

# DPP 4 Inhibitors - New paradigms in managing diabetes mellitus; A review

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### ABSTRACT

The management of diabetes mellitus has evolved in time since the discovery of disease. The race to reach the most appropriate glycemic goal has been attended by consequent development of multiple agents in the armamentarium of treating physician. Realization of incretin effect in the pathophysiology of disease and then demonstration of pharmacologic beneficial effects of incretin hormones holds promise for better management. DPP4 inhibitors by acting as incretin enhancers has drawn interest further due their potential beneficial disease modifying effects and increase in beta cell mass. This review elucidates the efficacy of available DPP4 inhibitors in management of disease. [IJEM 2008;12(8):27-42]

**Key words:** Type 2 diabetes mellitus, incretin, GLP-1, DPP 4 inhibitors

### INTRODUCTION

The prevalence of type 2 diabetes mellitus is rising dramatically with attendant increase of consecutive complications. The pathogenesis of type 2 diabetes involves three primary defects: insulin resistance, beta cell dysfunction and hepatic glucose overproduction. None of the currently available treatment options address the problem of islet cell dysfunction and they have their attending problems of lack of efficacy and side effects, hence there remain critical unmet medical needs in the treatment of this disease. Beta cell function is lost more than 50% once hyperglycemia is diagnosed and unattainable glycemic control is often a result of ongoing deterioration of beta cell function. A novel approach in treating diabetes mellitus is to utilize the physiological actions of endogenous incretin hormones; glucagon like peptide - 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP), the intestinal hormones released in response to nutrient ingestion. GIP is secreted by K cells from upper small intestine and GLP-1 is by L cells located in distal intestine when stimulated by intraluminal glucose. Incretin effect is the augmentation of glucose-stimulated insulin secretion by intestinally derived peptides, which are released in the presence of glucose in the gut. The observation that an oral glucose load was more effective at releasing insulin compared with the same amount of glucose given intravenously led to this theory. Studies

prove that both GIP and GLP-1 stimulate insulin release in glucose dependent manner in humans, contributing 50 – 70% of the postprandial insulin response and both are necessary for maintenance of normal glucose tolerance. Incretins stimulate insulin secretion only in presence of hyperglycemia with no response in normal or low glucose levels. Pathophysiology of diabetes mellitus also encompass a recently understood defect in incretin effect with decreased insulinotropic effect of GIP and decreased blood levels of GLP-1. Research shows a 15% reduction in post prandial levels of GLP-1 in patients with diabetes mellitus. Although hyperinsulinaemia is a hallmark of the first years after diagnosis, the first-phase insulin response (peak after a glucose load) is impaired or absent early in the disease. This first-phase insulin response is caused by incretins secreted from the small intestine after an oral glucose load. GIP and GLP-1 are rapidly inactivated by dipeptidyl peptidase 4 (DPP 4), a member of serine peptidase family. DPP4 is ubiquitous in distribution. Tissues which strongly express DPP 4 include the exocrine pancreas, kidney, gastrointestinal tract, biliary tract, thymus, lymph nodes, uterus, placenta, prostate, adrenal, sweat glands, salivary and mammary glands. DPP4 is anchored to the plasma membrane of endothelia of almost all organs examined and is also found in body fluids such as blood plasma and cerebrospinal fluid. Different pharmacologic strategies to enhance incretin effect in management of diabetes include continuous administration of GLP-1, DPP4 resistant GLP-1 analogues and DPP4 inhibitors. Data from clinical trials for later approach seem to be promising. The serendipity of almost all presently

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available oral hypoglycemic compounds, whose precise mechanism of action have not been known at the time of their discovery, underlines the fact that each one of them have some clinically relevant side effects. It is not often seen that clinical proof of concept of an entirely new oral treatment modality emerges for a major debilitating disease; the DPP4 inhibitors for treatment of type 2 diabetes do, however, represent such a concept. Other favorable effects of incretin hormones may have a therapeutic role in type 2 diabetes mellitus like inhibition of glucagon release, decreased hepatic gluconeogenesis, slowing of gastric emptying, central action in suppressing appetite with consequent weight loss, stimulation of replication and neogenesis and inhibition of apoptosis of beta cells of pancreas, later quality signifying importance as potential agent for the prevention of type 2 diabetes. As incretin receptor activation is only coupled to stimulation of insulin secretion in the presence of elevated blood glucose, therapies that are based on incretin enhancement have a low risk of hypoglycemia, which is a problem with current therapies. As confirmed from studies, DPP4 inhibitors increase meal stimulated active GLP-1 and GIP levels by two to three fold, increase insulin and c-peptide levels, reduced plasma glucagon levels, reduced glycemic excursion following glucose tolerance test, dose dependently reduced HbA1c and fasting plasma glucose. DPP4 inhibitors may have a beneficial disease modifying effects of attenuating loss of beta cell mass and function and normalizing beta-alpha cell ratio on chronic therapy for 2-3 months. Thus, DPP4 inhibitors have the potential both for assisting in achieving glycemic goals in anti-diabetic therapy and for modifying underlying disease course by correcting the islet cell dysfunctions characteristic of the disease. Studies have proven their role as monotherapy and as complementary adjuncts to ongoing oral therapy for diabetes mellitus. DPP4 inhibition have demonstrated even delay in the onset of overt diabetes, improvement in insulin sensitivity and reversal of glucose toxicity speculating their use in humans as a potential agent for the prevention of type2 diabetes. Because of the efficiency, safety, tolerability and oral route of administration, it is expected that DPP4 inhibition may be in first-line treatments of the early stage of type 2 diabetes, particularly in combination with metformin or thiazolidinediones. Concerns have been raised on selectivity of DPP IV inhibitors and side effect profile as inhibition of DPP8 and DPP9 (enzymes of same family as DPP4) have evoked severe toxicities in animal species. Thus, medicinal chemistry efforts focused on identifying a highly selective DPP4 inhibitor for clinical development. Optimization of this series led to the discovery of sitagliptin(MK431) and vildagliptin (LAF237), highly selective DPP4 inhibitors for the treatment of type2 diabetes, others in final stages of development are saxagliptin (BMS477118), alogliptin, demigliptin, SYR322, PHX1149, GRC8200, ilethiozolidide. DPP4 inhibitors may have the greatest impact in patients who are early in the disease process; however, whether they

are enough to get more patients to reach their goal HbA1c levels or they simply delay the start of insulin therapy remains in question. The present review evaluates the concept, therapeutic potential and limitations of DPP4 inhibitors as potential antidiabetic agents.

### Incretin physiology

Incretin hormones, GLP-1 and GIP are released from the L and K cells of the gastrointestinal tract, respectively, when those cells are stimulated by intraluminal glucose(1). L cells distributed mainly in ileum and colon secrete two forms of GLP-1: GLP-1 (7–37) and GLP-1 (7-36) with the former constituting 80% of total circulating GLP-1. K cells are distributed mainly in upper small intestine. The role of intestinal peptides in the regulation of postprandial insulin secretion was first identified by the observation that insulin secretion from pancreatic beta-cells was more robust after an

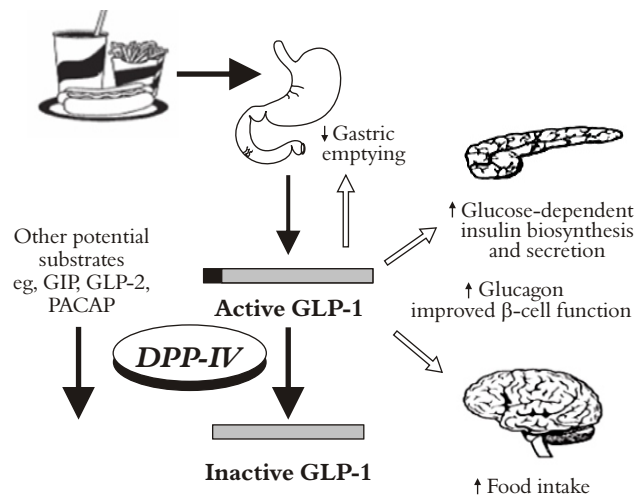
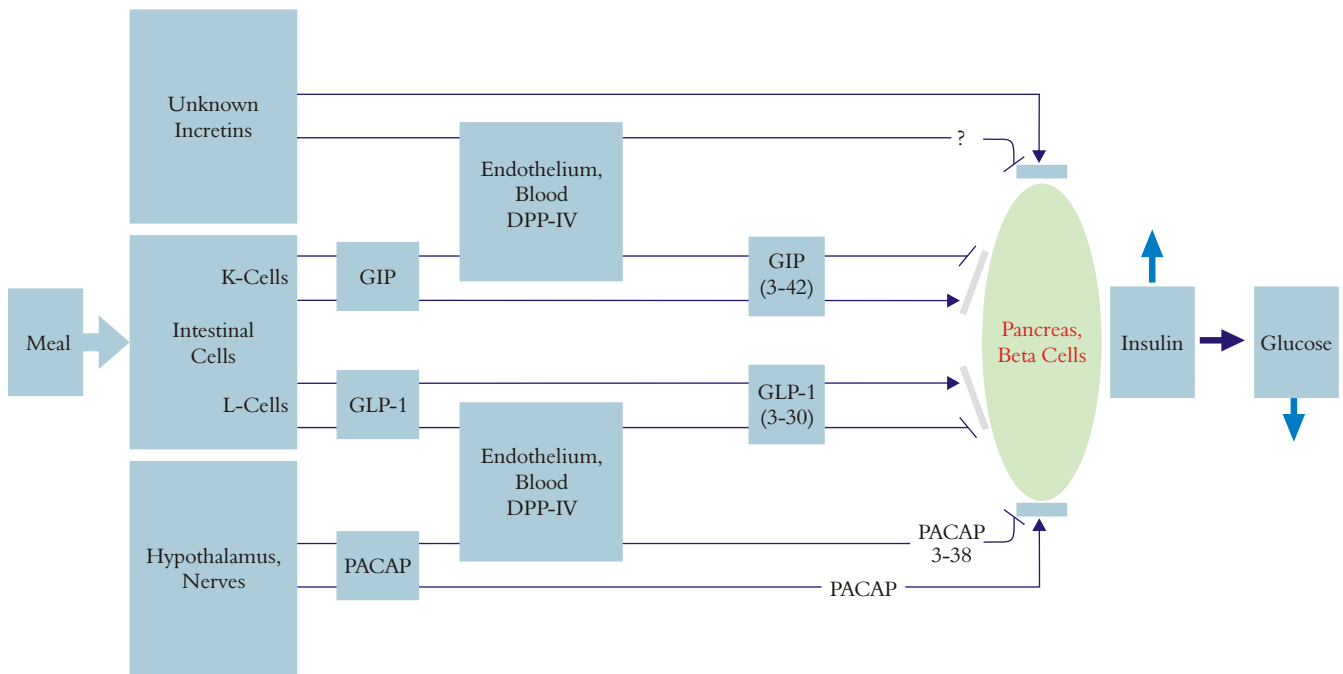


Figure 1: Depicting incretin physiology

oral glucose bolus than after an equivalent, intravenous glucose bolus(18). This “incretin effect” was attributed to the insulinotropic action of gut hormones, specifically GLP-1 and GIP(7,8,9,10). The hypothalamus also produces an incretin, pituitary adenylate cyclase-activating peptide (PACAP); the exact contribution of this peptide to insulin secretion is not clear yet. GIP induces  $\pm 60\%$  of the incretin effect and GLP-1 the rest(25). The uptake of carbohydrates and amino acids in the gut results in an endocrine response in the islets of Langerhans. It also causes neurotransmission to both the islets, the liver and via the nuclei of the medulla oblongata to the hypothalamus(26,27). After intake of carbohydrates a sixfold increase in the plasma concentration of incretin hormone GLP-1 is observed(25). GLP-1 and GIP are rapidly degraded by the enzyme system DPP4. The cleavage is rapid, which is the reason why native GLP-1 has a short half-life (2 min)(15). It is eliminated mainly through kidney (22). The highest concentrations of DPP4 are found in the kidneys, intestines, and bone marrow, while lower



GIP = Gastric Inhibitory Peptide; GLP-1 = Glucagon-Like Peptide-I; PACAP = Pituitary Adenyl-Cyclase-Activating Peptide.

**Figure 2:** Schematic overview of the production and action of the incretins: GIP, GLP-1 and PACAP on the Beta-cell. DPP-IV inhibitors inhibit the degradation of these incretins.

concentrations are present in the liver, pancreas, placenta, thymus, spleen, epithelial cells, vascular, endothelium, and lymphoid and myeloid cells(11,12,13). In addition to glucose, release of incretins is stimulated by fats and proteins in the gut lumen(30). Hormones also regulate GLP-1 secretion with insulin and somatostatin shown to inhibit GLP-1 release while GIP has been found to stimulate GLP-1 release.

Physiological doses of GIP act through the nervous system (either vagal or myenteric) to indirectly stimulate GLP-1 secretion, rather than acting directly at the level of the L cell. GLP-1 is released into the circulation after a meal. Significantly more GLP-1 is released after a liquid meal than a solid meal of identical composition. The majority of GLP-1 released appears to be in the form of GLP-1(7-36 amide) with levels reaching approximately 50 pM/L, whereas GLP-1(7-37) rises to 10 pM/L(30). The release of GLP-1 from the isolated perfused rat ileum required sodium implicating the brush-border sodium/glucose cotransporter in the glucose effect(30) also non transposable sugars, e.g., 2-deoxyglucose, or sugars using a different mechanism of transport, e.g., fructose and lactose, do not stimulate the release of GLP-1(30). The insulinotropic activity of GLP-1 is mediated through GLP-1 receptors on pancreatic cells. The release of GLP-1 in response to a meal occurs rapidly (within 10 minutes) in healthy individuals and is highly correlated with insulin secretion into the circulatory system(8). As incretin receptor activation is only coupled to stimulation of insulin

secretion in the presence of elevated blood glucose the incretins are euglycemics and not hypoglycemic. It is cleared from the plasma by the liver and the kidney(28).

**Table 1:** Effects van GLP-1 on several tissues

Tissue	Effect
Stomach	Delays gastric emptying
Small intestine	Slows gut motility
Liver	Stimulates glycogen synthesis
Fat	Stimulates glycogen synthesis Inhibits lipogenesis
Skeletal muscle	Stimulates glycogen synthesis
Exocrine pancreas	Inhibits enzyme release
Endocrine pancreas	Stimulates insulin release Stimulates somatostatin release Stimulates Beta-cell neogenesis Stimulates synthesis of proinsulin Inhibits glycogen synthesis Inhibits apoptosis of Beta-cells
Central nervous system	Inhibits food intake Stimulates satiety Increases body temperature Stimulates TSH, LH and vasopressin secretion
Kidney	Stimulates sodium excretion Inhibits H+ excretion Inhibits glomerular hyperfiltration
Heart	Increases blood pressure Increases heart rate

**Table 2:** Key actions of the incretin hormones GLP-1 (glucagon-like peptide-1) and GIP (glucose-dependent insulinotropic polypeptide)

GLP-1 and GIP	GIP-1 only
↓ plasma glucose	↑ feeling of satiety
↑ glucose-dependent insulin secretion	↓ food intake
↑ biosynthesis of insulin	↓ body weight
↑ expansion of beta-cell mass	↓ glucagon secretion
↑ beta cell survival*	↓ gastric acid secretion
↑ peripheral glucose uptake and disposal*	↓ hepatic insulin extraction
↓ gastric emptying rate	

Key: ↑ increase, ↓ decrease; \*noted in preclinical studies but yet to be confirmed in clinical studies

Incretin effect plays a crucial role in regulation of glucose metabolism in healthy individuals and is responsible for approximately 50–70% of postprandial insulin response(18). The biological activities of GLP-1, the main incretin, include glucose-dependent insulin secretion to aid tissue uptake of plasma glucose, suppression of postprandial glucagon to reduce hepatic glucose release, suppression of appetite, and slowing of gastric emptying thus avoiding sudden rise of glucose as food is absorbed from the gut evidence of which comes from studies relating dumping syndrome and incretins(5). Studies suggest that incretins play a role in proliferation of pancreatic beta-cells and differentiation of stem and precursor cells of pancreatic islands toward the beta-cells phenotype and induced expression of key genes for pancreatic beta-cells. Furthermore, administration of GLP-1 receptors activated metabolic pathways reducing pancreatic beta-cells

**Table 3:** Featuring physiological properties of incretins adapted from reference no. 89

Characteristic	GIP	GLP-1
Peptide	42 amino acid	30 amino acid
Released from	K cells of duodenum	L cells of ileum and colon
Active form	Single bioactive form	Two bioactive forms.
Inactivated by	DPP 4	DPP 4
Insulin secretion	stimulated	Stimulated
Glucagon secretion	-	Inhibited
Food intake	-	Reduced
G. I. motility	-	Decreases
Insulin biosynthesis	-	Stimulated
Beta cell proliferation	promoted	promoted
Type 2 diabetes	Secretion normal, response impaired	Secretion reduced, Response normal

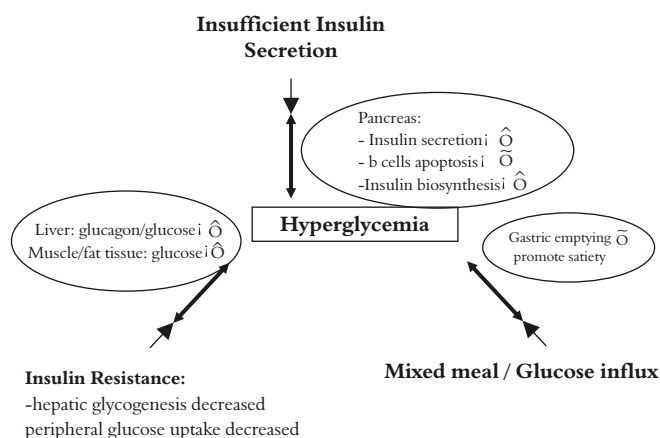
apoptosis(23). Studies also point towards improvement of peripheral insulin sensitivity, antagonistic actions to leptin on beta cells, inhibition of gastric acid secretion when infused in quantities that result in plasma concentrations similar to those observed after meals. Data from animal studies suggest that GLP-1 regulates maintenance of pancreatic beta cell

mass as a normal physiologic function(8,9,10). Extra-pancreatic actions also include the reduction of hepatic insulin clearance and apparently ‘insulin-like’ anabolic effects on skeletal muscle, liver and adipose tissue which serve to promote glucose uptake and metabolism and lipogenesis(29,30). The incretin metabolizing enzyme DPP4 is the founding member of a family of DPP4 activity and/or structure homologue (DASH) proteins, enzymes that are unified by their common postproline cleaving serine dipeptidyl peptidase mechanism(11). In addition to DPP4, family members include quiescent cell proline dipeptidase (QPP), DPP7, DPP8, DPP9, fibroblast activation protein, attractin, and DPP4(17). Based on the biological effects of the incretins and DPP4 enzyme system inhibition of latter presumably would result in increased serum levels of GLP-1, leading to a net antihyperglycemic effect. This effect has been demonstrated, in both animal and human models by improvement in glucose tolerance, enhancement of insulin secretion, and even delay in the onset of overt diabetes, improvement in insulin sensitivity and reversal of glucose toxicity. It has been suggested that DPP4 inhibition and its resultant preservation of endogenous GLP-1 activity may lead to beta-cell preservation and even increase in beta cell mass via augmentation of GLP-1’s antiapoptotic effects as has been proved in animal studies where DPP4 inhibition was associated with an enhancement of beta cell survival and neogenesis in streptozotocin treated diabetic rats(1,2,3).

### Incretins in Diabetes Mellitus

The incretin pathway appears to be attenuated in type 2 diabetes, making the pathway a target for development of new pharmacologic agents(4,5,6). Diabetic patients generally lack the glucose-lowering response to GIP, in contrast this response to GLP-1 is intact, but circulating levels of postprandial GLP-1 are deficient by 15%(24). In diabetic patients or individuals with impaired glucose tolerance (pre-diabetes) this reduced circulating concentrations of postprandial GLP-1 contributes to a blunted insulin secretory response to meals(8,9), this has been proven in studies(14). In patients with type 2 diabetes, insulinotropic activity of GLP-1 is preserved. The endogenous secretion of GIP in type2 diabetes is normal and exogenous administration of GIP does not increase the insulin response. Exogenous administration of GLP-1, however, does induce insulin secretion. Although hyperinsulinemia is a hallmark of the disease in initial years after diagnosis, the first phase insulin response (peak after a glucose load) is impaired or absent early in the disease. This first-phase insulin response is caused by incretins(25). In an effort to overcome this deficiency in patients with type 2 diabetes, DPP4 inhibitors have been a focus of interest for exerting a pharmacological GLP-1 effect(7,8,9,10). There is very little known thus far about whether a deficiency or an excess of GLP-1 production results in or contributes to the pathophysiology of disease. Probably the most established example is a role for excess

secretion of GLP-1 in the promotion of hyperinsulinemia in subjects with dumping syndrome following gastrectomy(30). In patients with type 2 diabetes mellitus, insulin release is no longer stimulated more by an oral as compared with same amount of intravenous glucose, suggesting the loss of incretin stimulation(25). However, there have been reports of elevated levels of GLP-1 in obese and diabetic patients(35) raising the possibility that beta cell insensitivity to GLP-1. In one study, the GLP-1 response to oral glucose was not altered in postmenopausal women with impaired glucose tolerance. At this time it seems reasonable to conclude that although enhancement of incretin function seem to have therapeutic potential, disease as such is not strongly associated with dysregulation of GLP-1 production or secretion(30).



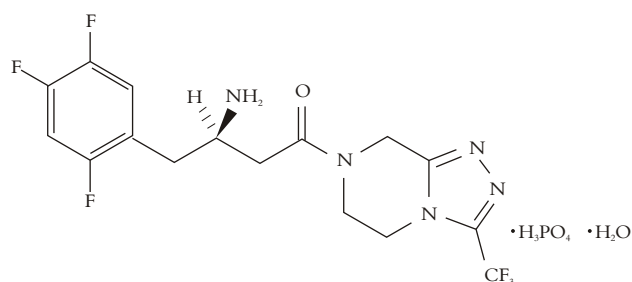
**Figure 3:** Role of DPP-IV inhibitors under hyperglycemia

### Chemistry of DPP4 Inhibitors

Sitagliptin is a potent, competitive, highly selective, reversible inhibitor of the DPP4 enzyme. The S-enantiomer is considerably less potent than the R-enantiomer. Sitagliptin inhibits DPP-4 with nanomolar potency (IC<sub>50</sub> 18 nM). Chemical structure of sitagliptin is shown in adjoining figure(11). The chemical name of sitagliptin phosphate monohydrate is 7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl)butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate (1:1) monohydrate. The CAS Registry Number is 654671-77-9. The empirical formula is C<sub>16</sub>H<sub>15</sub>F<sub>6</sub>N<sub>5</sub>O•H<sub>3</sub>PO<sub>4</sub>•H<sub>2</sub>O and the molecular weight is 523.32. Sitagliptin phosphate monohydrate is a white to off-white, crystalline, non-hygroscopic powder. It is soluble in water and N,N-dimethyl formamide; slightly soluble in methanol; very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol and isopropyl acetate.

### Therapeutic basis for use of DPP IV inhibitors

DPP4 inhibition prevents the inactivation of GLP-1, and this increases GLP-1 levels. The increase in GLP-1 levels is seen throughout 24 h, i.e., both after meal ingestion and in the fasting state. Acute beta cell function is improved by



**Sitagliptin phosphate**

7-[(3R)-3-amino-1-oxo-4-(2,4,5-trifluorophenyl) butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4-triazolo[4,3-a]pyrazine phosphate(1:1) monohydrate; C<sub>16</sub>H<sub>15</sub>F<sub>6</sub>N<sub>5</sub>O H<sub>3</sub>PO<sub>4</sub> H<sub>2</sub>O; M<sub>r</sub>=523.32

**Figure 4:** Sitagliptin phosphate

DPP4 inhibition. With preserved circadian rhythm throughout the day. The concentrations of active GIP are also increased throughout the 24 hour period after DPP-4 inhibition. This is, however, probably of less importance for the antidiabetic action of DPP4 inhibition, since GIP seems to have lost much of its insulinotropic action in diabetes and, furthermore, since GIP stimulates rather than inhibits glucagon secretion(35). Another important mechanism for improved glycemic control by DPP4 inhibition is inhibition of glucagon secretion, which is an effect by GLP-1 as well. A recent study showed that the reduction in glucagon levels in association with increased insulin secretion by administration of 100 mg vildagliptin to subjects with type 2 diabetes was accompanied by inhibition of hepatic glucose production, as determined by clamp technique using tracer glucose.

**Table 4:** Effects of Endogenous GLP I Versus DPP IV inhibition

Feature of Type 2 diabetes	Action of endogenous GLP-1 inhibitors?	Mimicked by DPP-IV
Impaired insulin secretion	Glucose-dependent stimulation of insulin	Yes
Hyperglucagonemia	Suppression of glucagon Secretion	Yes
Reduced pancreatic β-cell mass	Increased synthesis of proinsulin	Yes
Abnormally high rate of β-cell apoptosis	Inhibition of β-cell apoptosis	probably
Gastric emptying accelerated, decelerated, or normal	Deceleration of gastric emptying	Marginally
Hypercaloric energy intake/obesity	Suppression of appetite/induction of satiety Weight loss	Not obvious No

These findings are of great importance considering the inappropriately high glucagon secretion in subjects with type 2 diabetes. DPP4 inhibition may also improve insulin sensitivity. This has been found following treatment with vildagliptin using both an indirect measure of insulin sensitivity and the hyperinsulinemic euglycemic clamp

test(35). Sitagliptin has been shown to increase homeostasis model assessment Beta index (a marker for insulin secretion) and to reduce proinsulin-to-insulin ratio (a marker for beta cell function). Animal studies have also shown improved chronic beta cell function, such as increased cell mass, after DPP-4 inhibition, however, no such evidence exists in human. In contrast to GLP-1, DPP-4 inhibition does not seem to affect gastric emptying, as is evident by the lack of effect of DPP-4 inhibitors on the rate of increase in circulating glucose after meal ingestion, as evident in a study where vildagliptin did not affect the rate of gastric emptying of a tracer enriched meal(29,35). There is evidence to suggest that DPP4 inhibition as a strategy for improving glycaemic status is more effective in mild and moderate hyperglycaemic type 2 diabetes than in severe diabetes. This may reflect greater beta-cell reserve in earlier stages of disease development(29). Incretin therapy offers an alternative option to currently available hypoglycemic agents for nonpregnant adults with type 2 diabetes, with modest efficacy and a favorable weight-change profile(32). The possible advantage of DPP-IV inhibitors in comparison with GLP-1 analogues is that they cause little delay in gastric emptying, which might diminish gastrointestinal side effects. However, as antihyperglycemic agents they are less potent than GLP-1-receptor agonists or GLP analogues and effect starts later. Evidence suggests that sitagliptin is an efficacious antihyperglycemic agent when used as monotherapy or in combination with metformin or pioglitazone for the treatment of type 2 diabetes(25). Studies also suggest that vildagliptin is useful in the management of hyperglycemia in patients with type 2 diabetes as a monotherapeutic agent and when used in conjunction with metformin, pioglitazone, or insulin(31)

### Various DPP4 Inhibitors

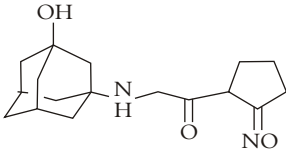
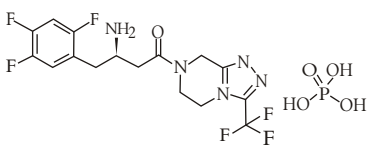
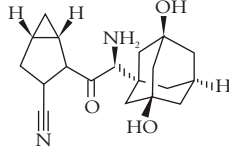
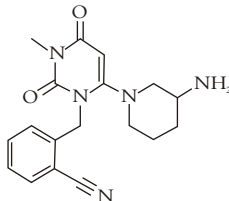
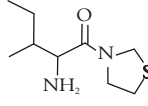
The only DPP4 inhibitor available for use is sitagliptin. Other which is about to be launched is vildagliptin. Saxagliptin, alogliptin, demogliptin are among others in que(88).

The various DPP4 inhibitor with chemical structure are as shown in the table 5 (88).

### Pharmacokinetics

Sitagliptin, a competitive reversible highly selective DPP4 inhibitor is an interesting compound from a pharmacokinetic standpoint. Dipeptidyl peptidase encompasses a large family of enzymes with ubiquitous expression in body; full scale inhibition of an enzyme system such as this could cause myriad deleterious effects. Sitagliptin exhibits a more than 2,600 fold higher affinity for DPP4 than for structurally related DPP8 and DPP9 (hours) after oral administration. Single doses of sitagliptin markedly and dose dependently inhibits plasma DPP4 activity, with approximately 80% or greater inhibition of DPP-IV activity occurring at 50 mg or greater over a 12-hour period and at 100 mg or greater over a 24-hour period(55, 59). It has a high oral bioavailability (F = 0.87) and area under the plasma

**Table 5:** Showing DPP-4 inhibitors with chemical structure

Name	Structure	Company (Originator)
LAF237	 Cyanopyrrolidine derivatives	Novartis
Sitagliptin/ Mk0431 (Januvia)	 Piperazines derivatives	Merck & amp; Co Inc.
Saxagliptin (BMS-	 1-cis-4,5-methanoproline nitrile	Bristo-Myers Squibb Co
SYR-322	 Pyrimidine derivatives	Takeda San Diego Inc.
PHX1149	-	Phenomix Corp
GRC-8200	Tricyclic derivatives*	Glenmark Pharm. Ltd.
I1c- Thiazolidide	 Amino acid cyclic amide derivative	Probiobdrug AG

**Table 6:** DPP-4 inhibitors in various stages of clinical development according to various databases in the public domain

Name	Company	Stage in development
Sitagliptin (Januvia)	Merck	Approved by FDA
Vildagliptin (Galvus)	Novartis	Filed to FDA
Alogliptin	Takeda	Phase III
Saxagliptin	Bristol-Myers Squibb	Phase III
PSN-9301	OSI Pharmaceuticals	Phase II
R1438	Roche	Phase II
TA-6666	Tanabe	Phase II
PHX1149	Phenomix	Phase II
GRC 8200	Glenmark Pharmaceuticals	Phase II
SYR-619	Takeda	Phase I
IS-021	Taisho Pharmaceuticals	Phase I
SSR 162359	Sanofi-Aventis	Phase I
ALS 2-0426	Alantos Pharmaceuticals	Phase I

concentration–time curve for sitagliptin increased in an approximately dose-dependent manner and was not meaningfully influenced by food. Following oral administration of a 100-mg dose to healthy subjects, sitagliptin was rapidly absorbed, with peak plasma concentrations (median  $T_{max}$ ) occurring 1 to 4 hours post-dose, mean plasma AUC of sitagliptin was 8.52  $mM \cdot hr$ ,  $C_{max}$  was 950 nM. The absolute bioavailability of sitagliptin is approximately 87%. Plasma AUC of sitagliptin increased in a dose-proportional manner, though dose proportionality was not established for  $C_{max}$  and  $C_{24hr}$  ( $C_{max}$  increased in a greater than dose-proportional manner and  $C_{24hr}$  increased in a less than dose-proportional manner). The intra-subject and inter-subject coefficients of variation for sitagliptin AUC were small (5.8% and 15.1%). The pharmacokinetics of sitagliptin were generally similar in healthy subjects and in patients with type 2 diabetes. Clinical trials to date have reported no correlation between changes in the pharmacokinetic parameters of sitagliptin and age, sex, race, or BMI(49). The metabolism and excretion of sitagliptin were investigated in humans after a single oral dose of 83 mg/193 Ci(56). The average volume of distribution ( $V_d$ ) at steady state is 198 L after a single dose of sitagliptin. Sitagliptin is moderately bound to plasma proteins (bound fraction = 38%). Sitagliptin is primarily excreted in an unchanged form in the urine (79–87%) via active tubular secretion. Mean fecal excretion was 13% of the administered dose. About 74% of total drug level is accounted by parent drug. Six metabolites were detected at trace levels, each representing less than 1–7% of the total in plasma. These metabolites were detected also in urine, at low levels. Metabolite profiles in feces were similar to those in urine and plasma. The terminal  $t_{1/2}$  of sitagliptin was 12.4 hours (11.8–14.4 hours) after a single 100-mg dose in healthy volunteers(48). Steady state was reached by day 2 of dosing and 90% of sitagliptin was excreted unchanged in urine. Renal clearance of sitagliptin averaged 388 mL/min and was largely uninfluenced by the dose administered. Excretion of sitagliptin involves active tubular secretion where it is transported by human organic anion transporter hOAT3 ( $K_m = 162 \mu M$ ), organic anion transporting polypeptide OATP4C1, and multidrug resistance P-glycoprotein (Pgp)(57). Sitagliptin did not inhibit hOAT1-mediated cidofovir uptake, but it showed weak inhibition of hOAT3-mediated cimetidine uptake ( $IC_{50} = 160 \mu M$ ). hOAT3-mediated sitagliptin uptake was inhibited by probenecid, ibuprofen, furosemide, fenofibric acid, quinapril, indapamide, and cimetidine. Sitagliptin did not inhibit Pgp-mediated transport of digoxin, verapamil, ritonavir, quinidine, and vinblastine. Cyclosporine A significantly inhibited Pgp mediated transport of sitagliptin ( $IC_{50} = 1 \mu M$ ). Our data indicate that sitagliptin is unlikely to be a perpetrator of drug-drug interactions with Pgp, hOAT1, or hOAT3 substrates at clinically relevant concentrations. Renal secretion of sitagliptin could be inhibited if coadministered with OAT3 inhibitors such as probenecid. In a clinical study

sitagliptin had a small effect on plasma digoxin concentrations indicating that sitagliptin may be a mild inhibitor of p-glycoprotein. However, the magnitude of interactions should be low, and the effects may not be clinically meaningful, due to the high safety margin of sitagliptin(57). (DPP-IV) inhibitor analogs undergone sequential oxidation and defluorination events resulting in the formation of GSH or NAC conjugates of the pyrrolidine moiety. A relatively small fraction of sitagliptin undergoes hepatic metabolism primarily via cytochromes P450 3A4 (major) and 2C8(minor)(18). Pretreatment of rats with prototypic CYP3A1 and 3A2 inducers (pregnenolone-16 $\alpha$ -carbonitrile and dexamethasone) enhanced the extent of bioactivation which, in turn, led to a higher degree of in vitro irreversible binding to microsomal proteins (5- and 9-fold increase, respectively)(58). In vitro data showed that sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4 and CYP1A2. However, when sitagliptin pharmacokinetics were studied in patients with moderate hepatic impairment (Child-Pugh score 7–9) significant differences in pharmacokinetic parameters were not found. Because of limited hepatic metabolism of sitagliptin by cytochrome P450 enzymes, it is not considered likely that any clinically relevant interactions exist with other drugs that use the cytochrome P450 system. This statement is supported by clinical trials(5). Because sitagliptin is primarily eliminated unchanged via renal excretion, dosage adjustments are required for patients with moderate to severe renal impairment. A 50% dose is recommended in patients with a creatinine clearance ( $CrCl$ )  $> 30$  to  $< 50$  ml/min, while 25% dose is recommended for patients with a  $CrCl < 30$  ml/min or in patients with end-stage renal disease requiring dialysis(31,42,43,44). As has been observed with sitagliptin, the pharmacokinetic parameters of another DPP4 inhibitor vildagliptin appear unaffected by age, sex, and BMI(29). Vildagliptin is rapidly absorbed with maximal concentrations being reached within 1–2 hours after an oral dose of the drug(30). Although available pharmacokinetic data for vildagliptin is limited, The primary metabolic pathway is hydrolysis via the liver, although a small, single dose study suggests no dose adjustment is necessary in hepatic impairment(50,51,52,53). The oral bioavailability of vildagliptin appears to be similar to sitagliptin ( $F = 0.85$ ). The reported volume of distribution at steady state is a mean of 70.5 L. Vildagliptin is hydrolyzed to a pharmacologically inactive metabolite. Excretion of this metabolite is carried out mainly through the urine (85%), with 15% excreted within the feces. The mean terminal  $t_{1/2}$  of vildagliptin has been reported to be between 1.68 and 2.54 hours(31). The disparity between the long duration of action of vildagliptin and the short plasma half-life is thought to be the result of the slow-binding inhibition kinetics seen with this agent(56). Steady-state plasma concentrations were reached on day 3, as indicated by evaluation of trough plasma concentrations over time. At all doses examined, the plasma AUC on day 10

increased in proportion to the dose administered. Maximum concentrations increased greater than dose proportionately while 24 hour plasma concentrations increased less than dose proportionately(31,45,46,47). Vildagliptin does not appear to induce or inhibit the cytochrome P450 enzyme system(30). The  $t_{1/2}$  was not affected by the presence of hepatic impairment when studied(33). Additional clinical trials are underway to evaluate the potential effects of renal impairment on the pharmacokinetic disposition and clinical activity of vildagliptin. Drug interaction data for vildagliptin are limited. However, clinically significant drug interactions have not been reported in clinical trials involving the coadministration of pioglitazone(34) metformin(35) or glyburide(31,45,46). The pharmacokinetics of sitagliptin was generally similar in healthy subjects and in patients with type 2 diabetes. A single-dose, open-label study was conducted to evaluate the pharmacokinetics of a reduced dose of sitagliptin (50-mg) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to < 80 ml/min), moderate (30 to < 50 ml/min), and severe (< 30 ml/min), as well as patients with end-stage renal disease (ESRD) on hemodialysis. Patients with mild renal insufficiency did not have a clinically meaningful increase in the plasma concentration of sitagliptin as compared to normal healthy control subjects. An approximately two fold increase in the plasma AUC of sitagliptin was observed in patients with moderate renal insufficiency and an approximately four fold increase was observed in patients with severe renal insufficiency and in patients with ESRD on hemodialysis, as compared to normal healthy control subjects. Sitagliptin was modestly removed by hemodialysis (13.5 % over a 3-4 hour hemodialysis session starting 4 hours post dose), hence it is recommended at reduced doses for use in patients with moderate or severe renal insufficiency including those with ESRD since experience in these patients is too limited. In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and  $C_{max}$  of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls differences which were not clinically significant. No dosage adjustment is necessary for patients with mild or moderate hepatic insufficiency (Child-Pugh score < 9). There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score > 9). However, because sitagliptin is primarily renally eliminated, severe hepatic insufficiency is not expected to affect the pharmacokinetics of sitagliptin. Likewise no dose adjustment is required based on age, as age did not have a clinically meaningful impact on the pharmacokinetics of sitagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data, although elderly subjects (65 to 80 years) had approximately 19 % higher plasma concentrations of sitagliptin compared to younger subjects. Gender, race, or body mass index had no

clinically meaningful effect on the pharmacokinetics of sitagliptin based on a composite analysis of Phase I pharmacokinetic data and on a population pharmacokinetic analysis of Phase I and Phase II data.

### Pharmacodynamic Evidence from Clinical Trials

Incretin based therapy with GLP-1 analogues or DPP4 inhibitors in adults with type 2 diabetes is moderately effective in improving glycemia, with greater reductions in postprandial glycemia and favorable (GLP-1 analogues) or neutral (DPP4 inhibitors) effects on weight. DPP4 inhibitors lead to increased serum levels of GLP-1 and GIP, exert most, if not all, of their pharmacological effects in humans by inhibiting the degradation of GLP-1, through this they cause some of the same effects as GLP-1 of a net antihyperglycemic effect with improvement in glucose tolerance, enhancement of insulin secretion, improves insulin sensitivity, inhibition of glucagon secretion, reverse glucose toxicity and even delay in the onset of overt diabetes(1,4). It has been suggested that DPP4 inhibition and its resultant preservation of endogenous GLP-1 activity may lead to beta cell preservation via augmentation of GLP-1 antiapoptotic effects. Though DPP4 inhibition has been associated with an enhancement of beta cell survival and neogenesis in streptozotocin-treated diabetic rats(4,12,19,21), this effect has not yet been demonstrated in humans. In patients with type 2 diabetes, administration of single oral doses of sitagliptin leads to inhibition of DPP-4 enzyme activity for a 24 hour period, resulting in a 2-3 fold increase in circulating levels of active GLP-1 and GIP, increased plasma levels of insulin and C-peptide, decreased glucagon concentrations, reduced fasting glucose, and reduced glucose excursion following an oral glucose load or a meal. In patients with moderate hypertension sitagliptin had a modest blood pressure lowering effect, although reductions have not been observed in subjects with normal blood pressure. Sitagliptin has been shown to increase homeostasis model assessment of beta index – HOMA B (a marker for insulin secretion) and to reduce proinsulin to insulin ratio (a marker for beta cell function)(36). HOMA-B is a computer-generated model that deduces beta cell function for a given subject from pairs of fasting glucose and insulin (or C-peptide) measurements. Unlike GLP-1, although, they seem to have only a marginal slowing effect on the rate of gastric emptying and no obvious effect on satiety or weight loss. Clinical trials have demonstrated safety and efficacy of sitagliptin for the management of hyperglycemia in type 2 diabetes. One phase III trial demonstrated that sitagliptin administered in 100-mg and 200-mg daily doses reduced hemoglobin A1c (A1C) levels by 0.79 and 0.94%, respectively, at 24 weeks. Patients with A1C levels > 9.0% showed greater reductions in A1C. Improvements in fasting plasma glucose and postprandial glucose levels were also reported with sitagliptin(60). Other studies also confirm the efficacy of sitagliptin as monotherapy and combination with metformin and pioglitazone(62,63) Vildagliptin, another upcoming DPP4

inhibitor, has proven its efficacy in type 2 diabetes as monotherapy and in combination with metformin, pioglitazone, and insulin at doses of 100 mg/day (64,65,66,67). Vildagliptin improves beta cell function in diabetic patients by increasing the insulin secretory tone (74). Fasting and post prandial plasma glucose was reduced, with sitagliptin appearing to be more effective than vildagliptin in reduction of fasting values (32). In a study in early stage T2DM patients, oral vildagliptin was associated with suppression of endogenous DPP-IV activity for 12 hours and suppression of postprandial and fasting plasma glucose concentrations (57). In addition, basal and postprandial GLP-1 concentrations were increased compared with placebo-treated subjects. Basal and postprandial glucagon levels were reduced, but no change in plasma insulin concentrations was observed. There was no change in body weight. Based on fasting glucose and insulin concentrations, there was no change in insulin resistance. A small reduction in postprandial glucose excursions paired with a small increase in postprandial insulin concentrations was seen although. A recent study showed that the reduction in glucagon levels in association with increased insulin secretion by administration of 100 mg vildagliptin to subjects with type 2 diabetes was accompanied by inhibition of hepatic glucose production, as determined by clamp technique using tracer glucose (49). These findings are of great importance considering the inappropriately high glucagon secretion in subjects with type 2 diabetes. Vildagliptin may also improve insulin sensitivity, evidence of which has been drawn from studies using both an indirect measure of insulin sensitivity (48) and the hyperinsulinemic euglycemic clamp test. Post-meal insulin sensitivity increased significantly with vildagliptin, as did insulin secretion related to insulin sensitivity (adaptation index), and the change in the adaptation index was significantly correlated with the change in HbA1c ( $r = -0.39$ ). The disposition index (acute insulin response multiplied by insulin sensitivity) increased four-fold in vildagliptin recipients at 12 weeks, the findings suggest that improvements in beta cell function and insulin resistance occur independent of acute increases in plasma GLP-1 and that these improvements persist in beyond cessation of vildagliptin administration. The two available DPP4 inhibitors have not been compared directly, but both appeared to lower HbA1c similarly compared with placebo (-0.74% vs -0.73% for sitagliptin and vildagliptin respectively). Combining available data from four trials, DPP4 inhibitors were slightly less effective compared with other hypoglycemic agents. In the individual trials, noninferiority was established when sitagliptin was compared with glipizide (25) and vildagliptin with thiazolidinediones (34,36), but noninferiority was not shown when vildagliptin was compared with metformin (68,69,70,71). Other studies also prove that incretin-based medications are noninferior compared with conventional therapies, including insulin glargine or biphasic aspart, glimepiride, metformin, glipizide,

or thiazolidinediones, with the exception of metformin being superior to vildagliptin. The magnitude of the reduction in HbA1c with incretin therapy was dependent on the baseline HbA1c so that greater reductions were seen in groups of participants with higher baseline HbA1c. Incretin therapy, though decreased both fasting and postprandial glycemia, improvements in postprandial glycaemic excursions were larger, based on mixed-meal tolerance testing. The preferential improvement in postprandial glycemia with incretin therapy addresses an important limitation of currently available pharmacologic therapies and provides an alternative option for targeting postprandial glycemia. Research has also been done for exploring extra pancreatic effects of DPP4 inhibitors. Thirteen trials reported data on weight with most suggesting a small increase in weight with DPP4 inhibitors compared with placebo. In noninferiority trials, sitagliptin had favorable weight profile compared with glipizide and vildagliptin had a favorable weight profile compared with thiazolidinediones. Trials on lipid profile didn't show any consistent changes in lipid profile with either sitagliptin (20,22,23,24,25) or vildagliptin, but there were some improvements in triglycerides (20,23,24,35) and low and high density lipoprotein. Relative to rosiglitazone, vildagliptin decreased total cholesterol, triglycerides, and low-density lipoprotein cholesterol but produced a smaller increase in high-density lipoprotein cholesterol (34). Relative to pioglitazone, vildagliptin decreased total and low density lipoprotein cholesterol (36). Vildagliptin also had favorable change in triglycerides compared with metformin (36). A recent study (46) showed that vildagliptin largely (by 85%) inhibited the triglyceride response to ingestion of a fat-rich meal. Vildagliptin improves plasma lipids and lipoprotein particle metabolism after a fat-rich meal, which would be of importance considering the relevance for prandial lipemia as a marker for cardiovascular diseases. Preclinical data have suggested the possibility that incretin mimetics and DPP-IV inhibitors might have activity in the arena of halting and even reversing the ongoing beta cell dysfunction. However, further clinical data are needed to definitively address this issue (33). Besides potentiating insulin response, animal studies with sitagliptin have shown additional benefits of protection against diet-induced obesity, indicating that DPP-IV inhibitors may afford this protection to humans (87).

### Add on Therapy

In patients with type 2 diabetes mellitus who had moderately severe hyperglycemia inadequately controlled by metformin alone, the addition of sitagliptin 100 mg once daily provided significant and sustained improvements in HbA1c and other glycaemic endpoints, including fasting glucose and post prandial glucose. In addition, sitagliptin provided statistically significant improvements in markers of  $\beta$ -cell function. Overall, the addition of sitagliptin to ongoing metformin therapy was well-tolerated with neutral effects on body weight relative to placebo, low incidence of hypoglycemia, and no worsening of gastrointestinal adverse

events(82,83). Sitagliptin 100 mg once daily added to ongoing pioglitazone therapy was effective and well tolerated in these patients with type 2 diabetes who had not achieved adequate glycemic control with pioglitazone alone(84). Another study provides add-on efficacy and safety results for sitagliptin, compared with a standard sulfonylurea agent, glipizide, in patients with inadequate glycaemic control on metformin monotherapy. The study results demonstrate that sitagliptin was non inferior to glipizide in HbA1c-lowering efficacy. Although both treatments were generally well tolerated, sitagliptin had a considerably lower risk of hypoglycaemia relative to glipizide and produced weight loss compared with weight gain with glipizide(85). In one study sitagliptin 100 mg once daily significantly improved glycemic control and beta cell function in patients with type 2 diabetes with inadequately controlled on glimepiride or glimepiride plus metformin therapy. The addition of sitagliptin was generally well tolerated, with a modest increase in hypoglycaemia and body weight, consistent with glimepiride therapy. Sitagliptin is not currently indicated for use with insulin although there are clinical trials in progress evaluating this combination(86). While consensus agrees that there is a strong scientific rationale of sitagliptin use even in patients taking insulin, proactive promotion of sitagliptin use in combination with insulin should be avoided until we have the phase III clinical trail on this combination. The addition of vildagliptin to on-going metformin therapy produced clinically meaningful dose-related reductions in HbA1c and fasting plasma glucose and appeared to reduce metformin-related GI adverse effects. Metformin patients who added vildagliptin (50mg qd or bid) also experienced a beneficial effect on blood pressure, relative to placebo. Although suggestive, the influence of vildagliptin on blood pressure remains to be clarified. Two 24 - week studies examining the combination of vildagliptin and pioglitazone showed that vildagliptin produces clinically meaningful reductions in HbA1c when combined with reduced-dose pioglitazone in drug-naïve patients and when added to full-dose glitazone treatment. A comparative trial versus rosiglitazone showed that vildagliptin produced a similar reduction in HbA1c, improved lipid measures, and did not produce weight gain compared with rosiglitazone. The addition of vildagliptin to insulin treatment produced a significant reduction in HbA1c that was particularly marked in older patients and appeared to reduce the frequency and severity of hypoglycemia(41).

### Mimetics versus Enhancers

The DPP-4 inhibitors approach GLP-1 insufficiency by enhancing incretin instead of mimicking it. By inhibiting DPP-4, the enzyme responsible for the breakdown of GLP-1, agents such as sitagliptin can prolong the action of GLP-1 and increase circulating levels. One of the major differences between the GLP-1 analogues and the incretin enhancers is that the former are proteins that must be injected, and the latter are chemicals that can be taken in pill form. Also, exenatide, being a protein must be kept in the refrigerator,

while sitagliptin doesn't require any special storage. DPP-4 inhibitors tend to be weight neutral with no effect on appetite and gastric emptying, while GLP-1 analogues seem to cause weight loss in overweight individuals owing to their unique action of delayed gastric emptying and suppression of appetite by a yet unknown central action(89).

EXANITIDE	SITAGLIPTIN
Incretin mimetic	Incretin enhancer
Nausea (44%)	Nausea (1.4%)
Slows GIT	No effect on GI motility
Weight loss	Weight neutral
Not recommended in creatinine clearance <30ml/min	Recommended at reduced dose
HbA1c reduction 0.8-1%	Hb A1c reduction 0.44- 0.8%
Twice daily dosing	Once daily dosing
Injectable	Oral

As quoted in an article by Deacon C F, Ahren B and Holst JJ(91), GLP-1 analogues share the characteristic of glucose dependent insulinotropicity and improvement of beta cell mass and function. Significant differences between the two have been seen on certain issues. Route of administration is oral for sitagliptin while injectable for exenatide. GLP-1 analogues administered subcutaneously follow a 12 or 24 hour pharmacokinetic profile, hence plasma concentrations relate to time of administration and principles of protraction (binding to albumin or formation of intermolecular aggregates of drug). In contrast, DPP4 inhibitors are not considered to have a primary effect in vivo. Rather their effects are secondary to changes in the levels of intact incretin hormones. Therefore, the dynamic response to DPP4 inhibitors is a result of enhanced levels of intact incretin hormones, reflecting natural release pattern in response to meal. The plasma levels of GLP-1 analogues reflect the dose administered, hence plasma levels can be used to monitor the dose. In contrast, there is a theoretical maximum level to which hormone rescue can achieve(i.e. the rise in intact version of each incretin can reach only 100% of amount of total hormone in circulation), which in turn depends on L cells' secretory capacity. It implies therefore that DPP4 inhibitors in contrast to GLP-1 analogues can't raise the plasma GLP-1 levels into the pharmacological range, meaning DPP4 inhibition can't take advantage of pharmacological levels of GLP-1. An example is weight loss seen with use of exenatide, is not observed with sitagliptin. Recent preliminary studies in animals suggest that exogenous GLP-1 can reduce severity of myocardial infarction independent of change in glucose and insulin concentration, whereas DPP4 inhibition alone doesn't have this effect suggesting pharmacologic concentration of GLP-1 are necessary for cardioprotection(93). Contrary to theoretical expectation, DPP4 inhibitors may not raise plasma levels of intact biologically active form of GLP-1 as much as expected increase to three to five fold, rather the

levels rise two fold on administration of sitagliptin or vildagliptin. It has been suggested that feedback of intact GLP-1 onto its own release is responsible for these contradictory results, phenomenon confirms in animal studies(94). Also there is a possibility that increase in ratio of intact (biologically active) to total GLP-1 have a bearing on therapeutic efficacy of DPP4 inhibition rather than change in levels of intact GLP-1, which is in contrast to GLP-1 analogues where latter is more important in clinical effect. Finally clinical efficacy of DPP4 inhibitors have multiple mediators; GLP-1 and GIP to begin with, but yet unidentified multiple mediators, keeping in view the ubiquitous expression of the enzyme have been proposed for observed clinical effect. This also results in different pharmacodynamic spectrum of effects than that observed after injection of GLP-1 analogues. Initial effects of DPP4 inhibition in human diabetes may be primarily mediated by GLP-1, but in long term when glucose levels fall insulinotropic effect of GIP may also contribute.

### **Clinical Utilities & Indications**

Sitagliptin, the FDA approved DPP4 inhibitor is indicated in patients with type 2 diabetes mellitus in patients 18 years of age and older who have failed dietary measures and exercise, as mono or combination therapeutic management with metformin, or with a sulfonylurea, or with a thiazolidinedione in once or twice daily dosing. Sitagliptin is not currently indicated for use with insulin although there are clinical trials in progress evaluating this combination (87).

### **Adverse Effects**

The most common adverse effects with the use of sitagliptin are upper respiratory tract infection(6.3% in the sitagliptin-pioglitazone group vs. 3.4% in the pioglitazone-only group), nasopharyngitis(5.2% in the sitagliptin group vs. 3.3% in the placebo group), urinary tract infections and headache(5.1% in the sitagliptinpioglitazone group vs. 3.9% in the pioglitazone - only group)(1). Gastrointestinal side effects including nausea, abdominal pain, and diarrhea have also been reported in some studies(3,10). DPP4 is a ubiquitous cell-membrane protein, expressed in many tissues, including lymphocytes, which has raised some concerns about the long-term effects of DPP4 inhibitors especially on immune function(32). It has been classified as schedule 4 prescription only medicine in poison schedule. DPP4 enzyme family also includes other members such as DPP8, DPP9 and QPP, and selective inhibition of DPP4 is highly desirable, because inhibition of two other enzymes, DPP8 and DPP9 has resulted in fatal toxicities in animal studies(16).The DPP 8/9 selective inhibitor produced alopecia, thrombocytopenia, reticulocytopenia, multiorgan histopathological changes, enlarged spleen and mortality in rats. This inhibitor also produced gastrointestinal toxicity in dogs. Furthermore, the DPP2 selective inhibitor produced reticulocytopenia in rats. However, investigation of the DPP4 selective inhibitors demonstrated no such toxicity(29). Sitagliptin package insert reports that a slight increase in

white blood cell count (~ 200 cells/microL) was observed in patients treated with sitagliptin compared to those receiving placebo. This small increase primarily results from an increase in the number of neutrophils. This observation was deemed clinically insignificant by investigators. The reported incidence of hypoglycemia in subjects receiving sitagliptin is similar to that in control subjects(76). Vildagliptin was generally well tolerated in phase III trials. One case of significant peripheral edema was reported(77). The most common adverse events reported with vildagliptin were mild and included nasopharyngitis, headache, and dizziness. Vildagliptin has been associated with very few episodes of hypoglycemia when used as monotherapy or in combination with other antihyperglycemic medications. No significant laboratory abnormalities have been observed during or resulting from trials involving vildagliptin. Potential of DPP4 to also cleave other bioactive may cause adverse events on administration of DPP4 inhibitors related to increased blood pressure, neurogenic inflammation, and immunological reactions however, no such adverse events have been reported in animal studies or in humans using DPP4 inhibition. It should also be emphasized that it has not been demonstrated that DPP4 indeed affects have been post marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin. These reactions include anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment, with some reports occurring after the first dose. The animal studies done to evaluate the carcinogenic potential showed increased incidence of combined liver adenoma and carcinoma at 500 mg/kg dose, which is considerably higher than routine dose of sitagliptin in humans. Sitagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a Chinese hamster ovary (CHO) chromosome aberration assay, an in vitro cytogenetics assay in CHO, an in vitro rat hepatocyte DNA alkaline elution assay, and an in vivo micronucleus assay. Isolated case reports of renal failure and rhabdomyolysis with sitagliptin and simvastatin exposure are quoted. Very few case reports from phillipines also report fatal haemorrhages, leukaemia, eosinophilia, erythema, skin exfoliation during sitagliptin use raise suspicion.

### **Contraindications**

Sitagliptin is to be avoided in patients with type1 diabetes and is not intended for use in the treatment of diabetic ketoacidosis, a disease that causes a reduced supply of oxygen to the tissues such as failure of the heart or lungs or a recent myocardial infarct, patients with alcohol intoxication (excessive alcohol consumption) or alcoholism(76). Patients with a history of chronic headache may report an increased headache, hence not ideal candidates(32). It should not be used in people who may be hypersensitive (allergic) to sitagliptin.

## Dose recommendations and route of administration

Sitagliptin tablets are commercially available as 100 mg (beige), 50 mg (light beige), and 25 mg (pink) tablet(5). Sitagliptin is also available in a combination product with metformin in doses of 50 mg sitagliptin/500 mg metformin and 50 mg sitagliptin/1,000 mg metformin. The usual recommended dose of sitagliptin is 100 mg once daily as monotherapy, combination with metformin, sulphonylurea (clinical experience is with glimepiride as dual therapy), or thiazolidinedione (clinical experience is with pioglitazone as dual therapy), although some studies concluded 50 mg twice daily being the most effective dose. However, the agent is available in three strengths to allow for lower dosing in patients with moderate to severe renal impairment. The sitagliptin-metformin combination should be taken twice daily with meals and titrated slowly to minimize potential gastrointestinal side effects associated with metformin. If a dose of Januvia is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day. In patients with normal renal function or mild renal insufficiency (creatinine clearance [CrCl] >50 mL/min, approximately corresponding to serum creatinine levels of <150 micromol/L in men and <133 micromol/L in women), dose is 100 mg daily; in patients with CrCl >30 to < 50 ml/min (approximately corresponding to serum creatinine levels of >150 to >265 micromol/L in men and >133 to >221 micromol/L in women), the dose is 50 mg/day; and in patients with CrCl < 30 ml/min (approximately corresponding to serum creatinine levels of >265 micromol/L in men and >221 micromol/L in women) or with end stage renal disease (ESRD) requiring haemodialysis or peritoneal dialysis, the dose is 25 mg daily. The recommended route of administration is oral and it can be taken with or without food. The strength of tablet to use also depends on the dose of the other antidiabetic medicines that the patient is taking. Patients already taking metformin, with or without a sulphonylurea, should take Janumet (trade name of sitagliptin metformin combination) containing the same dose of metformin. If Janumet is taken with a sulphonylurea, the dose of the sulphonylurea may need to be lowered, to avoid hypoglycemia. Janumet should be taken with food to avoid any stomach problems caused by metformin. Because of the pending FDA review of vildagliptin, the adult daily dosage for which the manufacturer will receive approval is not known, although one could assume that the dose in an adult with normal renal function will probably be 100 mg/day(73), though some studies recommend a dose as monotherapy 100mg/day and combination to metformin 50 mg/day. Trials showing vildagliptin improving beta cell function used dose of 100 mg twice daily(74).

## Overdosage

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be

clinically relevant, were observed in one study at a dose of 800 mg. There is no experience with doses above 800 mg in humans. In Phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 400 mg per day for periods of up to 28 days(76).

## Significant drug interactions

Because of limited hepatic metabolism of sitagliptin by cytochrome P450 enzymes 3A4 and 2C8, it is not considered likely that any clinically P450 system system(76). Drug interaction data for vildagliptin are limited. However, clinically significant drug interactions have not been reported in clinical trials involving the coadministration of pioglitazone(34) metformin(35) or glyburide(78) The pharmacokinetics of metformin was not altered when administered with sitagliptin. Similarly, sitagliptin pharmacokinetics was not altered when given in conjunction with metformin. No hypoglycemia was reported, and gastrointestinal adverse events were not significantly different when sitagliptin was added to metformin(34). Sitagliptin is a p glycoprotein substrate(7) and hence increased the area under the curve (11%) and the mean peak drug concentration (C<sub>max</sub>, 18%) of digoxin in one study, but the results were reported to be clinically insignificant(3), still patients receiving digoxin should be monitored when started on sitagliptin. Patients receiving sitagliptin and cyclosporine, another p glycoprotein substrate had increased the AUC and C<sub>max</sub> of sitagliptin by approximately 29% and 68%, respectively, though these modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. Moreover renal clearance of sitagliptin was also not meaningfully altered. Sitagliptin did not inhibit Pgp-mediated transport of digoxin, verapamil, ritonavir, quinidine, and vinblastine. hOAT3 mediated renal tubular uptake of sitagliptin was inhibited by probenecid, ibuprofen, furosemide, fenofibric acid, quinapril, indapamide, and cimetidine with IC<sub>50</sub> values of 5.6, 3.7, 1.7, 2.2, 6.2, 11, and 79 μM, respectively. Renal secretion of sitagliptin could be inhibited if coadministered with OAT3 inhibitors such as probenecid. However, the magnitude of interactions should be low, and the effects may not be clinically meaningful, due to the high safety margin of sitagliptin(57). Sitagliptin is not an inhibitor or inducer of cytochrome enzymes. Sitagliptin is not extensively bound to plasma proteins(38%). In clinical studies, as described below, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, simvastatin, rosiglitazone, warfarin, or oral contraceptives. The safety and efficacy of sitagliptin in combination with insulin, GLP-1 mimetics, or alpha glucosidase inhibitors has not been established. probenecid, NSAIDs, sulfa drugs, monoamine oxidase inhibitors or beta Although sitagliptin is not as likely to cause hypoglycemia as some other oral diabetes medications, caution needs to be exercised while prescribing any other drug that can potentially lower blood sugar such as blockers(55).

## Use in Select Patient Group

### Lactation

Sitagliptin is excreted in milk of lactating rat in a milk to plasma ratio of 4:1, no human studies available, hence caution is advised in women who are nursing(1). It is currently unknown whether sitagliptin is secreted in human breast milk, and the effects on nursing babies.

### Pregnancy

Sitagliptin is pregnancy Category B3. Sitagliptin crosses the placenta in rats and rabbits. There are no adequate and well-controlled studies with use in pregnant women. In animal studies the drug was not teratogenic doses up to 250 mg/kg/day during organogenesis, though a slight increase in the incidence of foetal rib abnormalities (absent, hypoplastic and wavy ribs), reduced birth weight was observed when given at 1000 mg/kg/day. Sitagliptin like other oral antihyperglycaemic agents, is not recommended for use in pregnancy(76).

### Pediatric use

*Safety has not been established*

### Geriatric population

Elderly subjects (65 to 80 years) had approximately 19% higher plasma concentrations of sitagliptin compared to younger subjects, however the results were not clinically significant, so recommended dose is same. However renal function need to be monitored(76).

### Renal insufficiency

In one study, patients with moderate renal insufficiency receiving 50 mg/day sitagliptin had a slightly greater increase in serum creatinine (0.05 mg/dl) than matched control subjects with the same degree of renal impairment receiving placebo(75), although the results were not clinically significant. Keeping in view the exclusive renal excretion the dose is modified to 50% and 25% of usual in moderate and severe renal insufficiency. The drug is modestly removed on hemodialysis so dose is reduced to 25% of usual in ESRD patients on MHDL.

### Hepatic insufficiency

In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), mean AUC and C<sub>max</sub> of sitagliptin increased approximately 21% and 13%, respectively, compared to healthy matched controls following administration of a single 100 mg dose of sitagliptin. These differences are not considered to be clinically meaningful, hence no dose adjustment is necessary for patients with mild or moderate hepatic insufficiency.

There is no clinical experience in patients with severe hepatic insufficiency (Child-Pugh score >9). However, because sitagliptin is primarily eliminated from kidneys, severe hepatic insufficiency is not expected to affect the pharmacokinetics of sitagliptin(76).

### Diabetic nephropathy

Sitagliptin was generally well tolerated and provided effective glycaemic control in patients with type 2 diabetes and

moderate to severe renal insufficiency, according to the results of a study reported in the June 1 online issue of Diabetes, Obesity and Metabolism. Overall adverse events were not significantly different between groups, and between group differences in the incidences of specific clinical adverse events were generally small(80)

Gender, BMI, Race- no dose adjustments recommended.

### Cost Perspectives

Usual daily dose of sitagliptin(Merck) costs Rs. 42. This can be compared to daily dose of metformin(Cipla) Rs. 2.80, glimepiride(Aventis) Rs. 10.34, pioglitazone(sunpharma) Rs. 1.80 Exanotide about Rs. 8000.

### Issues unsettled

#### *Other sources of DPP4 inhibition*

There are reports that commonly used antidiabetic drugs can affect circulating DPP4 activity. Metformin has been reported to reduce DPP IV activity in patients with type2 diabetes and in diabetic animal models. Metformin increased active levels of GLP-1 in obese, non-diabetic human males(61) and reduced inactivation of exogenously administered GLP-1 in obese-diabetic (ob/ob) mice. There are reports of reduced serum DPP4 activity brought about by the thiazolidindiones, meglitinide, and nateglinide(29).

#### *Role of NEP 24.11*

It is evident that the body possesses other enzymes which degrade incretin hormones, in particular neutral endopeptidase 24.11 (NEP-24.11). It is found in high concentrations in the kidney. A recent study demonstrated that whilst DPP4 inhibition improves the insulinotropic and antihyperglycaemic activity of GLP-1, the effect could be further enhanced by concomitant NEP-24.11 inhibition(29, 98).

#### *DPP4 inhibitors and Hypertension*

Sitagliptin, by blocking dipeptidyl peptidase IV, prevents metabolism of neuropeptide Y1-36 and thereby increases the effects of neuropeptide

Y1-36 released from renal sympathetic nerves on Y1 receptors leading to augmentation of neuropeptide Y1-36 induced enhancement of the renovascular effects of angiotensin II. The renal effects of dipeptidyl peptidase IV inhibitors in hypertensive diabetic patients merit a closer examination. To add to debate, a study in non diabetic hypertensives shows a decrease in blood pressure on administration of sitagliptin(81).

#### *Role in type1 diabetes*

Although presently not indicated for use in type1 diabetes, benefits have been suggested in combining DPP4 inhibitors with insulin therapy in type 1 diabetes. This is based on the observations that secretion of incretin hormones is normal in type1 diabetes(57) and that administration of GLP-1 can improve glycaemic control in type1 diabetes(29).

### Other indications of DPP4 inhibition

DPP4 inhibition has been suggested as a possible therapy for rheumatoid arthritis(95), neutropenia, acute anemia(96), prolongation of graft survival of organ transplantation(97), autoimmune encephalitis and other T cell mediated autoimmune mechanism(98). Some of these clinical effects may result from inhibition of related enzymes.

## CONCLUSION

In general, the safety profiles of most DPP-IV inhibitors are very promising but additional studies are certainly needed to obtain a thorough insight in the in vivo effects of DPP-IV inhibition. The beneficial effects of DPP-IV inhibitors on treatment for type 2 diabetes not only offer advantages over the current therapies but also provide more therapeutic applications beyond the treatment for diabetes due to the biological diversity of DPP-IV. So far, there is no sufficient data available to make sweeping generalization about the long-term effects of various DPP-4 inhibitors on Tcell signaling and immune functions in vivo. Cost effects also need a consideration before widespread use in developing nations as India. Careful postmarketing surveillance for adverse effects, especially among the DPP4 inhibitors, and continued evaluation in longer term studies and in clinical practice are required to determine the role of this new class among current pharmacotherapies for type 2 diabetes. Dual inhibition of NEP and DPP4, confirmed to be more effective in animal studies, is an arena of interest in future. Role of DPP4 inhibitors as disease modifying agents is also attractive. DPP4 inhibitors represent a breakthrough in management of diabetes in view of its safety, efficacy, effectiveness as monotherapy and in combination, preventive treatment in patients with impaired glucose tolerance or those at high risk of developing type2 diabetes and optimization of this class of drug is expected to have lasting benefits in socio-economic burden of diabetes mellitus.

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