Sitagliptin (Januvia®)

Classification:

Antidiabetic Agent

Pharmacology

JANUVIA® (sitagliptin) is a dipeptidyl peptidase-4 (DPP-4) inhibitor which slows the inactivation of endogenous incretin 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. Sitagliptin exerts its action by inhibiting the enzyme DPP-4 and this activity lasts for a 24-hour period.

Indication- FDA Approved

Indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Pharmacokinetics

Pharmacokinetic Parameter	Details
Absorption	The absolute bioavailability is approximately 87%. Oral administration of sitagliptin 100 mg is rapidly absorbed with a peak plasma concentration (T_{max}) occurring 1 to 4 hours postdose.
Distribution	38% reversibly bound to plasma proteins. The V_d of 100 mg IV sitagliptin is 198 L.
Metabolism	Approximately 16% of an oral dose is excreted as metabolites. Six metabolites were detected at trace levels and not expected to contribute to the activity of sitagliptin. The primary enzyme responsible for metabolism is CYP3A4 with contribution from CYP2C8.

Pharmacokinetic Parameter	Details
Excretion	79% of sitagliptin is excreted unchanged in the urine with metabolism being a minor pathway of elimination. The terminal $t_{1/2}$ following a 100 mg oral dose is approximately 12.4 hours and renal clearance is 350 mL/min.

Dosage/Administration

JANUVIA® (sitagliptin) is recommended at a dose of 100 mg once daily with or without food.

Dose adjustment is needed for moderate to severe renal impairment:

- eGFR 30-45 ml/min 50 mg once daily
- eGFR < 30 ml/min including end stage renal disease on dialysis 25 mg once daily

Use in Special Populations

Pregnancy

Limited data available in pregnant women and not sufficient to inform a drug-associated risk for major birth defects and miscarriage. There are risks to mother and fetus associated with poorly controlled diabetes in pregnancy. No adverse developmental effects were observed when sitagliptin was administered to pregnant rats and rabbits during organogenesis at oral doses up to 30-times and 20-times the clinical dose based on AUC. Healthcare providers are encouraged to report any prenatal exposure to sitagliptin by calling the pregnancy registry at 1-800-986-8999.

Lactation

There is no information regarding the presence of sitagliptin in human milk, the effects on the breastfed infant, or the effects on milk production. Sitagliptin is present in rat milk and therefore possibly present in human milk. Sitagliptin is secreted in the milk of lactating rats at a milk to plasma ratio of 4:1.

Pediatric Use

Safety and effectiveness of JANUVIA® (sitagliptin) in pediatric patients below the age of 18 years have not been established.

Geriatric Use

Studies utilizing JANUVIA® (sitagliptin) in patients 65 years and older in pre-approval clinical safety and efficacy studies were limited and consisted of 725 of the 3884 subjects (19%). Patients 75 years and older consisted of 61 of the 3884 subjects (1.6%). Available evidence has not identified differences in response between elderly and younger patients, although greater sensitivity in some older individuals cannot be ruled out. Since sitagliptin is primarily renally eliminated and aging may be associated with reduced renal function, renal function should be evaluated more frequently in elderly patients to see if dose adjustment may be necessary.

Renal Impairment

Sitagliptin is primarily excreted by the kidneys and exposure is increased in those with renal impairment. Lower doses are recommended in those with moderate to severe renal impairment (eGFR < 45ml/min).

Contraindications

History of serious hypersensitivity reaction to sitagliptin such as anaphylaxis or angioedema.

Precautions

- Pancreatitis: Postmarketing reports of hemorrhagic or necrotizing pancreatitis. If pancreatitis is suspected, promptly discontinue.
- Heart failure: Heart failure has been reported with two other members of the DPP-4 inhibitor class. Consider risk vs. benefit for those with risk factors for heart failure and monitor patients for signs and symptoms.
- Acute Renal Failure: Postmarketing reports of acute renal failure. Assess renal function prior to initiation and periodically thereafter.
- Increased risk of Hypoglycemia when sitagliptin added to insulin secretagogue (e.g. sulfonylurea) or insulin therapy. Consider lowering dose if sitagliptin is added to these therapies.
- Hypersensitivity reactions have been reported in postmarketing reports including anaphylaxis, angioedema and exfoliative skin conditions including Stevens-Johnson syndrome.
- Arthralgia and severe joint pain reported in patients taking DPP-4 inhibitors.
- Bullous pemphigoid noted in postmarketing reports. Tell patients to report the development of blisters or erosions.

Adverse Effects

Adverse reactions occurring in 5% or more of JANUVIA® (sitagliptin) treated patients and at a rate greater than placebo are:

- Upper respiratory tract infection 6.3%

- Nasopharyngitis 5.2%
- Headache 5.1%

Other notable adverse effects reported:

- Incidence of acute pancreatitis was 0.1 per 100 patient years in each group (4 patients in the sitagliptin group and 4 in the control group)
- Incidence of hypoglycemia in the monotherapy trials was 1.2% sitagliptin and 0.9% placebo group
- In a 12-week study the mean increase in Scr was 0.12 mg/dL for sitagliptin and 0.07 mg/dL for placebo, the clinical significance of this increase relative to placebo is not known
- No meaningful changes in vital signs or ECG including QTc interval were observed

Monitoring

- A1C quarterly for those not meeting glycemic goals (ADA goal <7% is recommended for most nonpregnant adults)
- A1C at least twice yearly for those meeting glycemic goals
- Monitor renal function baseline and periodically thereafter
- Monitor for hypoglycemia, particularly if added to insulin secretagogue (e.g. sulfonylurea) or insulin therapy
- Monitor for any signs or symptoms of new or worsening heart failure
- Hypersensitivity reactions and bullous pemphigoid including blisters or erosions

Interactions

Digoxin

Slight increase in AUC (11%), no dosage adjustment recommended

Insulin Secretagogues or Insulin

Coadministration may require lower dose to reduce risk of hypoglycemia. Rate of hypoglycemia (glucose < 70 mg/dL) 12.2% with sitagliptin 100 mg + glimepiride vs. 1.8% with glimepiride alone. Rate of severe hypoglycemia 0% for both. Rate of hypoglycemia 15.5% with sitagliptin 100 mg + insulin vs. 7.8% with insulin alone. Rate of severe hypoglycemia 0.6% for sitagliptin 100 mg + insulin vs. 0.3% for insulin alone. Severe hypoglycemia was defined as incidents requiring medical assistance, exhibiting depressed level/loss of consciousness or seizure.

Efficacy

Monotherapy Studies

Two monotherapy pre-approval studies were conducted in patients with type 2 diabetes, one 18 weeks in duration and the other 24 weeks in duration. Those entering the study currently on an antihyperglycemic agent underwent a 7-week washout period. Those with inadequate glycemic control (A1C 7% to 10%) after the washout were randomized after completing a 2-week single-blind placebo run-in period. In the 18-week study 521 patients were randomized and in the 24-week study 741 patients were randomized to the following treatment groups: placebo, sitagliptin 100 mg, or sitagliptin 200 mg. Those who failed to meet glycemic goals were treated with metformin rescue. In the 18-week study the A1C with sitagliptin 100 mg improved 0.6% over placebo and in the 24-week study the A1C improved 0.8% over placebo, both statistically significant with $p<0.001$. In the 18-week study FPG with sitagliptin 100 mg improved 20 points over placebo and in the 24-week study FPG improved 17 points over placebo, both statistically significant with $p<0.001$. In the 18-week study 9% of those on sitagliptin 100 mg required metformin rescue compared to 17% on placebo. In the 24-week study 9% of those on sitagliptin 100 mg required metformin rescue compared to 21% on placebo. sitagliptin 200 mg did not provide any greater glycemic effect than the 100 mg dose. sitagliptin lipid endpoints were similar to placebo. Body weight did not increase from baseline with sitagliptin.

A monotherapy safety study was conducted in 91 patients with type 2 diabetes and chronic renal insufficiency (eGFR < 50 ml/min). Those with moderate renal insufficiency received a 50 mg daily dose of sitagliptin. Those with severe renal insufficiency, end stage renal disease on hemodialysis or peritoneal dialysis received 25 mg daily of sitagliptin. The safety and tolerability of sitagliptin was similar to placebo. There was a small increase in serum creatine in those with moderate renal insufficiency relative to placebo. Reductions in A1C and FPG seen with sitagliptin in chronic renal insufficiency were similar to those seen with sitagliptin in the other monotherapy studies.

Combination Studies

Sitagliptin has been studied in combination with other medications for the treatment of type 2 diabetes. Metformin doses ranging from 1000 mg per day up to 2000 mg per day have been evaluated with sitagliptin 100 mg daily resulting in an additional reduction in A1C of 0.7% to 2.1% compared to metformin alone. Sitagliptin 100 mg has also been compared to glipizide (dose range 5 mg to 20 mg daily, mean 10 mg) as an add-on therapy for those inadequately controlled on metformin. The study findings indicate non-inferiority of sitagliptin to glipizide with A1C reduction of 0.5% for sitagliptin and 0.6% for glipizide. Of note, the rate of hypoglycemia was significantly higher with glipizide (32%) than with sitagliptin (4.9%) and those treated with sitagliptin had a reduction in body weight (-1.5 kg)

compared to those treated with glipizide which had an increase in body weight (1.1 kg).
Sitagliptin 100 mg was studied in combination with glimepiride (4 mg or more per day) with or without metformin. Sitagliptin plus glimepiride resulted in an A1C reduction of 0.6% compared to the combination of sitagliptin, glimepiride and metformin which resulted in an A1C reduction of 0.9%. The rate of hypoglycemia was higher with sitagliptin in combination with glimepiride (12.2%) vs. glimepiride alone (1.8%).
Three studies evaluated sitagliptin as add on therapy with a TZD, either pioglitazone or rosiglitazone, the rosiglitazone study also included metformin in the treatment regimen. These studies showed significant reductions in A1C ranging from 0.7 to 0.9% compared to placebo. One of the studies reported more weight gain with the combination of sitagliptin + pioglitazone (3.0 kg) compared to pioglitazone alone (1.9 kg).
Sitagliptin has also been studied in combination with insulin. One study utilized pre-mixed, long-acting, or intermediate acting insulin with or without metformin. Those with inadequate glycemic control were randomized to sitagliptin 100 mg daily or placebo. The median change from baseline in daily dose of insulin was zero in both groups. The group with the addition of sitagliptin had an additional A1C decrease of 0.6% over placebo. An increased rate of hypoglycemia was noted in the group treated with the addition of sitagliptin compared to placebo. A second study utilized insulin glargine with metformin and those with inadequate glucose control were randomized to either sitagliptin or placebo. After 30 weeks, the difference in sitagliptin over placebo in A1C reduction was 0.4%.

American Diabetes Association Treatment Guideline

Metformin is considered initial first-line treatment for type 2 diabetes unless there are contraindications to its use. The FDA has revised the labeling for metformin to reflect safety in those with eGFR 30 ml/min or greater. There is little systematic data available for other oral agents as initial therapy for type 2 diabetes. In those with contraindications or intolerance to metformin, initial therapy should be based on different clinical considerations. DPP-4 inhibitors (except saxagliptin in the setting of heart failure) are considered possible third-line options for those at high risk or have established ASCVD, CKD or HF. For those without these risks, DPP-4 inhibitors may be considered second-line to metformin use particularly for those with a compelling need to minimize hypoglycemia. Although DPP-4 inhibitors generally do not contribute to weight loss, they are considered weight neutral as opposed to sulfonylureas and insulin which may contribute to weight gain. In any circumstance, there is no benefit in adding a DPP-4 inhibitor to those that are already prescribed a GLP-1 RA.

Safety

Diabetic Ketoacidosis (DKA)

A population-based multicenter cohort study in those with Type 2 Diabetes evaluated new users of SGLT-2 inhibitors and DPP-4 inhibitors between 2013 and 2018. The primary outcome measure was the Cox proportional hazards model which estimated hazard ratios of DKA comparing SGLT-2 inhibitors (n=208,757) with matched DPP-4 inhibitors (n=208,757). During 370,454 person-years of follow-up, 521 patients were diagnosed with DKA. Compared with DPP-4 inhibitors, the SGLT-2 inhibitors were associated with an increased risk for DKA with a hazard ratio (HR) 2.85, an approximate 3-fold increased risk for DKA. The hazard ratio (HR) for specific SGLT-2 inhibitors were as follows: canagliflozin HR 3.65, empagliflozin HR 2.32, and dapagliflozin HR 1.87.

COVID-19

It has been suggested that SARS-CoV-2 may bind to dipeptidyl peptidase 4 when entering cells of the respiratory tract and DPP-4 may facilitate SARS-CoV-2 entry into target cells. Inhibition of this interaction could have potential therapeutic outcomes related to COVID-19 and sitagliptin is a potent inhibitor of DPP-4. To evaluate this potential therapeutic effect, a multicenter, case-control, retrospective, observational study evaluated sitagliptin added to standard of care (n=169) compared to standard care alone (n=169) in the treatment of Type 2 Diabetes for those hospitalized with COVID-19 infection. The primary outcome measure was assessment of mortality at the 30-day follow-up time point. Mortality was significantly reduced in the sitagliptin group compared to standard of care alone, 18% and 37% respectively. Other outcomes which also showed significant improvement in the sitagliptin group compared to the standard of care alone include overall improvement of clinical score, hospital discharge at day 30, glycemia, serum creatinine, CRP and oxygen saturation. The results of this small study should be replicated; however, the significance of these initial findings is compelling.

Dosage Forms

DPP-4 Inhibitors:
Januvia (Sitagliptin) 100 mg tab
Onglyza (Saxagliptin) 2.5 mg or 5 mg tab
Tradjenta (Linagliptin) 5 mg tab
Nesina (Alogliptin) 25 mg tab

Special Considerations

- Once daily dosing without regard to meals

- Low risk for hypoglycemia as monotherapy
- Low risk for hypoglycemia in combination with metformin or TZD
- Evaluated for use in chronic renal insufficiency, adjusted dosing required for eGFR < 45 ml/min
- Considered weight neutral antidiabetic agent
- No added benefit then added to GLP-1 receptor agonist

Summary/Conclusion

Oral agents for type 2 diabetes approved for the formulary are limited to glipizide (sulfonylurea), metformin (biguanide), pioglitazone (TZD) and repaglinide (meglitinide). DPP-4 inhibitors may be considered for the treatment of type 2 diabetes in those who are intolerant or have contraindications to the first-line treatment, metformin, such as those with severe renal impairment. Since DPP-4 inhibitor monotherapy has a low risk for hypoglycemia, it may be considered for those at high risk for hypoglycemia. DPP-4 inhibitors can be prescribed as an add-on drug therapy for those inadequately controlled on metformin, TZD or sulfonylurea, although the risk for hypoglycemia is greater when combined with a sulfonylurea. There is inadequate data to support DPP-4 inhibitor use with prandial insulin. Combination of a DPP-4 inhibitor with a GLP-1 receptor agonist does not provide additive glucose-lowering effects. Some of the DPP-4 inhibitors, saxagliptin and alogliptin, have been associated with an increased risk of heart failure resulting in hospitalization. DPP-4 inhibitors require dose adjustment in chronic kidney disease with the exception of linagliptin which is primarily eliminated via the enterohepatic system.

Recommendation

Addition of JANUVIA® (sitagliptin) to the formulary is recommended.

References

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5. Solerte SB, D'Addio F, Trevisan R, et al. Sitagliptin Treatment at the Time of Hospitalization was Associated with Reduced Mortality in Patients with Type 2

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