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SITAGLIPTIN: PROMISING HOPE OF PHARMACOTHERAPY FOR TYPE-2 DIABETES MELLITUS

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ABSTRACT: Type 2 diabetes is the most common form of the disease, accounting for about 90% to 95 % of all diagnosed cases of diabetes. It is estimated that diabetes currently affects million people worldwide. This figure is expected to rise to over 330 million by 2030 . It is a syndrome of disordered metabolism associated with hyperglycaemia due to either deficiency of insulin secretion, decreased release or reduction in biological effectiveness of insulin due to development of resistance by insulin receptors. In type 2 diabetes, the body does not produce enough insulin or the cells ignore the insulin. Over time, high blood sugar levels can increase the risk for serious complications, including heart disease, blindness, nerve damage and kidney damage. so new oral hypoglycemic drug that can control blood glucose with fewer adverse effects in patients with diabetes may be welcomed. Sitagliptin is the first and only prescription medication in a new class of oral antihyperglycemic agents, which enhance the body's own ability to lower blood glucose when it is elevated. This article gives an overview of the mechanism of action, the pharmacology, and the clinical efficacy and safety of sitagliptin in type 2 diabetes therapy.

Introduction:

Sitagliptin (Januvia TM) is a new medication recently approved (October 17th, 2006) by the FDA for the treatment of Type 2 Diabetes Mellitus (T2DM). It is the first agent in a new class of diabetes medications called dipeptidyl-peptidase-IV (DPP-4) inhibitors.[1,2] It prevents the breakdown of glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide, which are incretin hormones that act on alpha and beta pancreatic cells to stimulate insulin release and suppress glucagon in a glucose–dependent manner.[3] Sitagliptin is approved for use in type 2 diabetics as an adjunct to diet and exercise or in combination with metformin or peroxisome proliferator-activated receptor gamma (PPAR-ã) agonists (e.g. thiazolidinediones).[4] Over

2,700 diabetic patients have been treated with sitagliptin for a minimum of 12 weeks and results have demonstrated reductions in HbA1c (A1C) concentrations, as well as fasting and postprandial glucose levels.[5] This new class of agents provides healthcare providers with an additional modality for achieving glycemic control in type 2 diabetes.

What is SITAGLIPTIN?

Sitagliptin (BRANDNAME JANUVIA) is a new class of oral anti-hyperglycemic known as a DPP-4 inhibitor or incretin enhancer for the treatment of Type 2 diabetes mellitus (T2DM). Sitagliptin is dosed at 100mg daily {Cost $300/3 months, non-formulary SK & NIHB}. It may be taken with or without food {Availability: Canada: 100mg tablets only; USA: 25mg, 50mg and 100mg strengths}.[5] Sitagliptin inhibits GI mediated dipeptidyl-peptidase-4 (DPP-4) which is responsible for inactivation and degradation of incretin hormones. The increased action of incretin stimulates insulin release & reduces glucagon secretion, resulting in lower A1C and lower fasting & postprandial glucose levels. This action enhances the body's response to food while minimizing hypoglycaemia.[6]

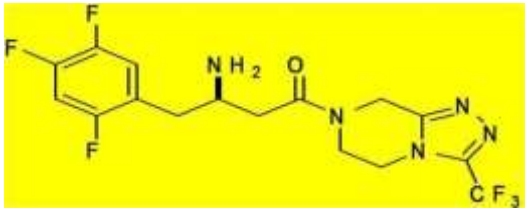

Fig-1 structure of sitagliptin [7]

CLINICAL PHARMACOLOGY: -

MECHANISM OF ACTION: -Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretin hormones glucagon-like peptide- 1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1 enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPP-IV activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma.[8] Sitagliptin reduces haemoglobin A1c (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion an inhibition of glucagon secretion.[9] GLP-1 has other widespread effects including delaying gastric emptying, significantly reducing glucagons levels and possible central effects on appetite .[10]

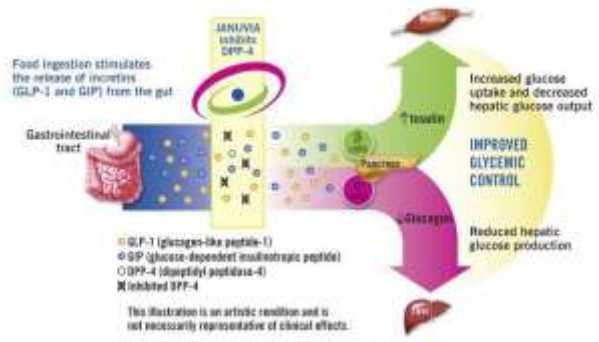

Fig- 2 mechanism of action [11]

PHARMACODYNAMIC AND PHARMACOKINETICS: -

Studies of sitagliptins, shown that the administration of sitagliptin results in inhibition of DPP-4 activity for a 24-hour period. Bioavailability of sitagliptin is approximately 87%. Half-life is between 8-14 hours. It is 38% bound to plasma proteins. It undergoes limited metabolism via CYP3A4 and CYP2C8. Elimination is mainly through urine. [12-13]

INDICATIONS, DOSING AND ADMINISTRATION: -Sitagliptin is approved for use as monotherapy in addition to diet and exercise or in combination with metformin or PPAR-ã agonists if monotherapy is not sufficient. The recommended dose for monotherapy or combination therapy is 100 mg by mouth daily taken with or without food. Because of its renal elimination, dose adjustments of sitagliptin are necessary in patients with renal dysfunction. A combination product of sitagliptin and metformin was approved by the FDA in April 2007. This product is marketed as Janumet TM and is available in the following strengths: 500 mg metformin/50 mg sitagliptin and 1000 mg metformin/50 mg sitagliptin. Janumet is approved for use as an adjunct to diet and exercise in patients with type 2 diabetes and in those not adequately controlled on metformin or sitagliptin alone. It should be administered orally twice daily with meals.[14]

ADVERSE EFFECTS [15-16]:

Common side effects include (compared to placebo):

1) Upper respiratory tract infection (4.5-6.3%)
2) Nasopharyngitis (5.2-6.3%)
3) Urinary tract infection (3.2%)
4) Headache (1.1-5.9%)
5) Arthralgias (3%)
6) Other side effects mayOther side effects may include sore throat, cough, fatigue, dizziness, edema, nausea, and diarrhea

CONTRAINDICATIONS [17] :-

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

Use in Pregnancy: -Januvia™ is not recommended for use in pregnancy as the safety has not been established.

Supplied: - Januvia™ is available as a 100 mg tablet.[18]

Drug properties: -

Sitagliptin is an orally-bioavailable selective DPP4 inhibitor that was discovered through the optimization of a class of β-aminoacid- derived DPP4 inhibitors5. It lowers DPP4 activity in a sustained manner following once daily administration, preserves the circulating levels of intact GIP and GLP1 following meals in both acute and chronic studies and reduces blood glucose levels without significant increases in hypoglycaemia.[19]

Dosage and Administration: -

Oral Adults with Type 2 diabetes: 100 mg once daily with or without food.[6]

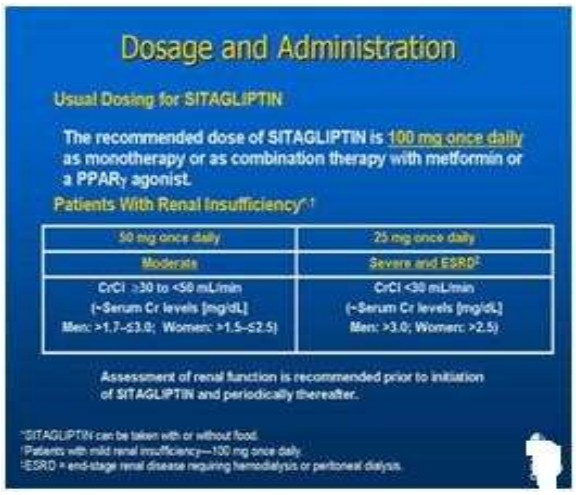

Fig 3 dosage and administration

DOSAGE FORMS AND STRENGTHS: -

100 mg tablets are beige, round, film-coated tablets with "277" on one side.

50 mg tablets are light beige, round, film-coated tablets with "112" on one side. 25 mg tablets are pink, round, film-coated tablets with "221" on one side.[20]

Who can take sitagliptin?

Sitagliptin is available on the Pharmaceutical Benefits Scheme (PBS) for people with type 2 diabetes, but there are some restrictions on its use. In general terms, you can get sitagliptin through the PBS if:

you are already taking metformin or a sulfonylurea.

your HbA1c (a measurement that reflects your average blood glucose levels over the last 10–12 weeks) is over 7%.

you cannot use a combination of metformin and a sulfonylurea, or the combination causes you intolerable side effects.

Sitagliptin is not taken on its own. You will need to continue taking your metformin or sulfonylurea when you start sitagliptin.[21]

Speak to your doctor if you have kidney problems. You may still be able to take sitagliptin, but your doctor will have to take this into account before prescribing.

How to take sitagliptin?

Take one sitagliptin tablet at the same time each day.[22]

USE IN SPECIFIC POPULATIONS

PREGNANCY: -

Pregnancy Category B:

Reproduction studies have been performed in rats and rabbits. Doses of sitagliptin up to 125 mg/kg (approximately 12 times the human exposure at the maximum recommended human dose) did not impair fertility or harm the fetus. There are, however, no adequate and well-controlled studies in pregnant womepn.

Nursing Mothers: -

Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1. It is not known whether sitagliptin is excreted in human milk.

Pediatric Use: -

Safety and effectiveness of JANUVIA in pediatric patients under 18 years of age have not been established.

Geriatric Use: -

Of the total number of subjects (N=3884) in pre-approval clinical safety and efficacy studies of JANUVIA, 725 patients were 65 years and over, while 61 patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects. While this and other reported clinical experience have not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out.[23]

Efficacy and tolerability of sitagliptin: -

The study presented was a randomized, double-blind, placebo-controlled study, which evaluated the efficacy and tolerability of sitagliptin in 743 patients with type 2 diabetes. The majority of the patients in this study had mild to moderate hyperglycaemia (mean baseline A1C of 7.8 - 7.9 percent). Patients were randomized to one of six treatment groups: placebo; sitagliptin (5mg, 12.5 mg, 25 mg, or 50 mg oral tablets twice daily); or the sulfonylurea, glipizide, 5 mg titrated to 20 mg. After a 12-week treatment period, sitagliptin significantly reduced A1C from baseline compared to placebo. The largest reduction in the patients treated with sitagliptin was 0.77 percent $p<0.001$, in the 50 mg twice-daily treatment group. Patients taking glipizide showed a 1.0 percent reduction from baseline in A1C. In the active treatment groups, placebo subtracted A1C results did not appear to reach a plateau.Treatment with sitagliptin was generally well tolerated and resulted in no significant weight gain. Patients treated with glipizide had an average weight gain of 1.1 kilogram relative to placebo. Adverse event reports of hypoglycaemia were observed in 4 percent of patients taking sitagliptin, 17 percent of patients taking glipizide and 2 percent of patients taking placebo. "The loss of efficacy with sulfonylureas is well described. Longer term studies with an appropriate once daily dose of sitagliptin will address the full efficacy and potential durability of sitagliptin versus glipizide," commented Russell Scott MD, PhD, Professor of Medicine, Director of Diabetes and Lipid Research Group, Christchurch Hospital and School of Medicine, New Zealand.[24]

Drug interaction: -

Digoxin: -There was a slight increase in the area under the curve (AUC, 11%) and mean peak drug concentration (Cmax, 18%) of digoxin with the co-administration of 100 mg sitagliptin for 10 days. Patients receiving digoxin should be monitored appropriately. No dosage adjustment of digoxin or JANUVIA is recommended. [24]

Clinical Results: -

FDA Approval: - FDA approval of Januvua was based on the pooled results of two double-blind, placebo-controlled monotherapy studies and two double-blind, placebo-controlled combination therapy studies.

Monotherapy Trials: -

The Januvia monotherapy trials had one with an 18-week duration and one with a 24-week duration. In the 18- week study, 521 subjects were randomized to placebo, Januvia 100 mg, or Januvia 200 mg, and in the 24-week study 741 subjects were randomized to placebo, Januvia 100 mg, or Januvia 200 mg. In both trials subjects went under a 7-week washout period then completed a 2-week, single-blind, placebo run-in period, before receiving treatment. Treatment with Januvia at 100 mg daily provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo. In the 18-week study, 9% of patients receiving Januvia 100 mg and 17% who received placebo required rescue therapy. In the 24-week study, 9 % of patients receiving Januvia 100 mg and 21% of patients receiving placebo required rescue therapy. The 200 mg daily dose did not provide greater glycemic efficacy than the 100 mg daily dose in either trial.[25]

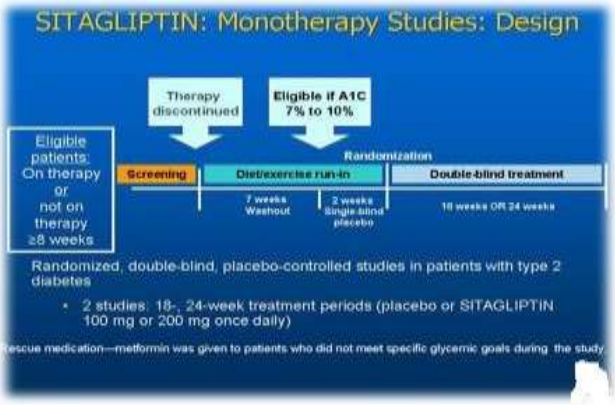

Fig 4 monotherapy trials

Combination Therapy Trials: -

The first randomized, double-blind, placebo-controlled trial enrolled 701 subjects. It was designed to compare Januvia in combination with metformin as treatment for 24 weeks. Subjects already on metformin at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo run-in period. Subjects on metformin and another antihyperglycemic agent and subjects not on any antihyperglycemic agents (off therapy for at least 8 weeks) were randomized after a run-in period of approximately 10 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Subjects were randomized to the addition of either 100 mg of Januvia or placebo, administered once daily. This combination provided significant improvements in A1C, FPG, and 2-hour PPG compared to placebo with metformin. Rescue glycemic therapy was used in 5% of those treated with Januvia 100 mg and 14% of those treated with placebo.

The second randomized, double-blind, placebo-controlled trial enrolled 353 subjects. It was designed to evaluate Januvia in combination with pioglitazone as treatment for 24 weeks. Patients on any oral antihyperglycemic agent in monotherapy or on a PPAR agent in combination therapy or not on an antihyperglycemic agent (off therapy for at least 8 weeks) were switched to monotherapy with pioglitazone (at a dose of 30-45 mg per day), and completed a run-in period of approximately 12 weeks in duration. After the run-in period on pioglitazone monotherapy, patients were randomized to the addition of either 100 mg of Januvia or placebo, administered once daily. This combination therapy demonstrated significant improvements in A1C and FPG compared to placebo with pioglitazone. Rescue therapy was used in 7% of patients treated with Januvia 100 mg and 14% of patients treated with placebo.[26]

Conclusion: -

Sitagliptin is a potent, competitive, reversible inhibitor of the DPP4 enzyme, and is the first agent in this class to be launched onto the world market that can be used by people with type 2 diabetes whose blood glucose cannot be controlled effectively with certain other medicines. Sitagliptin, a DPP4 inhibitor, offers a novel treatment option for patients with type 2 diabetes mellitus. improves glycaemic control by inhibiting DPP-4 inactivation of the incretin hormones glucagon - like peptide-1 and glucose-dependent insulinotropic polypeptide. sitagliptin act by increase active incretin and insulin levels, and decreases glucagon levels and postglucose-load glucose excursion. . Sitagliptin, it can be used as monotherapy or in various combination with other antidiabetic drugs,which led to promising new treatment option, especially for patients with early-stage type 2 diabetes and more severe hyperglycemia, although experience with this noble drug will further help it to establish its supremacy as oral drug for Type -2 DM.

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References: -

1) U.S. Food and Drug Administration: Center for Drug Evaluation and Research. Electronic References. Retrieved December 18, 2006, from http://www.fda.gov/bbs/topics/NEWS/2006/NEW01492.html
2) Sitagliptin. Prescribing Information. Electronic References.Retrieved December 18, 2006, from http;//www.fda.gov/cder/foi/label/2006/021995lbl.
3) Common drug review september 2008; sitagliptin-januvia merck frost Canada inc.
4) Gallwitz B. Sitagliptin: Profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes. Drugs Today (Barc) 2007; 43: 13-25.
5) Green BD, Flatt PR, Bailey CJ. Dipeptidyl peptidase IV (DPP IV) inhibitors: A newly emerging drug class for the treatment of type 2 diabetes. Diab Vasc Dis Res 2006; 3:159-65.
6) Product Monograph for Januvia. Merck Frosst Canada Ltd. Kirkland, Quebec, Canada H9H 3L1. December 13, 2007 Pharmacist's Letter. February 2008. New Drug: Januvia (Sitagliptin)
7) http://www.micromedex.com/. Accessed online.

8) http://www.google.co.in/imgres?imgurl=http://jpet.aspetjournals.org/content/321/2/673/F1.small.gif&imgrefurl=http://jpet.aspetjournals.org/content/321/2/673.
9) Blaschke F, Caglayan E, Hsueh WA. Peroxisome proliferator-activated receptor gamma agonists: their role as vasoprotective agents in diabetes. Endocrinol Metab ClinNorth Am 2006; 35:561-74.4
10) Perreiter . A, Loya .A, Sitigliptin (JanuviaTM): A New Mechanism for Treating Type 2 Diabetes Mellitus, Rx pharmacy corner E.P.C.M.S, volume 30, Number 3.5
11) http://www.google.co.in/imgres?imgurl=http://jpet.aspetjournals.org/content/321/2/673/F1.small.gif&imgrefurl=http://jpet.aspetjournals.org/content/321/2/673.
12) http://www.druglib.com/druginfo/januvia/indications_dosage/
13) Gallwitz B. Sitagliptin: Profile of a novel DPP-4 inhibitor for the treatment of type 2 diabetes. Drugs Today (Barc) 2007; 43: 13-25.
14) Herman GA, Stevens C, Van Dyck K. Pharmacokinetics and pharmacodynamics of sitagliptin, an inhibitor of dipeptidyl peptidase IV, in healthy subjects: results from two randomized, double-blind, placebo-controlled studies with single oral doses. Clin Pharmacol Ther 2005; 78: 675-88.
15) http://www.druglib.com/druginfo/januvia/indications_dosage/
16) Daniel D, Chris E, Peter K. Fresh from the Pipeline: Sitagliptin. Nat Rev Drug Discov 2007; 6:109-10.
17) Product monograph for Januvia. Merck Frosst Canada Ltd., Kirkland, QC, December 2007.Retrieved 21JAN2008; Available from: http://www.merckfrosst.ca140
18) Januvia. Lexi Drugs Online. 19782008 LexiComp Inc. Retrieved 24JAN2008; cited: http://online.lexi.com.cyber.usask.ca/crlonline?siteid=293 Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Groupl. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia2006 Nov; 49(11):2564-71.
19) Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H; Sitagliptin Study 023 Groupl . Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia2006 Nov; 49(11):2564-71 http://en.diagnosispro.com/drug_information-for/januvia-sitagliptin-tablets-merck-co-inc-dosage-forms- and-strengths/4471-260174.html
20) http://www.nps.org.au/consumers/publications/medicine_update/issues/sitagliptin
21) http://en.diagnosispro.com/drug_information-for/januvia-physicians-total-care-inc-8-use-in-specific- populations/6389-475473.html
22) http://scienceblog.com/community/older/2005/13/200512439.shtml
23) http://www.druglib.com/druginfo/januvia/interactions_overdosage_contraindications/
24) http://www.centerwatch.com/drug-information/fda-approvals/drug-details.aspx?DrugID=935