SITAGLIP

Sitagliptin 50/100

BRAND NAME Sitaglip

THERAPEUTIC CATEGORY Hypoglycemic

PHARMACOLOGIC CLASS Dipeptidyl peptidase-4 (DPP-4) inhibitor.

PRESENTATION Each film coated tablet contains Sitagliptin Phosphate Monohydrate equivalent to sitagliptin 50/100 mg.

MOLECULAR INTRODUCTION

Sitagliptin is the first in a new class drugs that inhibit the proteplytic activity of dipeptidyl peptidase-4 orally, thereby patenting the action of endogenous glucoregulatory peptides, known as incretins. It was approved by the US FDA for the treatment of type 2 diabetes mellitus in October 2006. It was first marketed in US as Januvia by Merck & Co. Sitagliptin phosphate monohydrate is described chemically as 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. Its empirical formula is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4 \cdot H_2O$ and a molecular weight is 523.32.

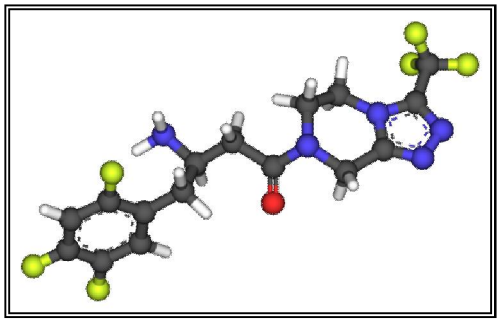

Fig 1 Ball and stick model of Sitagliptin

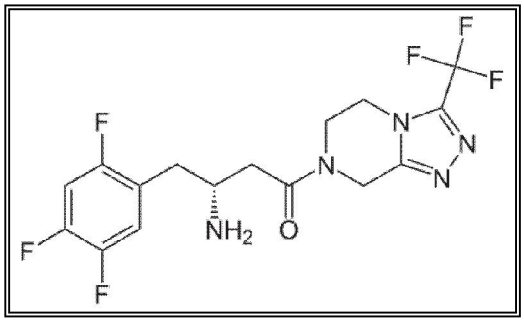

Fig2 Molecular structure of Sitagliptin

MECHANISM OF ACTION:

Sitagliptin prolongs the activity of proteins that increases the release of insulin after blood sugar rises, such as after meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4) which metabolizes the naturally occurring incretin hormones , glucagon-like peptide-1 (GLP-1) resulting in enhanced glucose-dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1 enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPP-IV activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma. Sitagliptin reduces hemoglobin A1C (HbA1c), fasting and postprandial glucose by glucose dependent stimulation of insulin secretion and inhibition of glucagon secretion. GLP-1 has other widespread effects including delaying gastric emptying, significantly reducing glucagon levels and possible central effect on appetite.

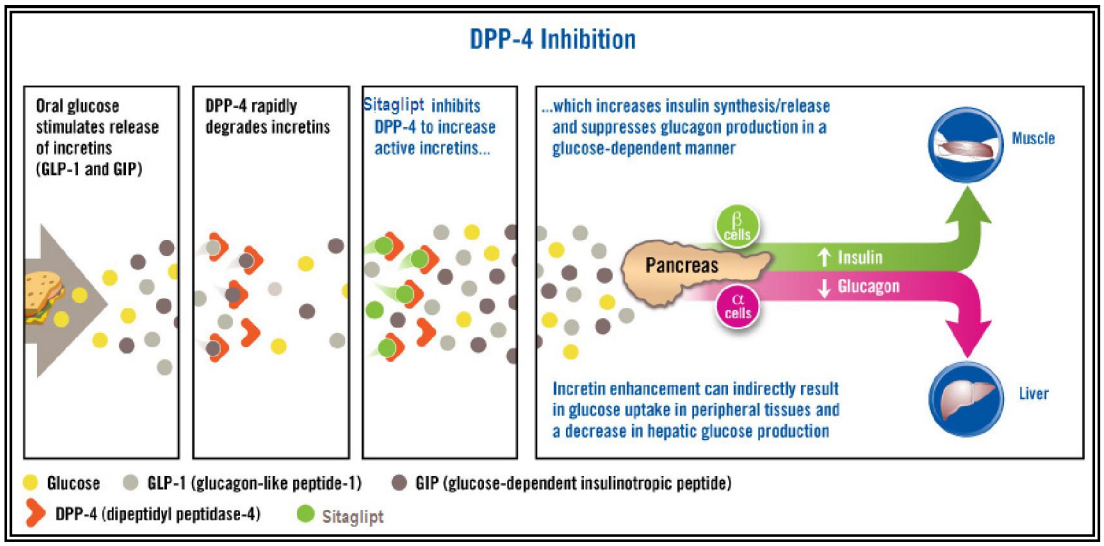

Fig 3. Mechanism of action of Sitaglipt

INDICATION

- To improve hyperglycemic condition in diabetes mellitus Type II.
- It can be given alone or in combination with other anti-hyperglycemic drugs.

DOSAGES AND ADMINISTRATION

- 100 mg/day with or without food.
- For patient with renal insufficiency:

Degree of renal Insufficiency	**Creatinine clearance (CrCl) ml/min**	**Corresponding Serum Creatinine levels mg/dl**		**Doses of Sitaglip mg /day**	**Remarks**
		Men	**Women**		
Mild	≥ 50	≤ 1.7	≤ 1.5	100	No dose adjustment necessary
Moderate	≥ 30 to < 50	1.7 to ≤ 3.0	1.5 to ≤ 2.5	50	
Severe and End-Stage renal Disease requiring hemodialysis or peritoneal dialysis	< 30	> 3.0	> 2.5	25	Administered without regard to timing of hemodialysis

- Since dosage adjustment is required based upon the renal function, **assessment of renal function is recommended prior to initiation of Sitaglipt** and periodically thereafter also.
- **Dosage of insulin secretagogue or insulin may need to be lowered** if they are being administered in parallel with Sitagliptin in order to reduce the risk of hypoglycemia.

PHARMACOKINETIC PROFILE

Absorption: Sitagliptin is rapidly absorbed after oral administration with absolute bioavailability of approximately 87 %. Co administration of a high-fat meal does not affect the pharmacokinetics of Sitaglip.

Distribution: Mean volume of distribution at steady state in healthy volunteers is approximately 198 L after single IV dose of 100 mg. 38 % of Sitagliptin is reversibly bound to plasma proteins

Merck & Co., Inc. Januvia ^{TM} tablets: full prescription info.

Metabolism: Sitagliptin undergoes minor metabolism primarily by cytochrome P450 (CYP) 3A4 and 2C8 to inactive metabolites.

Excretion: Sitagliptin undergoes primarily renal elimination (nearly equal to 79 % is excreted unchanged in the urine and 16 % metabolites), involving active tubular secretion and possibly human organic anion transporter-3 and/or glycoprotein transport. 13 % are excreted through feces

The elimination half life of sitagliptin is 12.4 hours.

ADVERSE EFFECT

- Headache
- Diarrhea
- Upper respiratory tract infection
- Nasopharyngitis.
- Acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing pancreatitis.
- Anaphylaxis
- Angioedema
- Exfoliative dermatitis
- Hypoglycemia (risk increased in conjunction with sulfonylurea)
- Steven-Johnson syndrome.

SPECIAL PRECAUTION

- **Renal Impairment**: Assessment of renal function is recommended prior to initiation of Sitaglipt. Should be used with caution in moderate to severe renal dysfunction and endstage renal disease (ESRD) requiring hemodialysis or peritoneal dialysis. Dosage adjustment is required in these cases.
- **Concurrent drug therapy**: Close blood glucose monitoring and Dosage adjustment of insulin secretagogue or insulin is required if they are being administered in parallel with Sitagliptin in order to reduce the risk of hypoglycemia.

- **Pancreatitis**: After initiation of Staglipt Patients should be carefully monitored for the signs and symptoms of pancreatitis. If pancreatitis is suspected, Sitaglipt should promptly be discontinued and appropriate management should be initiated.
- **Special Populations**:
    - Safety and efficacy have not been established in children under 18 years of age.
    - It is a pregnancy category B drug. Because there are no adequate, well-controlled studies of Sitagliptin in pregnant women, it should be used during pregnancy only if clearly needed.
    - Caution should be exercised with use of Sitagliptin in nursing women.

CONTRAINDICATION

- Drug is contra indicated in the patient with the history of a serious hypersensitive reaction to sitagliptin such as anaphylaxis or angiodema.
- Type I diabetes mellitus (insulin dependent Diabetes Mellitus)
- Diabetic ketoacidosis.

INTERACTION WITH OTHER DRUGS

- Caution should be taken in the concomitant administration with the drugs that can potentially lower blood sugar, such as probenecid, nonsteroidal anti inflammatory drugs (NSAIDs), aspirin or other salicylates, sulfa drugs, a monoamine oxidase inhibitor (MAOI) or beta-blockers.
- *Clin Pharmacol Ther* 2005; 78:675-88.

- Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Concomitant administration of 0.25 mg digoxin concomitantly with 100 mg of Sitagliptin daily for 10 days increased the plasma AUC of digoxin by 11%, and the plasma Cmax by 18%.

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