptin improves the ability of alpha cells to suppress glucagon secretion (by enhancing active incretin levels), which results in decreased glycogen breakdown and glucose synthesis. It increases insulin synthesis and release from pancreatic beta cells, which helps to reduce hepatic glucose overproduction.[5]

Indication

Sitagliptin is used in the treatment of type 2 diabetes for the patients with insufficient glucose control who are taking metformin, sulfonylureas, or combination of the both drugs. It mainly improves beta-cell function and beta-mass in type 2 diabetes.

Sitagliptin is very effective in reducing glycosylated hemoglobin (HbA1c), fasting blood sugar as well as postprandial blood sugar level when used as monotherapy and in combination with other oral hypoglycemic agents such as metformin or thiazolidinediones. When hyperglycemia is present it stimulates insulin secretion and inhibits glucagon secretion.[1]

The DPP-4 inhibitors are considered as weight neutral and it has been shown to reduce the cardiovascular risks such as triglycerides, low density lipoprotein cholesterol, high density lipoprotein cholesterol and blood pressure.[6]

Intravenous infusion of GLP- 1 produces natriuretic and diuretic responses. This is because the GLP-1 receptors are also present in the proximal tubules and glomerulus of the kidney; hence it can be used in the diabetic kidney disease.[4]

Pharmacokinetics and Pharmacodynamics

Absorption: orally, with or without food.

Protein binding: 38%

Volume of distribution (Vd): 198 Liter

Metabolism: limited metabolism via CYP 3A4, 2C8

Bioavailability: sitagliptin has 87% bioavailability after single oral dose of 100mg.

Elimination: 87% (79% unchanged) in urine; 13% in feces. Sitagliptin is excreted through both glomerular filtration and secretion into tubules.

Elimination half-life ($T_{½}$): 12.4 hr.[7]

Precautions

1. Sitagliptin should not be used in patients with:

Moderate or severe renal dysfunction or end-stage of renal disease – if used, reduce the dose:

CrCl* 30-50ml/min – 50mg daily

CrCl <30 ml/min – 25mg daily

Dialysis – 25mg daily

2. Severe liver dysfunction.
3. Patients under 18 years of age; safety and efficacy of sitagliptin have not yet been established.
4. Sitagliptin is not recommended for use in pregnancy (category B) or during lactation due to lack of adequate clinical trials, excretion in breast milk is unknown.

DPP-4 is expressed in many tissues, including lymphocytes, and as sitagliptin inhibits DPP-4, this has raised a concern over its effect on the immune system and inflammatory mediators. Other drugs in this class of agents have demonstrated increased liver function tests, skin reactions (vildagliptin, saxagliptin) and decreased lymphocytes (saxagliptin). Safety and efficacy of sitagliptin have not been established in patients with severe hepatic impairment.[5,7]

Drug-Interactions

Co-administration of digoxin and sitagliptin (11% ↑ AUC; 18% ↑ Cmax) –dosage adjustment for sitagliptin is not required. Patients being treated with digoxin and sitagliptin concurrently should be monitored.

Dosing

Now sitagliptin is available in 25mg, 50mg, and 100mg tablets. The recommended dose is 100mg once daily as monotherapy or in combination with metformin or a peroxisome proliferator-activated receptor gamma agonist (PPAR-gamma) e.g. thiazolidinediones (TZDs).

Patients with:

CrCl = 50 mL/min: 100 mg daily

CrCl = 30 to < 50 mL/min: 50 mg daily and

CrCl < 30 mL/min or on haemodialysis: 25 mg daily dose is required.[7]

Adverse Effects

Common adverse effects include:

1. Upper respiratory tract infection(URTI)- 4.5-6.3%
2. Nasopharyngitis- 5.2-6.3%
3. Urinary tract infection(UTI)- 3.2%
4. Headache - 5.9%
5. Arthralgia- 3%

Other adverse effects include sore throat, cough, fatigue, dizziness, edema, nausea, and diarrhea.

Hypersensitivity reactions such as anaphylaxis, angioedema, & exfoliated skin conditions (Stevens - Johnson syndrome) as well as increased liver function tests have been reported rarely.

Contra-Indications

Hypersensitivity to sitagliptin occurs in the patients with diabetic ketoacidosis or in the patients with Type I diabetes mellitus.[5]

Dosage Adjustment

1. Dosage adjustment for patients with renal dysfunction.

Dosage adjustment is required for patients with moderate and severe renal dysfunction, because sitagliptin is excreted primarily by the kidney, to achieve plasma concentrations similar to those in patients with normal renal function.

For patients with moderate and severe renal dysfunction lower doses are recommended. As well as for patients with end-stage renal disease (ESRD) who requires haemodialysis or peritoneal dialysis.[8]

50 mg once daily	25 mg once daily
Moderate Cr Cl ≥30 - 50 ml/min ≈ Serum Cr levels(mg/dl) Men >1.7 - 3.0 Women >1.5 - 2.5	Severe and ESRD Cr Cl <30 ml/min ≈ Serum Cr levels(mg/dl) Men > 3 Women > 2.5 or on dialysis

1. Hepatic impairment

Dosage adjustment is not required for sitagliptin in patients with mild or moderate hepatic

impairment. Clinical trial has not shown any data for dosage adjustment in the patients with severe hepatic impairment. However; this is because sitagliptin is primarily excreted through kidney, severe hepatic impairment is not expected to affect the pharmacokinetics of sitagliptin.[8]

2. Elderly patients

Dosage adjustment is not required for sitagliptin in elderly patients. Age do not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II clinical trial.[8]

Patient Information Points

1. If any patient is allergic to sitagliptin or any of the other ingredients of this medicine then inform them to not take.

2. If any patient develops dizziness and drowsiness then it may affect their ability to drive or working on machines. It is better to avoid driving and be careful while working on machines.

3. If patient miss a dose, inform them to take it as soon as they remember. If he/she does not remember until it is time for your next dose then skip the missed dose and go back to your regular schedule. Finally they should not take a double dose of this medicine.

4. Keep this sitagliptin out of sight and reach of children. Do not use this sitagliptin after the expiry date which is mentioned on the blister or package.

5. Inform to patients do not stop taking this sitagliptin without informing to their doctor. Continue to take this sitagliptin as long as their doctor prescribes.

Abbreviations

DPP-4: dipeptidyl peptidase-4 inhibitors.

GLP-1: glucagon- like peptide-1.

GIP: gastric inhibitory peptide.

HbA1c: glycosylated hemoglobin.

FDA: food and drug administration.

CrCl: creatinine clearance.

ESRD: end- stage renal disease.

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