

drug information perspectives

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- **Saxagliptin**

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SAXAGLIPTIN

TRADE NAME: Onglyza

CLASSIFICATION

- Oral hypoglycemic agent
- DPP-4 inhibitor
- Incretin enhancer
- Gliptin
- Cyanopyrrolidine

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 (INtestinal seCRETion of INsulin) 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 diabetes, saxagliptin increases the amount of active GLP-1 by 2- to 3-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.
- The postprandial glucose excursion (increase) after a meal is reduced by this drug in patients with T2DM.
- In mice, beta cell mass and function have been enhanced by DPP-4 inhibitors, but there is no evidence at present of a change in the progressive loss of pancreatic insulin secretion observed in humans with T2DM.
- GLP-1 also decreases gastric emptying and appetite but these effects are not usually seen with DPP-4 inhibitors and there is usually a neutral effect on weight.

PHARMACOKINETICS

Half-life:

- 2 hours (parent drug); 2.8 hours (active metabolite). However, due to prolonged binding by the parent drug and active metabolite to the active site on DPP-4, inhibition of DPP-4 lasts at least 24 hours.

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Absorption:

- Well absorbed orally with bioavailability at least 75%. Administration with food increases AUC 27%; not clinically significant.

Distribution:

- Negligible plasma protein binding.

Metabolism:

- Metabolized by CYP 3A4/5. One active metabolite (5-hydroxy saxagliptin) has half the DPP-4 inhibition of the parent drug.

Elimination:

- Hepatic (22%) and renal (78%). The urine contains the parent drug (11%) and the active metabolite (35%). A P-glycoprotein (Pgp) substrate.

Special populations:

- **Elderly:** Increased Cmax by 23% and AUC by 59% compared with younger subjects.

- **Hepatic impairment:** Mild to severe impairment (Child-Pugh A, B and C): AUC of the parent drug increases up to 77% and the AUC of the active metabolite decreases.

- **Renal impairment:** Mild impairment: Little change in pharmacokinetics. Moderate impairment, severe impairment and end-stage renal disease: Increased AUC 2.1-fold for the parent drug and 4.5-fold for the active metabolite. Removed by hemodialysis.

- **Sex difference:** 25% higher levels of the active metabolite in females.

- **Race:** No difference known.

USES AND EFFICACY

Uses:

- Effective treatment for **Type 2 diabetes mellitus**.

- May be used in combination with metformin, a sulfonylurea or (approved in the US and UK) a glitazone.

Approved in the US as monotherapy.

- In patients with baseline HbA1c approximately 8%, this drug reduces HbA1c by 0.5-0.94% from baseline, with higher reductions if the baseline is higher, e.g. HbA1c is reduced by 0.84-2.5% if baseline HbA1c is 9% or above. Reduces fasting plasma glucose and postprandial glucose.

Clinical course:

- DPP-4 is inhibited for 24 hours after a dose. A decrease in fasting plasma glucose is detectable and maximal by week 2. Decreases in HbA1c are noticeable by week 4, with most benefit seen by 12 weeks.

Major clinical trials

Monotherapy in treatment-naive T2DM patients (2009): A randomized, double-blind, placebo-controlled trial compared saxagliptin 2.5, 5 and 10mg per day or placebo plus diet and exercise in 401 patients with T2DM, baseline HbA1c 7-10% (average 7.9%). Among excluded patients were those with NYHA CHF stage III/IV, a recent cardiovascular event, or immunodeficiency. After 24 weeks, HbA1c decreased relative to baseline by 0.43%, 0.46%, or 0.54% with saxagliptin, respectively, and increased by 0.19% with placebo. Response was proportional to baseline HbA1c, as patients with baseline of 9% or higher developed reductions of 0.84-1.25% in HbA1c. Fasting plasma glucose, postprandial glucose and postprandial glucagon were reduced with each drug dose, and HOMA-2beta (an indicator of beta-cell function) increased approximately 14%. With a 5mg daily dose, 38% of patients achieved a goal of HbA1c below 7%, significantly different from placebo (24%). At this dose, 20% of patients discontinued the study due to lack of efficacy, compared with 26% in the placebo group. More common adverse events with the 5mg dose were headache, urinary tract infection, sinusitis, influenza and dermatologic reactions. Body weight did not increase. [Curr Med Res Opin 2009;25(10):2401-2411.] **Study limitations:** Rescue metformin was allowed if needed. This was an industry-sponsored trial.

Combination therapy in patients not adequately controlled with metformin alone (2009): A double-blind trial randomized 743 patients with T2DM, mean HbA1c 8.1%, who were not adequately controlled with metformin, to metformin plus either placebo or saxagliptin 2.5, 5 or 10mg daily, plus diet and exercise for 24 weeks. Withdrawal rates were high (25% with saxagliptin, 37% with placebo), mainly due to lack of efficacy. All saxagliptin dosages decreased HbA1c (0.58-0.69% vs. baseline), fasting plasma glucose, postprandial glucose and postprandial glucagon decreased, and HOMA-2beta increased 18%. Hypoglycemic events occurred in 0.5% with saxagliptin vs. 0.6% with placebo, and all patients lost weight. The gastrointestinal adverse effects associated with metformin were not enhanced by adding saxagliptin. [Diabetes Care 2009;32(9):1649-1655.] **Study Limitations:** Rescue pioglitazone was allowed if needed. This was an industry-sponsored trial. Metformin doses ranged from 500 to 2550mg daily with no information provided on the breakdown in each study arm.

Comparisons

Vs. Sitagliptin

A randomized double-blind non-inferiority trial in 801 patients inadequately controlled by metformin, diet and exercise (average HbA1c 7.7%) compared the addition of saxagliptin versus sitagliptin. After 18 weeks, saxagliptin was not statistically inferior to sitagliptin in lowering HbA1c (0.52% vs. 0.62%, respectively) or other parameters. Adverse events were similar, with numerically more upper respiratory tract infections with saxagliptin and more back pain, nausea and arthralgia reported for sitagliptin. **Study limitations:** Funded by the manufacturer of saxagliptin.

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 oral regimen once daily with or without food.
- Neutral effect on weight.
- Reduces postprandial blood glucose levels.
- No dose titration needed.

Disadvantages:

- Potential drug interactions.
- DPP-4 is present in many cells throughout the body, including lymphocytes, and many neuropeptides and cytokines may be substrates. The long-term safety of DPP-4 inhibition is unknown.
- No data on effects on mortality, long-term complications and health-related quality of life.
- A similar drug sitagliptin has been associated with pancreatitis. In rats, sitagliptin has produced increased pancreatic ductal cell turnover, and less commonly ductal metaplasia, which along with pancreatitis are risk factors for pancreatic ductal cancer. The consequences of this in humans are unknown.

Place in therapy:

- A weight-neutral addition to the glucose control provided by metformin, sulfonylureas or glitazones in T2DM, with little risk of hypoglycemia. Provides similar efficacy to other DPP-4 inhibitors, e.g. sitagliptin. Generally slightly less effective at glucose control than metformin or sulfonylureas.

CONTRAINDICATIONS AND PRECAUTIONS

Contraindications:

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

Precautions:

- Assess renal function before and during therapy (eliminated partly by the kidneys).

- Patients with lymphocyte abnormalities (decreased lymphocyte count may occur; dose-related).
- Patients with immunodeficiency (decreased lymphocyte count and infections may occur; immunocompromised patients were excluded from most clinical trials).
- **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 if possible.
- **Lactation:** No data. Avoid.

SIDE EFFECTS

The incidence when using a 5mg dose is given in brackets.

Cardiovascular:

- Rare. A postmarketing cardiovascular safety study is ongoing, with results expected in 2016.
- Increased heart rate (with larger than recommended doses).
- Hypertension (6.3% combined with glyburide vs. 2.2% with glyburide alone).
- Peripheral edema (mainly pedal edema, 8.1% combined with glitazones vs. 4.3% with glitazones alone).

CNS:

- Headache (up to 9.4% vs. 4-7% with placebo).
- Malaise (3 case reports).

Endocrine/Metabolic:

- Hypoglycemia (usually no hypoglycemia; rare cases, mostly mild-moderate). May be more common when combined with a sulfonylurea (14.6% combined with glyburide vs. 10.1% with glyburide alone).
- No effects on lipids.

Gastrointestinal:

- Gastroenteritis (2.3% vs. 0.9% with placebo).
- Abdominal pain (1.7% vs. 0.5% with placebo).

Hematologic:

- Decrease in lymphocyte count (0.5%, dose-related, more common with larger than recommended doses (10mg and 20mg doses); usually small decreases of 100 cells/microL).
- Anemia (5.8% combined with metformin vs. 1.7% with metformin alone).
- Eosinophilia (3.1% combined with metformin vs. 0% with metformin alone).

Hypersensitivity:

- Rash (2-4%).
- Urticaria, facial edema (1.5% vs. 0.4% with placebo).
- Anaphylaxis (2 case reports).

Musculoskeletal:

- Arthralgia (4-6% vs. 3% with placebo).
- Creatine kinase increased (0.2% vs. 0% with placebo).

Other:

- Infections: urinary tract infection (8.5% vs. 4.2% with placebo); influenza (3.8% vs. 1.1% with placebo); upper respiratory tract infection (9.1% combined with glitazones vs. 7.1% with glitazones alone); bronchitis (9.4% combined with metformin vs. 6.1% with metformin alone; 10.7% combined with glyburide vs. 8.2% with glyburide alone).
- Nasopharyngitis (6.9% combined with metformin vs. 4% with metformin alone).
- Sinusitis (5.7% vs. 3.2% with placebo).
- Lack of efficacy (20% vs. 26% with placebo).
- Back pain (6.6% vs. 5.3% with placebo).

- Usually no change in weight. Weight may increase when combined with a sulfonylurea (0.8kg vs. 0.3kg with glyburide alone). Weight may increase when combined with a glitazone (1.4kg vs. 0.9kg with glitazone alone).

INTERACTIONS

Metabolized by CYP 3A4/5. A P-glycoprotein substrate. Does not induce or inhibit common CYP enzymes or Pgp.

DRUG	EFFECT	MECHANISM	IMPORTANCE
Drugs that induce CYP 3A4/5 e.g. rifampin	Decreased saxagliptin levels	Increased metabolism (CYP 3A4)	Caution
Drugs that inhibit CYP3A4/5	Increased saxagliptin levels	Decreased metabolism (CYP3A4/5)	Moderate inhibitors*-caution, monitor response. Strong inhibitors** - maximum saxagliptin daily dose of 2.5mg
Grapefruit juice	Increased saxagliptin levels	Decreased metabolism (CYP 3A4)	Theoretical, caution
Sulfonylurea drugs	Increased risk of hypoglycemia	Additive increased insulin release	Caution, monitor and reduce dose of sulfonylurea if necessary

*Moderate inhibitors of CYP3A4/5 include amprenavir, diltiazem, erythromycin, fluconazole, fosamprenavir, and verapamil.

**Strong inhibitors of CYP3A4/5 include atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, and telithromycin.

Interactions lacking

A lack of clinically important *pharmacokinetic* interaction has been documented with the following drugs:

- Antacid containing aluminum hydroxide, magnesium hydroxide and simethicone
- Digoxin
- Glyburide
- Metformin
- Omeprazole
- Pioglitazone
- Simvastatin

DOSAGE

Adults:

- Oral: 5mg once daily. A greater dose does not provide a greater effect on blood glucose and is more likely to cause lymphopenia. Consider a lower dose of sulfonylurea when using in combination with saxagliptin 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 moderate to severe liver impairment (increased AUC).

Renal impairment:

- No dosage adjustment required in mild renal impairment. Contraindicated in moderate and severe renal failure (increased AUC).

NURSING IMPLICATIONS

Administer with or without food.

Ensure patients are receiving a diabetic diet and an exercise program. Emphasize that antidiabetic drugs are used in concert with diet and exercise.

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

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

If diabetic treatment is being started or changed, construct a flow sheet to record the date, administration times and dosage of all hypoglycemic agents, including insulin, and results of blood and/or urine glucose tests.

PATIENT INSTRUCTIONS

Saxagliptin (SAX-a-glip-tin) is used to treat Type 2 diabetes.

Following your diet, exercise, and weight loss program is necessary to control your diabetes, and for the effectiveness of drug treatment.

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

Take saxagliptin 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, 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 symptoms occur (eg, headache, rash, stuffy nose, frequent urination, unusual or persistent infection), 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: 5 mg.

References are available on request.