Sitagliptin a DPP-4 Inhibitor

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Abstract: Diabetes mellitus (DM) is a worldwide rising concern that leads to an increased rate of mortality, morbidity and health-care costs. DM is a chronic, endocrine disorder associated with hyperglycemia. The current estimated DM prevalence is over 422 millions and has been progressively increasing over the past decades. Consequently, it is considered a significant problem in health care setting. Health care professional WHO deals with such patients need to have an adequate information and Drug therapy management including drug and its regime that are presently available in The market. This review provides an overview of the potential diabetic drugs and their Mechanisms. Here, it will be proved beneficial for health care professional. Sitagliptin is a Member of the gliptin class of antidiabetic medications. It’s mechanism of action is Through inhibition of dipeptidyl peptidase-4 (DPP-4), an enzyme that acts to degrade and Inactivate glucagon like peptide-1 (GLP-1), DPP-4 is an enzyme that is involved in the Rapid metabolism of incretin, such as glucagon like peptide. Sitagliptin spersas to be Highly selective for DPP-4 and has 2600 times selectivity for DPP-4 compared with DPP-8 and DPP-9. Sitagliptin under the trade name Januvia was the first agent developed in The class of DPP-4 inhibitors approved by FDA in oct 2006. Sitagliptin exhibit excellent Oral bioavailability in preclinical species.

- **Introduction**: Sitagliptin previously named MK-0431 and commercialized as the phosphate salt Januvia, was developed by Merck 2006. Sitagliptin is an oral antihyperglycemic drug and belongs to the gliptin class of antidiabetic, characterised by their dipeptidyl peptidase-4 inhibiting activity. This pharmaceutical compound is used either alone or in combination with other oral antihyperglycemic agents for the treatment of type 2 diabetes and chronic disease. Sitagliptin, sold under the brand name Januvia among others, is an anti-diabetic medication used to treat type 2 diabetes. In the United Kingdom it is listed as less preferred than metformin or a sulfonylurea. It is taken by mouth. It is also available in the fixed-dose combination medication sitagliptin/metformin. Dipeptidyl peptidase-4 (DPP-4) inhibition is an established glucose-lowering therapy in type 2 Diabetes. It has a low risk of hypoglycemia and other adverse events and is not associated with Weight gain. It is used mainly as add-on to metformin when metformin alone is insufficient for Glycemic control, particularly when there is a desire to minimize the risk for hypoglycemia. It is also Used as first line therapy when metformin is not tolerated, in subjects with renal insufficiency and In combination with thiazolidinediones, sodium glucose transport protein 2 (SGLT2) inhibitors, and insulin. It may also be a possibility for DPP-4 inhibition as first line glucose-lowering therapy when an islet-directed approach is desirable. The development of the DPP-4 inhibition concept for glucose-lowering therapy in type 2 diabetes originated on the fundament of the incretin concept. The term incretin was coined by Starling in the early 1900s to mean a gut hormone which stimulates the internal secretion of the pancreas (1). This concept was further developed by La Barre and Still (2) and Heller (3) in the 1930s when they showed that administration of gut extracts to experimental animals resulted in lowering of circulating glucose. They suggested that this effect is mediated by increased secretion of insulin. Furthermore, in the 1960s the novel radiominunoassay technique made it possible to demonstrate that an oral administration of glucose indeed elicits a stronger increase in circulating insulin than an intravenous glucose administration even at the same glucose levels (4, 5). These important findings further documented the existence of the incretin concept in relation to oral glucose ingestion. The incretin concept was later developed further by identifying the gut hormones glucose-dependent insulino tropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) as main incretin hormones (6, 7) and the development of GLP-1 as a potential treatment of type 2 diabetes (8). To leverage on this potential of GLP-1 a glucose-lowering medication in T2D, DPP-4 inhibitors were developed to prevent the inactivation of endogenous GLP-1. The development of DPP-4 inhibition as a glucose-lowering principle started in the 1990s with basic studies, continue in the 2000s with clinical studies for introduction of the concept to the market and was further developed in the 2010s with studies in special groups and long-term outcome studies with focus on cardiovascular diseases. Besides these clinical studies, also mechanistic studies have been performed to understand the underlying mechanisms of action and the low risk for hypoglycemia. Figure 1 shows the milestones of this development. This article will focus on the main steps in the path of developing DPP-4 inhibition as a glucose-lowering therapy.

- **Discovery and further history**: The emergence of glucagon-like peptide 1 (GLP-1) as a well validated approach to the treatment of type 2 diabetes and preclinical validation of dipeptidyl peptidase IV (DPP-4) inhibition as an alternate, oral approach to GLP-1 Therapy prompted the initiation of a DPP-4 inhibitor program at Merck in 1999. DPP-4
Inhibitors threeo- and allo-isoleucyl thiazolidide were in-licensed to jump start the program; however, development was discontinued due to profound toxicity in rat and dog safety Studies. The observation that both compounds inhibit the related proline peptidases DPP8 and DPP9 led to the hypothesis that inhibition of DPP8 and/or DPP9 could evoke Severe toxicities in preclinical species. Indeed, the observed toxicities were recapitulated With a selective dual DPP8/9 inhibitor but not with an inhibitor selective for DPP-4. Thus, Medicinal chemistry efforts focused on identifying a highly selective DPP-4 inhibitor for Clinical development. Initial work in an alpha-amino acid series related to isoleucyl Thiazolidide was discontinued due to lack of selectivity; however, SAR studies on two Screening leads led to the identification of a highly selective beta-amino acid piperazine Series. In an effort to stabilize the piperazine moiety, which was extensively metabolized In vivo, a series of bicyclic derivatives were prepared, culminating in the identification of a Potent and selective triazolopiperazine series. Unlike their monocyclic counterparts, These analogs typically showed excellent pharmacokinetic properties in preclinical species. Optimization of this series led to the discovery of JANUVIA (sitagliptin), a highly selective DPP-4 inhibitor for the treatment of type 2 diabetes.

- **Pharmacokinetics:**
  - Single dose studies were carried out with a solution of the Phosphate salt of sitagliptin in saline for Both intravenous (IV) and oral (gavage) administration. For the placental transfer and milk excretion Studies, the phosphate salt was formulated in 0.5% aqueous methylcellulose containing 5 mM HCl. Most metabolism, excretion, and tissue distribution studies were carried out with [14C]sitagliptin. Plasma concentrations of sitagliptin (molecular weight of free base =407.32) were determined by a Validated LC-MS/MS assay that had a lower limit of Quantification of 1.0 and 5.0 ng/mL (2.46 and 12.3 nM) in rat and dog plasma, Respectively. The validated assay demonstrated good linearity and Reproducibility for Sitagliptin in the concentration range of 1.0 to 10,000 ng/mL in rat plasma, and 5.0 to 20,000 ng/mL in dog plasma. The within and between run assay precision were 11% or Less for both ratt and dog quality control (QC) samples, except at the limit of Quantification where precision was better than 14%. Totalhydroge.
  - radioactivity in tissues, blood, Plasma, urine, bile, and facces was determined by liquid scintillation counting, with or Without prior combustion. Metabolite identification was accomplished by LC-MS and by Comparison with authentic synthetic standards (M1, N-sulfate conjugate only). Two of the Metabolites (M2 and M5) were purified from dog urine and identified by NMR analysis And hydrogen-deuterium exchange. The results of the non-clinical absorption, Distribution, metabolism and excretion (ADME) studies Indicated that sitagliptin was Rapidly absorbed and was a moderate to high clearance drug, with a relatively short Plasma half-life.

1. **Absorption:**
   - In rats, following single IV administration of sitagliptin at doses of 0.5,2, and 5 mg/kg in males and 2 mg/kg in females, plasma concentrations of parent Drug declined in a time dependent manner, with the pharmacokinetic parameters Adequately described by non compartmental analysis of The sitagliptin plasma Concentration versus time data. The mean sitagliptin plasma clearance (CLp) was ~40 to 48 mL/min/kg at the three doses in males and 67 mL/min/kg in females; Blood clearance was estimated to be approximately the same as plasma Clearance (blood-to-plasma ratio was approximately unity). The mean values for The steady-state volume of distribution (Vdss) and terminal half-life (t1/2) were ~7 To 9 L/kg and ~2 hr, respectively, in both males and females. The renal clearances Of unbound drug was calculated to be ~34 mL/min/kg, by dividing the mean total Plasma clearance (~45 mL/min/kg) by the fraction unbound in plasma (0.67), an Multiplying by the fraction of dose excreted unchanged into urine (~0.5). This Value exceeded the glomerular filtration rate (~5 mL/min/kg in rats), implying that Sitagliptin was subject to active renal elimination in rats. The dose dependence of The oral pharmacokinetics of sitagliptin was evaluated after single administration of Four dose levels in male rats (2, 20, 60, and 180 mg/kg) and 2 dose levels in Female rats (2 and 180 mg/kg). The data indicated that over the dose range studied, absorption of sitagliptin Was not saturable, while elimination may have decreased somewhat with dose, as indicated by the ~181- and 159-fold increase in the area under the plasma concentration-time curve (AUC) observed in male and female rats, respectively, between 2 and 180 mg/kg. Oral bioavailability at 2 mg/kg was 59% and 82% in male and female rats, respectively. Sitagliptin plasma concentration-time data was collected in the dog following IV administration at 0.a And 1.5 mg/kg. Mean CLp, Vdss, and t1/2 values were ~9 mL/min/kg, 3 L/kg, and 4 hr, respectively. Blood clearance was estimated to be approximately the same as plasma clearance (blood-to-plasma Ratio was approximately unity). Dose-dependent oral pharmacokinetics was evaluated after single administration at four dose levels (0.4, 1.6, 10, and 30 mg/kg). Plasma AUC increased proportionately with dose, indicating that Absorption and elimination of sitagliptin were not saturable over the dose range studied. The oral bioavailability was 89% at 0.4 mg/kg and 97% at 1.6 mg/kg.

2. **Distribution:**
   - In rats, [14C]sitagliptin-related radioactivity was distributed widely Throughout the body following IV administration, but was cleared efficiently from all Tissues. However, caecum, intestine, liver and kidneys contained relatively high Concentrations of sitagliptin related material even after 24hr. Enterohepatic Circulation can therefore
not be ruled out. Sitagliptin was seen to cross the rat and Rabbit placenta readily. Sitagliptin was shown to be a substrate of the mouse and Human P-glycoprotein (Pgp), and the human renal organic anion transporter. In the in vitro interaction studies via Pgp transport (studies PK012 and PK017), cyclosporine A (potent inhibitor of Pgp) was used as a positive control. A Concentration of 10 µM cyclosporine A strongly inhibited basolateral to apical Transport of sitagliptin In LLC-MDR1 cells. This suggested that drug interactions Via Pgp were possible. The potential of sitagliptin to cause drug interactions with hOAT1 and hOAT3 substrates was evaluated in vitro. At concentrations of 0.1 to 500 µM, sitagliptin had no inhibitory effect on hOAT1- a known inhibitor of organic anion transporters. Showed potent inhibition with an IC50 of 3.9 ± 0.9 µM. Sitagliptin was a weak inhibitor of hOAT3-Mediated cimetidine uptake with an IC50 value of 160 ± 17 µM, Whereas probenecid significantly inhibited hOAT3-mediated transport of Cimetidine with an IC50 of 3.1 ± 1.2 µM. Since the IC50 values of sitagliptin for hOAT1 (>500 µM) and hOAT3 (160 µM) are so much higher than its plasma concentrations, Cmax ~1 µM at 100 mg, it is unlikely that it will cause clinically Meaningful Interactions with substrates of these transporters.

3. Metabolism:
In vitro assays indicated that at clinically relevant concentrations, Sitagliptin did not inhibit cytochrome P450s or Pgp, nor did it induce human CYP3A4. The sitagliptin metabolites, which were present at low to trace levels in plasma, were formed by N-sulfation, N-carbamoyl glucuronidation, hydroxylation of the triazolopiperazine ring, and by oxidative desaturation of the piperazine ring followed by cyclization via the primary amine. All the metabolites detected in human plasma were observed in rat and dog, however, not all observed metabolites were present in the same matrix as observed in humans. Due to the minor metabolism of this compound, consequences of the differences in metabolism between human, rat, and dog on the observed pharmacokinetics are not expected. The observed in vitro metabolism was in agreement with the in vivo metabolism. Only metabolite M1 was not observed in vitro.

4. Excretion:
In vitro plasma protein binding was low in mouse, rat, rabbit, dog, and Human. Sitagliptin was excreted primarily unchanged in human, rat, and dog. In dogs and humans, sitagliptin was cleared primarily by renal excretion of parent drug, while in rats it was cleared by both renal and biliary excretion. Approximately 5 to 16% of a radiolabeled dose was recovered as phase I and II metabolites in the excreta. Furthermore, sitagliptin observed in bile from dogs was significantly lower than in human faeces and rat bile. Sitagliptin was secreted into rat milk; this is mentioned in section 5.3 of the SPC. As it is unknown if sitagliptin is excreted into human breast milk, it should not be used during breastfeeding.

- Structure:

- Mechanism of action:
Inhibition of DPP-4 by sitagliptin slows DPP-4 mediated inactivation of incretins like GLP-1 and GIP. Incretins are released throughout the day and upregulated in response to meals as part of glucose homeostasis. Reduced inhibition of incretins increases insulin synthesis and decreases glucagon release in a manner dependent on glucose concentration. These effects lead to an overall increase in blood glucose control which is demonstrated by reduced glycosylated hemoglobin.
Concentrations of the active, intact hormones are increased by sitagliptin, thereby increasing and prolonging the action of these hormones. Incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), are released by the intestine throughout the day, and levels are increased in response to a meal. These hormones are rapidly inactivated by the enzyme, DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are normal or elevated, GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells by intracellular signaling pathways involving cyclic AMP. GLP-1 also lowers glucagon secretion from pancreatic alpha cells leading to reduced hepatic glucose production, and GLP-1 slows gastric emptying time. Sitagliptin increases insulin release and decreases glucagon levels in the circulation in a glucose-dependent manner; GLP-1 does not increase insulin secretion when the glucose concentration is less than 90 mg/dL. The contributions of GIP, which increases insulin secretion and regulates fat metabolism, to the overall effects of sitagliptin are unclear at this time. Sitagliptin is of benefit in patients with type 2 diabetes mellitus as their GLP-1 concentrations are decreased in response to a meal. Sitagliptin demonstrates selectivity for DPP-4 and does not inhibit DPP-8 or DPP-9 activity in vitro at concentrations approximating those from therapeutic doses. The long-term safety of DPP-4 inhibitors are currently under investigation as DPP-4 is not an enzyme specific for the breakdown of incretin hormones. In fact, DPP-4 is responsible for the metabolism of many peptides including peptide YY, neuropeptide Y, and growth hormone-releasing hormone. DPP-4 is involved with T-cell
activation and is expressed on lymphocytes as CD26. Whether there are long-term neurological or Immunological consequences of inhibiting DPP-4 is unclear at this time.

- **Method of synthesis:**
  A highly efficient synthesis of sitagliptin, a potent and Selective DPP-4 inhibitor for the treatment of type 2 diabetes mellitus (T2DM), has been Developed. The key dehydrositagliptin intermediate 9 is prepared in three steps in one Pot and directly isolated in 82% yield and >99.6 wt % purity. Highly enantioselective Hydrogenation of dehydrositagliptin 9, with as low as 0.15 mol % of Rh(I)/tBu JOSIPHOS, Affords sitagliptin, which is finally isolated as its phosphate salt with nearly perfect optical And chemical purity. This environmentally friendly, ‘green’ synthesis significantly reduces The total waste generated per kilogram of sitagliptin produced in comparison the First-generation route and completely eliminates aqueous waste streams. The efficiency Of this cost-effective process, which has been implemented on manufacturing scale, Results in up to 65% overall isolated yield.

- **Medical use:**

1. Sitagliptin is used with a proper diet and exercise program and possibly with other medications to control high blood sugar.
2. It is used in people with type 2 diabetes. Controlling high blood sugar helps prevent kidney damage, blindness, nerve problems, loss of limbs, and sexual function problems.

3. Proper control of diabetes may also lessen your risk of a heart attack or stroke.

4. Sitagliptin is a diabetes drug that works by increasing levels of natural substances called incretins. Incretins help to control blood sugar by increasing insulin release, especially after a meal.

5. They also decrease the amount of sugar your liver makes.

- **Adverse effect:-**

1. **Severe:-**
   - Pancreatitis
   - Exfoliative dermatitis
   - Vasculitis
   - Pemphigus
   - Angioedema
   - Anaphylactoid reaction
   - Rhabdomyolysis
   - Renal failure (unspecified)
   - Interstitial nephritis
   - Heart failure

2. **Moderate:-**
   - Peripheral edema
   - Stomatitis
   - Oral ulceration
   - Constipation
   - Bullous rash
   - Elevated hepatic enzymes

3. **Mild :-**
   - Infection
   - Pharyngitis
   - Headache
   - Diarrhea
   - Abdominal pain
   - Nausea
   - Vomiting
   - Rash
   - Urticaria
   - Myalgia
   - Arthralgia
   - Back pain

- **Treatment of overdose:-**

1. Sitagliptin is a highly selective orally active dipeptidyl peptidase-4 inhibitors recently approved in the United state for treatment of type -2 diabetes. Ten healthy subjects received single oral doses of 25, 50, 100, 200 and 400 mg final market image tablets in 5 separate treatment periods in randomized fashion to assess dose proportionality. Blood (upto 72h post – dose) and urine (upto 24h paot-dose) samples for sitagliptin pharmacokinetic analysis were collected at prespecified times following administration of sitagliptin. Dose proportionality of AUC (0-infinity), Cmax and C(24h) was assessed using a power- law model. The result of the study indicate that plasma AUC (0-infinity) increased any dose proportional manner over the 25-400mg dose range. Over the same dose range, plasma Cmax increase in a greater than dose proportional manner and C24h increase in a modestly less than dose proportional manner. No clinically meaningfully difference in Tmax or apparent t(½) were noted across the dose range. Difference in the percentage of the
sitagliptin dose exerted unchanged in urine (72.5% pulled across doses) and renal clearance (344ml/min pulled across doses) were not statistically significant.

2. Sitagliptin treatment significantly reduce blood pressure and was well tolerated in type-2 diabetic and non-diabetic hypertensive patients.

3. Sitagliptin (100mg) treatment for 3 months decrease inflammatory markers C reactive proteins (CRP), interleukin-6 (IL-6), myeloperoxidase (MPO), monocyte chemotactic protein 1 (MCP-1) in type 2 diabetic patients with atherosclerosis.

- **CONTRAINDICATION:-** Sitagliptin has been associated with severe hypersensitivity Reactions, including anaphylaxis, angioedema, and Stevens–Johnson syndrome. This agent is contraindicated in individual’s with sensitivity to sitagliptin or any of its components. Sitagliptin has been associated with postmarketing reports of Pancreatitis. Caution should be used in individuals with a history of pancreatitis; sitagliptin should be discontinued if Pancreatitis is suspected. Although there are no data to suggest that pancreatitis is a class effect of these agents at this time, it would be prudent to discontinue saxagliptin as well if pancreatitis is suspected. For patients with renal insufficiency, dosage adjustments are required for both sitagliptin and saxagliptin to minimize the risk of hypoglycemia. It is important to monitor renal function, in addition to glycemic control, after initiating therapy.

- **Drug interactions:-** Clinically significant drug interactions are not expected Saxagliptin metabolism, however, involves the action of CYP450 isoenzymes 3A4/5, leading to the potential for inter actions with inhibitors and inducers of this system. In vivo studies of the effect of saxagliptin on the pharmacokinetics of metformin, glyburide (DiaBeta, Sanofi-Aventis), pioglitazone (Actos, Takeda/Lilly), digoxin (Lanoxin, GlaxoSmithKline), simvastatin (Zocor, Merck), diltiazem (e.g., Cardizem, Abbott; Tiazac, Forest), and ketoconazole (Nizoral, Janssen) demonstrate a lack of
effect. In a review of the effect of other agents on saxagliptin, the concomitant administration of ketoconazole, a strong inhibitor of the CYP 450 3A4/5 and P-glycoprotein systems, leads to an increase in the Cmax and AUC level of saxagliptin, with a related decrease in the Cmax and AUC level of its metabolite. This effect has also been seen with diltiazem, a moderate inhibitor of the CYP 450 3A4 system. A dose reduction of 50% is recommended when saxagliptin is used with strong CYP 450 3A4/5 inhibitors. Additional monitoring or alternative agents may be necessary when moderate inhibitors are used with saxagliptin.

- **Conventional marketed formulation:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Forms</th>
<th>Dosage Change in Renal Dysfunction</th>
<th>Dosage Change in Hepatic Dysfunction</th>
<th>Excretion</th>
<th>DPP-4 Inhibition</th>
<th>Half Life (Hours)</th>
<th>Metabolism</th>
<th>Available in Fixed-Dose Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>25 mg, 50 mg, 100 mg</td>
<td>Yes</td>
<td>No</td>
<td>Renal (~80% unchanged as parent)</td>
<td>Max ~97%; &gt;90% &gt;24 h post-dose</td>
<td>8-24</td>
<td>Not appreciably metabolized</td>
<td>With metformin, With simvastatin</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5 mg, 5 mg</td>
<td>Yes</td>
<td>No</td>
<td>Renal (12-29% as parent, 21-52% as metabolite)</td>
<td>Max ~80%; &gt;70% &gt;24 h post-dose</td>
<td>2-4 (parent) 3-7 (metabolite)</td>
<td>Hepatically metabolized to active metabolite (via P450 3A4/5)</td>
<td>With metformin, With dapagliptin</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>50 mg</td>
<td>Dose: 50 mg bid; 50 mg qD in eGFR &lt;65 ml/min</td>
<td>Yes</td>
<td>Not recommended in severe dysfunction. Liver testing before administration</td>
<td>Renal (22% as parent, 55% as primary metabolite)</td>
<td>Max ~95%; &gt;80% &gt;12 h post-dose</td>
<td>1/6-4/6</td>
<td>Hydrolysed to inactive metabolite (P450 enzyme independent)</td>
</tr>
<tr>
<td>Alegliptin</td>
<td>6.25 mg, 12.5 mg, 25 mg</td>
<td>Yes</td>
<td>No</td>
<td>Renal (&gt;70% unchanged as parent)</td>
<td>Max ~90%; &gt;75% &gt;24 h post-dose</td>
<td>12-21</td>
<td>Not appreciably metabolized</td>
<td>With metformin, With pioglitazone</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>5 mg</td>
<td>No</td>
<td>No</td>
<td>Biliary (&gt;70% unchanged as parent), &lt;1% via kidney</td>
<td>Max ~80%; &gt;70% &gt;24 h post-dose</td>
<td>10-40</td>
<td>Not appreciably metabolized</td>
<td>With metformin, With empagliflozic</td>
</tr>
</tbody>
</table>

- **Novel marketed formulation:**

**Description**

Field Of The Invention[0001] The present invention provides a novel and improved process for the preparation of Sitagliptin of Formula I And its pharmaceutically acceptable salts.

![Formula I](image)
[0003] Sitagliptin phosphate is glucagon like peptide 1 metabolism modulator, hypoglycemic agent and dipeptidyl Peptidase IV inhibitor. Sitagliptin phosphate is currently marketed in the under the trade name of JANUVIA® in its Monohydrate form. JANUVIA® is indicated to improve glycemic control in patients with type 2 diabetes mellitus. Its Chemical name 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 monohydrate and the molecular Formula is C16H15F6N5O.H3PO4.H2O with a molecular Weight of 523.32. The structural Formula of Sitagliptin phosphate monohydrate is:

PCT Publication No. WO 03/004498 assigned to Merck & Co., describes a class of beta- amino tetrahydrotriazolo [4,3-a]pyrazines, which are potent inhibitors of DP-IV and therefore useful for the treatment of Type 2 diabetes. Specifically disclosed in WO 03/004498 is 7-[(3R)-3-amino-4-(2,4,5-trifluorophenyl)butanoyl]-3-(trifluoromethyl)-5,6,7,8-Tetrahydro-1,2,4-triazolo[4,3-a]pyrazine hydrochloride. This application also discloses a method of introducing a chiral Amine group using a chiral pyrazine derivative and to prepare Sitagliptin by Arndt-Eistert Homologation using t-butyloxyCarbonylamino-4-(2,4,5-trifluorophenyl)-butyric acid. The process is shown in the scheme given below:
Example 1:

Preparation of \((Z)-3\text{-amino-1-(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-4-(2,4,5-trifluorophenyl)but-2-en-1-one}\). To the mixture of 4-oxo-4-(3-(trifluoromethyl)-5,6-dihydro[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)-1-(2,4,5-trifluorophenyl)butan-2-one (427.0g) (prepared as per US 7,326,708 B2 (or J.Am.Chem.Soc. 2009,131,8798-8804)) and Methanol (1000ml) was purged dry ammonia gas (53.6g) at 25-30°C, heated to reflux (60-65°C) and maintained the Reaction mass at the same temperature for about 3.0-4.0 hrs. Cooled the reaction mass to 0-5°C, filtered the precipitated Solid and washed with chilled methanol. Dried the wet cake at 60-65°C to obtain 340.0g of the title compound. Molar Yield 79.8%; purity by HPLC: 98.99%.
• **Patent:** It was developed, and is marketed by Merck and Co under the trade name of Januvia tablet containing sitagliptin phosphate, an orally active inhibitor of dipeptidyl Peptidase-4 (DPP-4) enzymes.

• **Category:** Antidiabetic agent or Oral hypoglycemic agent.

• **Dose:** Sitagliptin 200 mg once daily

• **Half life:** Approximately 12.4 hours. Other studies have reported a half life of approximately 11 hours.

• **Storage:** Store at room temperature away from light and moisture. Do not store in the bathroom. Keep all medications away from children and pets. Do not flush medications down the toilet or pour them into a drain unless instructed to do so. Properly discard this product when it is expired or no longer needed. Consult your pharmacist or local waste disposal company.

• **Precautions:** Before using this medication, tell your doctor or pharmacist your medical history, especially of: kidney disease, heart failure, disease of the pancreas (pancreatitis), stones in your gallbladder (gallstones). You may experience blurred vision, dizziness, or drowsiness due to extremely low or high blood sugar. Do not drive, use machinery, or do any activity that requires alertness or clear vision until you are sure you can perform such activities safely. Limit alcohol while taking this medication because it can increase your risk of developing low blood sugar. It may be harder to control your blood sugar when your body is stressed (such as due to fever, infection, injury, or surgery). Consult your doctor because increased stress may require a change in your treatment plan, medications, or blood.

• **Conclusion:** Although sitagliptin and saxagliptin are both approved as Adjunctive therapies to diet and exercise in type-2 diabetes, Current data suggest that metformin or a sulfonylurea is generally necessary as a first-line treatment for significantly lowering blood glucose levels. The potential benefits of DPP-4 Inhibitors include complementary mechanism of action With other antidiabetic medications, a favorable adverse effect Profile, and a neutral effect on weight. With a low risk of Hypoglycemia, sitagliptin and saxagliptin are advantageous For patients who are close to their target HbA1c but who continually experience elevated glucose levels after meals. As to The advantages of selecting one DPP-4 inhibitor over another. Comparative clinical data are unavailable. Specific characteristics of these agents (i.e., dose adjustments for renal impairment, drug interactions), as well as future clinical experience And trial data, will serve as a guide for selection. Identifying appropriate patients for DPP-4 therapy should Include an evaluation of the cost, the risk of hypoglycemia, and The modest treatment effect associated with this drug class. Other DDP-4 inhibitors, including vildagliptin (Galvus, Novartis) and alogliptin (Takeda), are currently in development.