drug information perspectives

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Contents

SITAGLIPTIN

TRADE NAME: Januvia

CLASSIFICATION
- Oral hypoglycemic
- DPP-4 inhibitor
- Incretin enhancer
- Gliptin

ACTION
- A selective inhibitor of the dipeptidyl peptidase-4 (DPP-4) enzyme.
- Lowers blood glucose levels by increasing insulin secretion and decreasing hepatic glucose production.
- Enhances the glucose-stimulated insulin secretion response to GLP-1 and GIP, which are released when food in the GI tract raises blood glucose levels above 3.05 mmol/L (55mg/dL).
- GLP-1 and GIP are incretin peptides that lower blood glucose levels by stimulating insulin release from pancreatic beta cells. Patients with Type 2 diabetes mellitus (T2DM) have an impaired GLP-1 and GIP response to food and less insulin secretion. In diabetics, sitagliptin increases the amount of active GLP-1 approximately 2-fold by inhibiting the enzyme that rapidly inactivates it, DPP-4. Enhanced GLP-1 also reduces glucagon secretion which leads to less hepatic glucose production. Active GIP is also increased but this is not crucial to the mechanism since GIP does not enhance glucose-induced insulin secretion in diabetics.
- In mice, beta cell mass and function have been enhanced, but there is no evidence at this time of a change in the progressive loss of pancreatic insulin secretion observed in humans with T2DM.
- The postprandial glucose excursion (increase) after a meal is decreased in patients with T2DM and those without T2DM.
- GLP-1 also decreases gastric emptying and appetite.

PHARMACOKINETICS
Half-life: 10-14 hours.

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Absorption
- Well absorbed orally with bioavailability 87%. Peak serum level 3-4 hours after a dose. Administration with food does not alter absorption.

Distribution
- Low plasma protein binding (38%).

Metabolism
- Only 16% metabolized, mainly by CYP3A4, with some metabolism by CYP2C8, to inactive metabolites.

Elimination
- Mainly eliminated in urine as unchanged drug (71-87% of dose). Urine contains some metabolites (13% of dose). Active renal excretion is involved with transport by OAT-3, OATP4C1, and p-glycoprotein. Thirteen percent of a dose is eliminated in feces (10% of dose as unchanged drug, 3% as metabolites).

Special populations
- ***Elderly***: Limited data.
- ***Hepatic impairment***: Moderate impairment (Child-Pugh score 7-9): AUC increases 21%, Cmax by 13%.
- ***Renal impairment***: Mild impairment: Slight increase in AUC, Cmax and half-life. Moderate impairment: AUC doubles. Severe impairment and end-stage renal disease: 4-fold increase in AUC. Only a small amount is removed by hemodialysis (13% four hours post-dose).
- ***Sex difference***: None known.
- ***Race***: No difference known.

USES AND EFFICACY
Uses
- Effective treatment for **Type 2 diabetes mellitus**.
- May be used alone or in combination with metformin or with metformin plus a sulfonylurea.
- Reduces HbA1c by 0.6-1.0% from baseline (with greater reductions if baseline is higher, e.g. HbA1c is reduced by 1.8% if baseline HbA1c is greater than 10%) compared with placebo. Reduces fasting plasma glucose and 2-hour postprandial glucose.

Clinical course
- GLP-1 remains at least 77% inhibited for 24 hours after a dose. A decrease in fasting plasma glucose is detectable by week 3 and stable by week 6. Decreases in HbA1c are noticeable by week 6, with most benefit seen by 12-18 weeks. Effects may last 4 weeks after discontinuation.

Major clinical trials
Monotherapy (2006): A randomized, double-blind, placebo-controlled study compared sitagliptin 100mg, 200mg and placebo in 741 patients with Type 2 diabetes mellitus with baseline HbA1c 7-10% (average 8.0%). After 24 weeks, HbA1c decreased relative to baseline by 0.94% with the 100mg dosage and 0.79% with the 200mg dosage, with no difference between doses. Response was greater in patients with baseline HbA1c above 9%, in whom this value was reduced by 1.5% by both doses. Significant reductions were observed in fasting plasma glucose and 2-hour postprandial glucose, and HOMA-beta (an indicator of beta-cell function) increased. HOMA-IR (used to indicate insulin sensitivity) was not changed. [Diabetes Care 2006;29:2632-2637.] *Study limitations*: Rescue metformin was allowed if needed in this industry-sponsored trial.

Combination therapy in patients not adequately controlled with metformin alone (2006): A double-blind trial randomized 701 patients with Type 2 diabetes mellitus, mean HbA1c 8.0%, who were not adequately controlled on metformin, to placebo or sitagliptin 100mg once daily for 24 weeks. In the sitagliptin group, HbA1c decreased by 0.67% from baseline, 47% of patients achieved an HbA1c level below 7%, and fasting plasma glucose and 2-hour postprandial glucose decreased, while fasting insulin levels and HOMA-beta increased. There was no increase in hypoglycemic events or weight gain.[Diabetes Care 2006;29:2638-2643.] *Study limitations*: Funded by the manufacturer.

Comparisons

Vs. metformin

A randomized double-blind trial compared metformin, sitagliptin and the combination in 1091 patients inadequately controlled by diet and exercise (average HbA1c 8.8%). After 24 weeks, monotherapy with metformin 1000-2000mg per day showed a trend towards a greater reduction in HbA1c than sitagliptin 100mg/day. Combinations of sitagliptin and metformin had additive benefit on HbA1c and fasting plasma glucose. Hypoglycemic events were rare and the gastrointestinal adverse effects associated with metformin were not enhanced by adding sitagliptin.

Vs. sulfonylureas

A non-inferiority trial compared the effect of adding sitagliptin or glipizide in patients not adequately controlled by metformin. Efficacy was similar after 1 year; however, patients treated with glipizide experienced more frequent hypoglycemia (32% versus 5%) and gained weight.

Advantages

- Does not usually cause hypoglycemia, since incretins do not have an effect when blood glucose is below 3.05 mmol/L (55mg/dL). However, hypoglycemia can occur if combined with drugs that stimulate insulin release.
- Simple regimen once daily with or without food.
- Neutral effect on weight.
- Reduces postprandial blood glucose levels.

Disadvantages

- Slightly increased risk of upper respiratory tract and urinary tract infection; clinical significance unknown.
- DPP-4 is present in many cells throughout the body, including lymphocytes and neuropeptides. Thus the full long-term effects of DPP-4 inhibition are unknown.

Place in therapy

- A weight-neutral addition to the glucose control provided by metformin in T2DM, with little risk of hypoglycemia. Generally slightly less effective at glucose reduction than other hypoglycemic drugs.

Investigational/Unapproved Uses

- ***Combination with sulfonylureas alone***: Not beneficial in one study when added to treatment with a sulfonylurea alone, and has increased the incidence of hypoglycemic events. This combination is approved in the US and the UK with the caution that the dose of sulfonylurea may need to be reduced.
- ***Combination with thiazolidinediones***: Sitagliptin has enhanced the benefit of pioglitazone in patients with Type 2 diabetes mellitus. This combination has been approved in the United States and the UK.

CONTRAINDICATIONS AND PRECAUTIONS:

Contraindications

- **Hypersensitivity**
- **Type 1 diabetes**
- **Diabetic ketoacidosis**
- **Children** (no data)
- **Congestive heart failure** (lack of safety data)
- **Severe liver impairment** (lack of safety data)
- **Moderate or severe renal impairment** (lack of safety data)

Precautions

- Assess renal function before and during therapy (since the drug is eliminated mainly by the kidneys).
- Report unexpected or serious reactions to Canada Vigilance, the Canadian adverse drug reaction monitoring program.

PREGNANCY AND LACTATION

- ***Pregnancy***: Not teratogenic in animals. No human data. Avoid.
- ***Lactation***: No data. Avoid.

SIDE EFFECTS

Cardiovascular:
- Hypertension (2.3% vs. 0.8% with metformin); small decreases in blood pressure also reported.
- Peripheral edema (1.6% vs. 1.1% with placebo).
- Peripheral coldness (1 case).
- Myocardial infarction (five case reports, two fatal cases).

CNS:
- Dizziness (1.5% when combined with metformin vs. 0.8% with metformin alone); headache (cases).

Endocrine/Metabolic:
- Hypoglycemia (1.1% vs. 0.6% with placebo; 1.1-2.2% when combined with metformin versus 0.5-1.1% with metformin alone; 7.5% when combined with glimepiride versus 2.8% with glimepiride alone versus 0.9% with glimepiride plus metformin).
- Increased blood glucose (35 case reports).

Gastrointestinal:
- Constipation (2.9% vs. 1.4% with placebo).
- Diarrhea (4.6% vs. 2.4% with placebo).
- Nausea (2.1% vs. 1.2% with placebo).
- Abdominal pain (2.1% vs. 1.6% with placebo).
- Pancreatitis (88 case reports).

Hematologic: Small increase in neutrophils by 5-10%, resulting in an increase in white blood cell count.

Hepatic: Increased liver enzymes (5 cases, one with positive dechallenge).

Hypersensitivity: Anaphylaxis, angioedema, Stevens-Johnson syndrome (can occur after the first dose).

Musculoskeletal:
- Arthralgia (3% when combined with metformin vs. 0.4% with metformin alone).

Other:
- Nasopharyngitis (5.2% vs. 3.3% with placebo).
- Viral upper respiratory tract infection (1.1% vs. 0.3% with placebo).
- Urinary tract infection (1.9% when combined with metformin vs. 0.8% with metformin alone).
- Usually weight neutral; weight gain in 6 case reports.
- Small increases in uric acid levels by about 10 micromol/L.
- Small decreases in alkaline phosphatase by about 4%.
- Small increases in HDL by about 2%, decreases in triglycerides 11-17%.
- Deafness (1 case), tinnitus (2 cases).
- Pulmonary embolism (2 fatal cases).
- Lack of efficacy (common in one study if high baseline HbA1c; 29 case reports).
- Decreased renal function (case reports).

INTERACTIONS

Does not inhibit P450 enzymes and does not induce CYP3A4. Does not inhibit OAT1 but may be a weak inhibitor of OAT3 uptake, theoretically interacting with cimetidine. OAT3, OATP4C1 and MDR1 Pgp move it in and out of renal tubule cells. It is a substrate for P-glycoprotein but does not inhibit Pgp transport of verapamil, ritonavir, quinidine or vinblastine.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Cyclosporine	Increased sitagliptin level by 68%	P-glycoprotein inhibition leading to increased intestinal absorption	Theoretical
Digoxin	Increased digoxin level by 18%	P-glycoprotein inhibition	Caution, monitor
OAT3 inhibitors and substrates*	Increased sitagliptin levels	Decreased renal secretion of sitagliptin	Theoretical
Sulfonyulurea drugs	Increased risk of hypoglycemia	Additive increased insulin release	Caution, monitor and reduce dose of sulfonylurea if necessary

*OAT3 inhibitors and substrates include: Cimetidine, fenafibrate, furosemide, ibuprofen, indapamide, probenecid, quinapril.

Interactions lacking
A lack of pharmacokinetic interaction has been documented with
- Glyburide
- Rosiglitazone
- Simvastatin
- Warfarin

DOSAGE

Adults
- Oral: 100mg once daily. Increasing the dose does not provide greater effect on blood glucose. When combined with metformin and a sulfonylurea drug, a lower dose of sulfonylurea should be considered in order to reduce the risk of hypoglycemia.

Elderly
- No dosage adjustment required; however, the elderly may have reduced renal function, see Renal Impairment.

Hepatic impairment
- Contraindicated in severe liver impairment. Elimination is mainly renal, and no dosage adjustment is recommended in mild-moderate liver dysfunction.

Renal impairment
- Contraindicated in moderate and severe renal impairment in Canada. For monotherapy in the United States, lower doses are recommended of 50mg once daily in patients with moderate renal impairment (ClCr 0.5-0.82 mL/s (30-49 mL/min)), or 25mg once daily in severe renal impairment (ClCr less than 0.5 mL/s (30 mL/min)) and end stage renal impairment requiring dialysis.

NURSING IMPLICATIONS
This drug can be administered with or without food.

Ensure patients are receiving a diabetic diet and an exercise program. Emphasize that antidiabetic drugs are not a substitute for diet and exercise.

This drug rarely causes hypoglycemia. Observe patients (particularly elderly or debilitated individuals) for signs of drug-induced hypoglycemia (sweating, dizziness, pallor, tremor, tachycardia, confusion, fainting).

Record the presence and, according to the patient, estimated severity of symptoms of diabetes mellitus and associated hyperglycemia (polyuria, thirst, recurrent blurred vision, paresthesias, fatigue).

If treatment is being initiated, construct a flow sheet recording the date, accurate administration times and dosage of all hypoglycemic agents, including insulin, and results of all blood and/or urine glucose tests.

PATIENT INSTRUCTIONS
Sitagliptin (sit-a-GLIP-tin) is used to treat Type 2 diabetes.

Following your diet, exercise, and weight loss program is important for controlling glucose (sugar), and for the effectiveness of drug treatment.

Before taking this drug, be sure that your physician is aware of any heart, liver and kidney problems that you may have; all other drugs that you are taking; and if you are pregnant or breast-feeding.

Take sitagliptin exactly as prescribed by your physician. It must be taken regularly to be effective. This drug may be taken with food or on an empty stomach. It is usually taken once a day. Taking it at the same time each day will make it easier to remember.

If you miss a dose, take it as soon as you remember it, unless it is almost time for the next dose. Do not take a double dose to make up for a missed dose.

Low blood sugar (hypoglycemia) is very uncommon with this medication. Symptoms of hypoglycemia are sweating, dizziness, lightheadedness, confusion, shakiness, drowsiness, marked hunger, fast heartbeat, trouble concentrating, headache that doesn't go away, or blurred vision. If any of these symptoms occur, take some sugar, fruit juice, a snack, or a meal. Contact your physician immediately.

Other side effects are infrequent; but if any persistent or bothersome effects occur (eg, rash, yellow skin, nausea, vomiting, abdominal pain, joint pain), contact your physician.

If you have experienced an unexpected or serious reaction to this drug, this can be reported to Health Canada's monitoring program (tollfree telephone 1-866-234-2345, tollfree fax 1-866-678-6789). Note that this is not an emergency number.

Store this drug in its original container, away from heat, light and moisture, and out of the reach of children.

PRESENTATION
Tablets: 100 mg.
Also available combined with metformin.