Sitawok (Sitagliptin) Safety Information

Undesirable effects of Sitagliptin

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled clinical studies as both monotherapy and combination therapy with Metformin, Pioglitazone, or Rosiglitazone and Metformin, the overall incidence of adverse reactions, hypoglycemia, and discontinuation of therapy due to clinical adverse reactions with **Sitawok (Sitagliptin)** were similar to placebo. In combination with Glimepiride, with or without Metformin, the overall incidence of clinical adverse reactions with Sitagliptin was higher than with placebo, in part related to a higher incidence of hypoglycemia **(see Table 3)**; the incidence of discontinuation due to clinical adverse reactions was similar to placebo.

Two placebo-controlled **monotherapy studies**, one of 18- and one of 24-week duration, included patients treated with Sitagliptin 100 mg daily, Sitagliptin 200 mg daily, and placebo. Five placebo-controlled add-on combination therapy studies were also conducted: one with Metformin; one with Pioglitazone; one with Metformin and Rosiglitazone; one with Glimepiride (with or without Metformin); and one with insulin (with or without Metformin). In these trials, patients with inadequate glycemic control on a stable dose of the background therapy were randomized to add-on therapy with Sitagliptin 100 mg daily or placebo. The adverse reactions, excluding hypoglycemia, reported regardless of investigator assessment of causality in ≥ 5% of patients treated with Sitagliptin 100 mg daily and more commonly than in patients treated with placebo, are shown in **Table 1** for the clinical trials of at least 18 weeks duration. Incidences of hypoglycemia are shown in **Table 3.**

Table 1. Placebo-Controlled Clinical Studies of Sitagliptin Monotherapy or Add-on Combination Therapy with Pioglitazone, Metformin + Rosiglitazone, or Glimepiride +/- Metformin: Adverse Reactions (Excluding Hypoglycemia) Reported in - 5% of Patients and More Commonly than in Patients Given Placebo, Regardless of Investigator Assessment of Causality†

	Number of Patients (%)	
Monotherapy (18 or 24 weeks)	**Sitagliptin 100 mg**	**Placebo**
	N = 443	N = 363
Nasopharyngitis	23 (5.2)	12 (3.3)
Combination with Pioglitazone (24 weeks)	**Sitagliptin 100 mg + Pioglitazone**	**Placebo + Pioglitazone**
	N = 175	N = 178
Upper Respiratory Tract Infection	11 (6.3)	6 (3.4)
Headache	9 (5.1)	7 (3.9)
Combination with Metformin + Rosiglitazone (18 weeks)	**Sitagliptin 100 mg + Metformin + Rosiglitazone**	**Placebo + Metformin + Rosiglitazone**
	N = 181	N = 97
Upper Respiratory Tract Infection	10 (5.5)	5 (5.2)
Nasopharyngitis	11 (6.1)	4 (4.1)
Combination with Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Nasopharyngitis	14 (6.3)	10 (4.6)
Headache	13 (5.9)	5 (2.3)

† Intent-to-treat population

In the 24-week study of patients receiving Sitagliptin as add-on combination therapy with Metformin, there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo.

In the 24-week study of patients receiving Sitagliptin as add-on therapy to insulin (with or without Metformin), there were no adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients and more commonly than in patients given placebo, except for hypoglycemia **(see Table 3)**.

In the study of Sitagliptin as add-on combination therapy with Metformin and Rosiglitazone **(Table 1)**, through Week 54 the adverse reactions reported regardless of investigator assessment of causality in ≥5% of patients treated with Sitagliptin and more commonly than in patients treated with placebo were: upper respiratory tract infection (Sitagliptin, 15.5%; placebo, 6.2%), nasopharyngitis (11.0%, 9.3%), peripheral edema (8.3%, 5.2%), and headache (5.5%, 4.1%). In a pooled analysis of the two monotherapy studies, the add-on to Metformin study, and the add-on to Pioglitazone study, the incidence of selected gastrointestinal adverse reactions in patients treated with Sitagliptin was as follows: abdominal pain (Sitagliptin 100 mg, 2.3%; placebo, 2.1%), nausea (1.4%, 0.6%), and diarrhoea (3.0%, 2.3%).

In an additional, 24-week, placebo-controlled factorial study of initial therapy with Sitagliptin in combination with Metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in **Table 2**.

Table 2. Initial Therapy with Combination of Sitagliptin and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥ 5% of Patients Receiving Combination Therapy (and Greater than in Patients Receiving Metformin alone, Sitagliptin alone, and Placebo)†

	Number of Patients (%)			
	Placebo	**Sitagliptin 100 mg QD**	**Metformin 500 or 1000 mg bid ††**	**Sitagliptin 50 mg bid + Metformin 500 or 1000 mg bid ††**
	N = 176	N = 179	N = 364††	N = 372††
Upper Respiratory Infection	9 (5.1)	8 (4.5)	19 (5.2)	23 (6.2)
Headache	5 (2.8)	2 (1.1)	14 (3.8)	22 (5.9)

† Intent-to-treat population.
†† Data pooled for the patients given the lower and higher doses of Metformin.

In a 24-week study of initial therapy with Sitagliptin in combination with Pioglitazone, there were no adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients and more commonly than in patients given Pioglitazone alone.

No clinically meaningful changes in vital signs or in ECG (including in QTc interval) were observed in patients treated with Sitagliptin.

In a pooled analysis of 19 double-blind clinical trials that included data from 10,246 patients randomized to receive Sitagliptin 100 mg/day (N=5429) or corresponding (active or placebo) control (N=4817), the incidence of acute pancreatitis was 0.1 per 100 patient-years in each group (4 patients with an event in 4708 patient-years for Sitagliptin and 4 patients with an event in 3942 patient-years for control).

Hypoglycemia

In all (N=9) studies, adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia. A concurrent blood glucose measurement was not required although most (74%) reports of hypoglycemia were accompanied by a blood glucose measurement ≤70 mg/dL. When Sitagliptin was co-administered with a sulfonylurea or with insulin, the percentage of patients with at least one adverse reaction of hypoglycemia was higher than in the corresponding placebo group **(Table 3).**

Table 3 Incidence and Rate of Hypoglycemia[†] in Placebo-Controlled Clinical Studies when Sitagliptin was used as Add-On Therapy to Glimepiride (with or without Metformin) or Insulin (with or without Metformin), Regardless of Investigator Assessment of Causality

Add-On to Glimepiride (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Glimepiride (+/- Metformin)**	**Placebo + Glimepiride (+/- Metformin)**
	N = 222	N = 219
Overall (%)	27 (12.2)	4 (1.8)
Rate (episodes/patient-year)[‡]	0.59	0.24
Severe (%)[§]	0 (0.0)	0 (0.0)
Add-On to Insulin (+/- Metformin) (24 weeks)	**Sitagliptin 100 mg + Insulin (+/- Metformin)**	**Placebo + Insulin (+/- Metformin)**
	N = 322	N = 319
Overall (%)	50 (15.5)	25 (7.8)
Rate (episodes/patient-year) [‡]	1.06	0.51
Severe (%)[§]	2 (0.6)	1 (0.3)

[†] Adverse reactions of hypoglycemia were based on all reports of symptomatic hypoglycemia; a concurrent glucose measurement was not required; intent-to-treat population.
[‡] Based on total number of events (i.e., a single patient may have had multiple events).
[§] Severe events of hypoglycemia were defined as those events requiring medical assistance or exhibiting depressed level/loss of consciousness or seizure.

In a pooled analysis of the two monotherapy studies, the add-on to Metformin study, and the add-on to Pioglitazone study, the overall incidence of adverse reactions of hypoglycemia was 1.2% in patients treated with Sitagliptin 100 mg and 0.9% in patients treated with placebo.

In the study of Sitagliptin as add-on combination therapy with Metformin and Rosiglitazone, the overall incidence of hypoglycemia was 2.2% in patients given add-on Sitagliptin and 0.0% in patients given add-on placebo through Week 18. Through Week 54, the overall incidence of hypoglycemia was 3.9% in patients given add-on Sitagliptin and 1.0% in patients given add-on placebo.

In the 24-week, placebo-controlled factorial study of initial therapy with Sitagliptin in combination with Metformin, the incidence of hypoglycemia was 0.6% in patients given placebo, 0.6% in patients given Sitagliptin alone, 0.8% in patients given Metformin alone, and 1.6% in patients given Sitagliptin in combination with Metformin.

In the study of Sitagliptin as initial therapy with Pioglitazone, one patient taking Sitagliptin experienced a severe episode of hypoglycemia. There were no severe hypoglycemia episodes reported in other studies except in the study involving co-administration with insulin.

Postmarketing Experience

Additional adverse reactions have been identified during postapproval use of Sitagliptin as monotherapy and/or in combination with other antihyperglycaemic agents. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions including Arthralgia, anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis, and exfoliative skin conditions including Stevens-Johnson syndrome; hepatic enzyme elevations; acute pancreatitis, including fatal and non-fatal hemorrhagic and necrotizing pancreatitis; worsening renal function, including acute renal failure (sometimes requiring dialysis); constipation; vomiting; headache, bullous pemphigoid, myalgia; pain in extremity; back pain; mouth ulceration; stomatitis; rhabdomyolysis.

During controlled clinical trials in healthy subjects, single doses of up to 800 mg Sitagliptin were administered. Maximal mean increases in QTc of 8.0 msec were observed in one study at a dose of 800 mg Sitagliptin, a mean effect that is not considered clinically important. There is no experience with doses above 800 mg in clinical studies. In Phase I multiple-dose studies, there were no dose-related

clinical adverse reactions observed with Sitagliptin with doses of up to 600 mg per day for periods of up to 10 days and 400 mg per day for up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy as indicated by the patient's clinical status. Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour haemodialysis session. Prolonged haemodialysis may be considered if clinically appropriate. It is not known if Sitagliptin is dialyzable by peritoneal dialysis.

Special warnings and precautions for use

Pancreatitis

- There have been postmarketing reports of acute pancreatitis, including fatal and non-fatal haemorrhagic or necrotizing pancreatitis, in patients taking Sitagliptin.
- After initiation of Sitagliptin, patients should be observed carefully for signs and symptoms of pancreatitis.
- If pancreatitis is suspected, Sitagliptin should promptly be discontinued, and appropriate management should be initiated.
- It is unknown whether patients with a history of pancreatitis are at increased risk for the development of pancreatitis while using Sitagliptin.

Heart Failure

- An association between dipeptidyl peptidase-4 (DPP-4) inhibitor treatment and heart failure has been observed in cardiovascular outcomes trials for two other members of the DPP-4 inhibitor class.
- These trials evaluated patients with type 2 diabetes mellitus and atherosclerotic cardiovascular disease. Consider the risks and benefits of Sitagliptin prior to initiating treatment in patients at risk for heart failure, such as those with a prior history of heart failure and a history of renal impairment and observe these patients for signs and symptoms of heart failure during therapy.
- Advise patients of the characteristic symptoms of heart failure and to immediately report such symptoms. If heart failure develops, evaluate and manage according to current standards of care and consider discontinuation of Sitagliptin.

Acute Renal Failure

- Assessment of renal function is recommended prior to initiating Sitagliptin and periodically thereafter. A dosage adjustment is recommended in patients with moderate or severe renal impairment and in patients with ESRD requiring haemodialysis or peritoneal dialysis.

- Caution should be used to ensure that the correct dose of Sitagliptin is prescribed for patients with moderate (creatinine clearance ≥ 30 to <50 mL/min) or severe (creatinine clearance <30 mL/min) renal impairment.
- There have been postmarketing reports of worsening renal function, including acute renal failure, sometimes requiring dialysis. A subset of these reports involved patients with renal impairment, some of whom were prescribed inappropriate doses of Sitagliptin. A return to baseline levels of renal impairment has been observed with supportive treatment and discontinuation of potentially causative agents. Consideration can be given to cautiously reinitiating Sitagliptin if another etiology is deemed likely to have precipitated the acute worsening of renal function.
- Sitagliptin has not been found to be nephrotoxic in preclinical studies at clinically relevant doses, or in clinical trials.

Hypoglycemia with Concomitant Use with Insulin or Insulin Secretagogues

- When Sitagliptin was used in combination with a sulfonylurea or with insulin, medications known to cause hypoglycemia, the incidence of hypoglycemia was increased over that of placebo used in combination with a sulfonylurea or with insulin. Therefore, a lower dose of sulfonylurea or insulin may be required to reduce the risk of hypoglycemia.

Hypersensitivity Reactions

- There have been postmarketing reports of serious hypersensitivity reactions in patients treated with Sitagliptin. These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Onset of these reactions occurred within the first 3 months after initiation of treatment with Sitagliptin, with some reports occurring after the first dose.
- If a hypersensitivity reaction is suspected, discontinue Sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes.

- Angioedema has also been reported with other DPP-4 inhibitors. Use caution in a patient with a history of angioedema with another DPP-4 inhibitor because it is unknown whether such patients will be predisposed to angioedema with Sitagliptin.

Severe and Disabling Arthralgia

- There have been postmarketing reports of severe and disabling arthralgia in patients taking DPP-4 inhibitors. The time to onset of symptoms following initiation of drug therapy varied from one day to years. Patients experienced relief of symptoms upon discontinuation of the medication. A subset of patients experienced a recurrence of symptoms when restarting the same drug or a different DPP-4 inhibitor. Consider DPP-4 inhibitors as a possible cause for severe joint pain and discontinue drug if appropriate.

Bullous Pemphigoid

- Postmarketing cases of bullous pemphigoid requiring hospitalization have been reported with DPP-4 inhibitor use. In reported cases, patients typically recovered with topical or systemic immunosuppressive treatment and discontinuation of the DPP-4 inhibitor.
- Tell patients to report development of blisters or erosions while receiving Sitagliptin. If bullous pemphigoid is suspected, Sitagliptin should be discontinued and referral to a dermatologist should be considered for diagnosis and appropriate treatment.

Macrovascular Outcomes

- There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with Sitagliptin or any other anti-diabetic drug.

Reference:

- Prescribing information of Product